Insulin Delivery Systems and Continuous Glucose Monitoring

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Diabetes mellitus (DM), commonly known as diabetes, is a chronic medical condition characterized by elevated blood glucose levels. This can occur due to insufficient insulin production by the pancreas, an organ located in the abdomen, or the body's inadequate response to insulin. Insulin is a hormone that enables glucose to enter cells, providing them with energy. In diabetes, blood sugar accumulates due to a lack of insulin or the body's improper response to it. Diabetes is classified into two main types:

- Type 1 diabetes mellitus (T1DM): The pancreas produces little or no insulin.
- Type 2 diabetes mellitus (T2DM): The body's cells do not respond effectively to insulin, and sometimes the pancreas does not produce enough insulin.

Managing diabetes necessitates regular monitoring and treatment, which often includes lifestyle adjustments, self-care, and medication to regulate blood glucose levels and reduce the risk of complications. Plan members diagnosed with Type 1 or Type 2 diabetes who meet specific medical necessity criteria and adhere to the American Diabetes Association (ADA) standards of care may be eligible for certain supplies and equipment covered by the plan, such as blood sugar monitoring tools

and insulin injection devices. Those with advanced disease or requiring more frequent insulin administration may qualify for continuous glucose monitoring and specialized insulin delivery systems.

- For details on the medical necessity criteria for medical nutrition counseling, refer to the Plan Clinical Guideline: Medical Nutrition Therapy (CG010).
- For information on the medical necessity criteria for diabetes equipment and supplies, consult the Plan Clinical Guideline: Diabetes Equipment and Supplies (CG028). A prescription or recommendation from a physician or licensed healthcare professional is required for diabetic supplies and equipment.
- The Plan also covers home glucose monitors and self-monitoring blood sugar products as an alternative to continuous glucose monitors (CGMs). To obtain a standard blood glucose meter from the preferred brand, please contact CVS/Caremark, the Plan's Prescription Benefit Manager.

Definitions

"Artificial Pancreas" devices are closed-loop, integrated continuous blood glucose monitor and insulin delivery system. Special built-in software measures the blood glucose similar to continuous glucose monitoring and automatically releases a specified amount of insulin in real-time and without patient interaction. The system may also have a glucagon administration component for episodes of hypoglycemia for which it is then referred to as a bihormonal, fully-automated artificial pancreas.

"Basal Rate" is the steady flow at which low levels of short-acting insulin are released to control blood glucose between meals and during sleep; this measurement ranges by time of day and is used in insulin pumps.

"Blood Glucose" is the main sugar found in the blood and the body's main source of energy. It is also called glucose or blood sugar. The blood level of glucose is noted in milligrams per deciliter (mg/dL). When blood sugar is too high for long periods of time, complications can occur as a result of blood vessel damage.

"Blood Glucose Monitors" are small, portable machines used to check blood glucose levels in the ambulatory setting. A member will prick his/her fingertip and place a small sample of blood into the device for a glucose reading. There are a number of different types of blood glucose monitors for specialized situations, such as those for members with visual impairments.

"Bolus" is an extra amount of insulin taken to cover an expected rise in blood glucose, often related to a meal or snack.

"Cartridge" (or a reservoir) holds the insulin and is locked into an external continuous subcutaneous insulin infusion pump device.

"Continuous Glucose Monitoring (CGM)" serves as an alternative to self-monitoring of blood glucose (SMBG) with a home glucose monitor for patients who have diabetes and require multiple daily measurements.

"Disposable Insulin Infusion Pumps" are insulin-delivery devices that consist of disposable components. Both the OmniPod and V-Go insulin delivery systems have disposable components, but they differ in that the OmniPod system is programmable, whereas the V-Go system is non-programmable.

"External Continuous Subcutaneous Insulin Infusion (CSII) Pumps" or **"Insulin Infusion Pumps"** are non-implantable insulin-delivery devices that can be worn on a belt, kept in a pocket, or attached directly to the skin. An insulin pump connects to narrow, flexible plastic tubing that ends with a needle inserted just under the skin. Users set the pump to give a basal amount of insulin continuously throughout the day. Pumps release bolus doses of insulin (several units at a time) at meals and at times when blood glucose is too high, based on programming done by the user. Insulin infusion pumps serve as an alternative to multiple daily injections of insulin. The infusion cannula should be changed every 2-3 days to avoid lipid hypertrophy at the infusion site. Insulin infusion pumps can be differentiated by programmable/non-programmable, disposable/reusable, and subcutaneous/transdermal/implantable.

"Flash Glucose Monitoring" refers to glucose monitoring that does not have an alarm, does not require self-monitoring of blood glucose (SMBG), and functions intermittently and on-demand rather than continuously (e.g., FreeStyle Libre System).

"Gestational Diabetes Mellitus (GDM)" is a type of diabetes mellitus that develops only during pregnancy and usually disappears upon delivery, but increases the risk that the mother will develop diabetes later. GDM is managed with meal planning, activity, oral agents, and, in some cases, insulin.

"Hemoglobin A1c (HbA1c)" is a test that measures a person's average blood glucose level over the past 2 to 3 months. It is also known as "A1C" or "glycosylated hemoglobin". A1C should be measured at least twice annually for stable glycemic control and at least quarterly for unstable glycemic control.

A1C test results may be affected by age, certain conditions, ethnicity, genetic traits, and pregnancy; the ADA recommends that treating providers review for discrepancies between A1c results and blood glucose results.

"Hyperglycemia" is excessive blood glucose. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours. Postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

"Hypoglycemia Unawareness" is a state in which a person does not feel or recognize the symptoms of hypoglycemia. People who have frequent episodes of hypoglycemia may no longer experience the warning signs of it.

"Hypoglycemia" is a condition that occurs when one's blood glucose is lower than normal, usually less than 70 mg/dL. Signs include hunger, nervousness, shakiness, perspiration, dizziness or lightheadedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. Hypoglycemia is treated by consuming a carbohydrate-rich food such as a glucose tablet or juice. It may also be treated with an injection of glucagon if the person is unconscious or unable to swallow.

"Implantable Insulin Pump" is a device similar in function to an external insulin pump, however the components are implanted rather than worn or carried externally.

"Infusion Set" connects the insulin in an external continuous subcutaneous insulin infusion pump delivery device to a person's body. The set consists of narrow, flexible plastic tubing that ends with a needle inserted just under the skin.

"Insulin" is a hormone made by the beta cells of the pancreas. Insulin allows glucose to enter the cells in the body for use in energy production, and when it is inadequate, the sugar remains in the blood leading to diabetes. There are a variety of oral and parenteral medications that can increase insulin production, increase the body's sensitivity to existing insulin and reduce blood sugar. Insulin can also be injected or infused when lifestyle changes and non-insulin medications are inadequate.

"Remote Glucose Monitoring" refers to the transmission of blood glucose readings to an external device, such as the patient's phone, computer, or to a physician/healthcare provider. It can be a standalone device or integrated into the continuous glucose monitor system.

"Type 1 Diabetes" is an autoimmune condition that occurs when the beta cells of the pancreas are unable to produce enough insulin and therefore blood glucose cannot enter cells to be used for energy. Type 1 diabetes is often referred to as "insulin-dependent" because these patients require insulin daily to maintain their blood glucose at acceptable levels.

"Type 2 Diabetes" is a condition that occurs when either the pancreas doesn't produce enough insulin or the body cells become resistant to insulin. Type 2 diabetes is much more common than Type 1, and is often treated with combinations of lifestyle changes and non-insulin medications, although insulin can be required later in the disease course. Many individuals with Type 2 Diabetes are "insulin-requiring".

Clinical Indications

General Criteria

The Plan considers **insulin pump delivery systems or continuous glucose monitoring systems (CGMS) and its components** medically necessary when **ALL** of the following general criteria are met **AND** the medical necessity criteria for the devices below are met:

1. The requested product has received U.S. Food and Drug Administration (FDA) approval/clearance **AND** is age-appropriate for the member; ***AND***
2. The member has a diagnosis of diabetes mellitus; ***AND***
3. Recent clinical documentation[ɳ] within the last six (6) months is provided showing **ALL** of the following:
    a. A prescription for the requested product with **ALL** of the following:
        i. Product to be dispensed; ***and***
        ii. Quantity to be dispensed (or frequency of testing); ***and***
        iii. Prescriber's signature and date; ***and***
    b. Hemoglobin A1c test results.

    NOTE: [ɳ]All of the above documentation must be updated every 6 months to show compliance with treatment options. If any of the required documentation is more than 6 months old, it must be updated as soon as possible before any renewal request for coverage.
4. Additional criteria, as outlined below, must also be met depending on the specific equipment and supplies requested:

External Insulin Pump Delivery Systems Criteria

- ➔ *For members who have been on an external insulin pump delivery system prior to enrollment with the Plan, please see* Continued Care Criteria *below.*
- ➔ *For a replacement, see* Replacement Insulin Pumps Criteria *below.*

The Plan considers **non-implantable insulin infusion pumps and supplies** medically necessary when **ALL** of the following criteria are met:

1. The "General Criteria" for equipment and supplies above are met; ***AND***
2. Prescribed by or in consultation with an endocrinologist or other provider experienced in diabetes technology and management***; AND***
3. Chart documentation is provided for the member showing **ALL** of the following:
    a. Diagnosis of type 1 or type 2 diabetes mellitus with uncontrolled hyperglycemia***; and***
    b. Is beta cell autoantibody positive **OR** insulinopenic, as confirmed by **BOTH** of the following:
        i. A fasting C-peptide level measured with a concurrently obtained fasting glucose less than or equal to (≤) 225 mg/dL; ***and***
        ii. The measured fasting C-peptide level meets **ONE** of the following:
            1. is undetectable (absolute insulin deficiency)***; or***
            2. is less than or equal to 110% of the lower limit of normal established by the laboratory***; or***
            3. is less than or equal to 200% of the lower limit of normal established by the laboratory AND the member has documentation of renal insufficiency and creatinine clearance less than or equal to (≤) 50 ml/minute; ***and***
    c. At least **ONE** of the following:
        i. Diagnosis of type-1 diabetes***; or***
        ii. A child, where multiple daily insulin injections would be impractical or inappropriate***; or***
        iii. Complications of inadequate glycemic control (e.g., neuropathy, nephropathy, retinopathy) indicative of more intensive insulin regimens***; or***
        iv. Dawn phenomenon unresponsive to management with long-acting insulin agents (e.g., insulin glargine or detemir)***; or***
        v. For initial requests, HbA1c greater than 7% or above individualized target, despite an adequate regimen of multiple daily injections***; or***
        vi. Hypoglycemic episodes requiring third-party assistance (e.g., seizure, loss of consciousness, glucagon administration, transport to an emergency room, hospitalization)***; or***

vii. Recurrent hypoglycemia (<70 mg/dL on at least two occasions despite adherence to recommended diabetic treatment plan)***; or***

viii. Pregnancy or planning for pregnancy; ***or***

[NOTE: Earlier initiation of insulin infusion pumps may be indicated in women at high risk of fetal or maternal complications of diabetes and pregnancy.]

ix. Wide swings in blood glucose values before meal time (e.g., regular fluctuations of preprandial blood glucose to levels <70 mg/dL and/or >140 mg/dL); ***and***

d. Completion of a comprehensive diabetes education program***; and***
e. Currently uses three (3) or more insulin injections daily***; and***
f. History of frequent self-adjustments of insulin doses for at least 6 months prior***; and***
g. Self-monitors blood glucose at least three (3) times per day (e.g., before meals and at bedtime) for the immediate two (2) months prior***; and***
h. Member or designated caregiver can be adequately trained and is motivated to adhere to blood glucose monitoring at least 3 times per day, or the member qualifies for continuous glucose monitoring***; and***
i. Provider team (e.g., physician, nurses, diabetes educators, and dietitians) is experienced in diabetes technology and management and can provide ongoing education, follow-up and support.

When **BOTH** the General Criteria and External Insulin Pump Delivery Systems Criteria above are met **OR** were previously met and the member has a continued documented need for an insulin pump delivery system, the Plan considers the following quantities medically necessary:

Table 1: External Insulin Pump Delivery Systems & Supplies Medically Necessary Quantities

Insulin Infusion Supply	Quantity‡ Per 3 Months	Quantity‡ Per 1 Year
Infusion set (A4230, A4231)	45	180
Supplies for maintenance of insulin infusion pump (A4226)	13	52
Needles or syringes (A4206, A4215, A4232)	60	240
External ambulatory infusion pump, insulin (E0784)	-	1 per 4 years (unless malfunctioning and/or out of warranty)
External ambulatory infusion pump, insulin, using therapeutic continuous	-	1 per 4 years (unless malfunctioning and/or out of

Insulin Infusion Supply	Quantity‡ Per 3 Months	Quantity‡ Per 1 Year
glucose sensing (E0787)		warranty)
Cartridges or syringe reservoirs (S5565-S5566, J1817)	30	120
Sterile insertion-site dressing (i.e., Tegaderm) (A6257)	45 / 3 boxes	180

‡Quantities are suggested guidance and are subject to review of the medical record and prescription. Requests that exceed the suggested quantity must be submitted with clinical documentation of medical necessity.

Replacement Insulin Pump Delivery Systems Criteria

Replacement Insulin Pump Delivery Systems are considered **NOT** medically necessary for the purpose of adding convenience features or new technologies (e.g., adding a wireless communication system to the glucose monitor). Replacement insulin pumps are considered medically necessary when recent chart documentation (within last 6 months) indicates **ALL** of the following:

1. the member continues to meet the General Criteria above***; AND***
2. the member has demonstrated adherence to diabetes management and use of devices***; AND***
3. The request is for **ONE** of the following:
    a. A pediatric member requiring a replacement pump with larger insulin reservoir due to growth**; *or***
    b. Replacement of a malfunctioning pump that is no longer under warranty OR cannot be refurbished and restored to fully functional order.

Professional Diagnostic or Short-Term Continuous Glucose Monitoring (CGM) Systems Criteria

NOTE: Coverage for long-term continuous glucose monitors (CGMs), which includes real-time CGM (rtCGM) (e.g., Dexcom), intermittently scanned CGM (isCGM) devices (e.g., Freestyle Libre) which are occasionally called "flash" CGM systems, and implantable glucose monitoring systems (e.g., Eversense) requires satisfaction of the Plan's Continuous Glucose Monitors (CGMs) Prescription Products (PG121).

For members who have been on a professional diagnostic or short-term CGM prior to enrollment with the Plan, please see Continued Care Criteria below.

The Plan considers **Professional Diagnostic or Short-Term Continuous Glucose Monitoring Systems and its components**[#] medically necessary when the member meets ALL of the following criteria:

1. The "**General Criteria**" for equipment and supplies above; ***AND***
2. Documented diagnosis of diabetes mellitus; ***AND***
3. Short-term CGM is necessary, as indicated by **BOTH** of the following:
    a. Additional information on blood glucose levels is needed, as indicated by at least **ONE** of the following:
        i. Dawn phenomenon, known or suspected; ***or***
        ii. Hypoglycemic unawareness; ***or***
        iii. Nocturnal hyperglycemia, known or suspected; ***or***
        iv. Postprandial hyperglycemia, known or suspected; ***or***
        v. Significant change to the treatment regimen, such as starting insulin or transitioning from multiple daily doses to an insulin pump; ***or***
        vi. Unexplained hyperglycemia; ***and***
    b. Monitoring is limited to a maximum of three (3) to 14 days and for no more than 2 episodes within a 12-month period.

When the **General Criteria**, along with the criteria for **Professional Diagnostic or Short-Term Continuous Glucose Monitoring (CGM) Systems** **is** satisfied, or have been satisfied in the past, and the member demonstrates an ongoing documented need for a CGM, the Plan deems the following quantities to be medically necessary:

Table 2[#]: Professional Diagnostic/Short-Term CGMS Medically Necessary Quantities

CGM System	FDA-approved or cleared for	Components	Wear Time	Quantity[‡] per 12-month period
Abbott Freestyle Libre Pro	≥18 years old	disposable combined wired glucose sensor/transmitter and a separate touchscreen reader device	14 days	2
Dexcom G6 Pro	2 years and older	disposable	10 days	2

CGM System	FDA-approved or cleared for	Components	Wear Time	Quantity[‡] per 12-month period
		wired glucose sensor/transmitter and a separate touchscreen reader device		
Medtronic iPro 2	Not specified	disposable wired sensor and a data transmitter, which is attached to the sensor	6 days	2

[#]*This is not an exhaustive list. When medical necessity criteria is met for products not listed, quantities for supplies will reflect FDA-approved or cleared indications for use.*

[‡]*Quantities are suggested guidance and are subject to review of the medical record and prescription. Requests that exceed the suggested quantity must be submitted with clinical documentation of medical necessity.*

Artificial Pancreas / Hybrid Closed-Loop Insulin Delivery Systems[#]

➔ *For members who have been on this hybrid insulin system prior to enrollment with the Plan, please see* Continued Care Criteria *below.*

The Plan considers **hybrid, closed-loop insulin delivery systems** medically necessary when **ALL** of the following criteria are met:

1. The "**General Criteria**" for equipment and supplies above are met; ***AND***
2. The member meets the criteria for a new or replacement "external insulin infusion pump"; ***AND***
3. The member meets the criteria for a new or replacement "continuous glucose monitoring" (see PG121); ***AND***
4. The member has documented adherence to a diabetic treatment plan and can be trained (or member's guardian) to use the device; ***AND***
5. The requested system is FDA approved or cleared **AND** is being prescribed for use in accordance to the device-specific FDA limitations (when applicable), such as:
    a. Appropriate age recommendations or restrictions (see table 3); ***or***
    b. No contraindications to requested system; ***or***
    c. No interference by medications (e.g., Tylenol [acetaminophen], ascorbic acid, hydroxyurea depending on CGM integration); ***or***
    d. No hearing or visual impairments prevent recognition of pump signals and/or alarms; ***or***

e. Daily insulin dosage (units) meets minimum dosage requirements for device functionality.

Table 3[5]: FDA-approved/cleared Artificial Pancreas/Hybrid Closed-Loop Insulin Delivery Systems

System	Manufacturer	Type	Age Indication	CGM[3] Integration	Insulin Dosing
iLet Bionic Pancreas	Beta Bionics	Closed-loop	≥6 years (T1DM)	Dexcom G6/7, Freestyle Libre 3 Plus	Fully automated insulin delivery based on qualitative meal announcements
MiniMed 630G	Medtronic	LGS[1]	≥14 years (T2DM)	Guardian Sensor 3	Suspends insulin delivery at preset low glucose threshold
MiniMed 780G	Medtronic	HCL[2]	≥7 years (T1DM)	Guardian Sensor 4	Auto-adjusts basal insulin; manual bolus; provides autocorrections as needed; meal detection
Omnipod 5	Insulet	HCL[2]	≥2 years (T1DM), ≥18 years (T2DM)	Dexcom G6/7, Freestyle Libre 2 Plus	Auto-adjusts basal insulin; manual bolus
t:slim X2 with Basal-IQ	Tandem	LGS[1]	≥6 years	Dexcom G6	Suspends insulin delivery based on predicted low glucose
t:slim X2 with Control-IQ	Tandem	HCL[2]	≥6 years (T1DM)	Dexcom G6/7, Freestyle Libre 2 Plus	Auto-adjusts basal insulin; manual bolus
Tandem Mobi	Tandem	HCL[2]	≥6 years	Dexcom G6/7	Auto-adjusts basal insulin; manual bolus

[1]LGS: Low Glucose Suspend

[2]HCL: Hybrid Closed-Loop

[3]CGM: Continuous Glucose Monitoring

[5]*NOTE: The information provided in this table is based on the current FDA approvals and indications for each device as of the reviewed date noted within* Clinical Guideline Revision/History Information*. The features, functionalities, and indications for these devices may change over time as manufacturers develop new technologies and receive updated regulatory approvals. Always refer to the*

manufacturer's official documentation and the most recent FDA approval status for the most accurate and up-to-date information on each device.

Continued Care Criteria for Continuing Treatment After Initial Trial

The Plan considers **professional diagnostic or short-term continuous glucose monitoring, insulin delivery systems, and hybrid closed-loop insulin delivery systems** (**including members who have been on the device/monitor prior to enrollment with the Plan**) medically necessary when **ALL** of the following criteria are met:

1. The member continues to meet the **"General Criteria"** above.
2. There is documented provider evaluation within the last 6 months that demonstrates the member's adherence to their diabetic treatment plan and devices. This evaluation should assess the member's compliance with the prescribed treatment regimen and use of the professional diagnostic or short-term continuous glucose monitoring system, insulin delivery system, or hybrid closed-loop insulin delivery system.

Experimental or Investigational / Not Medically Necessary

The Plan does not consider medically necessary the replacement or repair of units or associated equipment when lost or damaged due to neglect or improper care.

The following products, supplies, or indications are considered experimental, investigational, or convenience features:

1. Fully-Automated Bihormonal Artificial Pancreas Devices
    a. *Rationale:* At this time, there are no commercially available or FDA approved bihormonal artificial pancreas systems. Several small cross-over studies looking at this device demonstrated a lower mean glucose in the intervention group and fewer episodes of hypoglycemia. However, there have been no long-term safety or efficacy studies, and some of the existing studies have found similar results between single hormone (insulin) and bi-hormonal (insulin and glucagon) systems.
2. GlucoWatch Biographer Monitor (Cygnus Inc.) or any other hypoglycemic wristband alarm (A9280)
    a. *Rationale:* The clinical utility of these devices has not yet been demonstrated in any randomized clinical trials. The MITRE (Minimally Invasive Technology Role and Evaluation) study was a large clinical trial on 400 patients with diabetes on insulin. The study concluded that there was a small, short-term clinical benefit that subsided over

time. Furthermore, the Biographer monitor had less impact on HbA1C than both standard treatment and continuous blood glucose monitoring.[20-21, 32, 92, 114]

3. Implantable Insulin Pumps
    a. *Rationale:* There have been studies demonstrating potential clinical benefit of implantable insulin pumps, however they do not currently have U.S. Food and Drug Administration (FDA) approval at this time, and the ADA 2023 guidelines do not mention implantable insulin pumps as a recommended treatment for diabetes.
4. Lasette™ Laser Blood Glucose Monitoring Device or other similar laser lancets
    a. *Rationale*: Evidence for the clinical benefit of laser blood glucose monitoring over standard blood glucose monitoring is limited in the medical literature; therefore, these devices are considered experimental or investigational.
5. Remote Glucose Monitoring (e.g., mySentry, MiniMed Connect, Dexcom Share) is not covered as a separately reimbursable or standalone device or service. Integrated remote glucose monitoring, such as when a CGM device has the ability to share data to a smart phone or through an app, may be considered medically necessary when the clinical criteria for CGM are met.
    a. *Rationale:* There is limited evidence that telemonitoring or otherwise sharing glucose values results in an improvement in outcomes. A 2017 study by Lee et al conducted on 107 patients, 54 of which were frequent users of self-telemonitoring and 53 who were not, showed a small but significant difference in A1c values at 6 months. This study was limited by its non-randomized nature, small population, and potential confounding factors. Other studies have shown no benefit of telemonitoring of diabetes patients in terms of glycemic control. The use of standalone devices or telemonitoring services for remote glucose monitoring has yet to be fully explored, and further data is needed to determine if there is any potential benefit to this technology.[123, 124, 126]
6. Subcutaneous insulin infusers, including but not limited to, i-Port
    a. *Rationale:* There is a lack of clinical evidence supporting the use of insulin infusers and diabetes outcomes. Blevins et al (2008) conducted a randomized controlled crossover trial comparing outcomes of i-Port vs. standard insulin injection in 74 patients. A1c levels were similar among all subjects at the initiation and completion of the study, demonstrating no observable clinical benefit. Patients did report that it was more difficult to control their blood sugar levels with standard insulin injections; however the differences were non-significant ($p=0.16$).[14]

Applicable Billing Codes (CPT/HCPCS/ICD-10 Codes)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
95249	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; patient-provided equipment, sensor placement, hook-up, calibration of monitor, patient training, and printout of recording
95250	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; physician or other qualified health care professional (office) provided equipment, sensor placement, hook-up, calibration of monitor, patient training, removal of sensor, and printout of recording
95251	Ambulatory continuous glucose monitoring of interstitial tissue fluid via a subcutaneous sensor for a minimum of 72 hours; analysis, interpretation and report
A4224	Supplies for maintenance of insulin infusion catheter, per week
A4225	Supplies for external insulin infusion pump, syringe type cartridge, sterile, each
A4226	Supplies for maintenance of insulin infusion pump with dosage rate adjustment using therapeutic continuous glucose sensing, per week
A4230	Infusion set for external insulin pump, nonneedle cannula type
A4231	Infusion set for external insulin pump, needle type
A4232	Syringe with needle for external insulin pump, sterile, 3 cc
A4238	Supply allowance for adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A6257	Transparent film, sterile, 16 sq in or less, each dressing
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories [medically necessary when programmable]

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
	[NOTE: Omnipod Dash has been available only under the pharmacy benefit as of April 2021. All other external insulin delivery systems will remain under medical benefit.]
A9275	Home glucose disposable monitor, includes test strips
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with non-durable medical equipment interstitial continuous glucose monitoring system, one unit = 1 day supply
A9277	Transmitter; external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
A9278	Receiver (monitor); external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
A9279	Monitoring feature/device, stand-alone or integrated, any type, includes all accessories, components and electronics, not otherwise classified
E2102	Adjunctive, non-implanted continuous glucose monitor or receiver
E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver
E0784	External ambulatory infusion pump, insulin
E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
G0308	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new 180 day implantable sensor, including system activation
G0309	Supply allowance for therapeutic continuous glucose monitor (CGM), includes all supplies and accessories, 1 month supply = 1 unit of service [that is, a device that does not require a finger stick, e.g., Dexcom G5]
K0601	Replacement battery for external infusion pump owned by patient, silver oxide, 1.5 volt, each

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
K0602	Replacement battery for external infusion pump owned by patient, silver oxide, 3 volt, each
K0603	Replacement battery for external infusion pump owned by patient, alkaline, 1.5 volt, each
K0604	Replacement battery for external infusion pump owned by patient, lithium, 3.6 volt, each
K0605	Replacement battery for external infusion pump owned by patient, lithium, 4.5 volt, each
S1030	Continuous noninvasive glucose monitoring device, purchase (For physician interpretation of data, use CPT code)
S1031	Continuous noninvasive glucose monitoring device, rental, including sensor, sensor replacement, and download to monitor (For physician interpretation of data, use CPT code)
S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
S1036	Transmitter; external, for use with artificial pancreas device system
S1037	Receiver (monitor); external, for use with artificial pancreas device system
ICD-10 codes considered medically necessary if criteria are met:	
E08	Diabetes mellitus due to underlying condition
E08.0	Diabetes mellitus due to underlying condition with hyperosmolarity
E08.00	Diabetes mellitus due to underlying condition with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E08.01	Diabetes mellitus due to underlying condition with hyperosmolarity with coma

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E08.1	Diabetes mellitus due to underlying condition with ketoacidosis
E08.10	Diabetes mellitus due to underlying condition with ketoacidosis without coma
E08.11	Diabetes mellitus due to underlying condition with ketoacidosis with coma
E08.2	Diabetes mellitus due to underlying condition with kidney complications
E08.21	Diabetes mellitus due to underlying condition with diabetic nephropathy
E08.22	Diabetes mellitus due to underlying condition with diabetic chronic kidney disease
E08.29	Diabetes mellitus due to underlying condition with other diabetic kidney complication
E08.3	Diabetes mellitus due to underlying condition with ophthalmic complications
E08.31	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy
E08.311	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy with macular edema
E08.319	Diabetes mellitus due to underlying condition with unspecified diabetic retinopathy without macular edema
E08.32	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy
E08.321	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy with macular edema
E08.329	Diabetes mellitus due to underlying condition with mild nonproliferative diabetic retinopathy without macular edema
E08.33	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy
E08.331	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy with macular edema

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E08.339	Diabetes mellitus due to underlying condition with moderate nonproliferative diabetic retinopathy without macular edema
E08.34	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy
E08.341	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy with macular edema
E08.349	Diabetes mellitus due to underlying condition with severe nonproliferative diabetic retinopathy without macular edema
E08.35	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy
E08.351	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with macular edema
E08.352	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E08.353	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E08.354	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E08.355	Diabetes mellitus due to underlying condition with stable proliferative diabetic retinopathy
E08.359	Diabetes mellitus due to underlying condition with proliferative diabetic retinopathy without macular edema
E08.36	Diabetes mellitus due to underlying condition with diabetic cataract
E08.37	Diabetes mellitus due to underlying condition with diabetic macular edema, resolved following treatment
E08.39	Diabetes mellitus due to underlying condition with other diabetic ophthalmic complication

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E08.4	Diabetes mellitus due to underlying condition with neurological complications
E08.40	Diabetes mellitus due to underlying condition with diabetic neuropathy, unspecified
E08.41	Diabetes mellitus due to underlying condition with diabetic mononeuropathy
E08.42	Diabetes mellitus due to underlying condition with diabetic polyneuropathy
E08.43	Diabetes mellitus due to underlying condition with diabetic autonomic (poly)neuropathy
E08.44	Diabetes mellitus due to underlying condition with diabetic amyotrophy
E08.49	Diabetes mellitus due to underlying condition with other diabetic neurological complication
E08.5	Diabetes mellitus due to underlying condition with circulatory complications
E08.51	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy without gangrene
E08.52	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
E08.59	Diabetes mellitus due to underlying condition with other circulatory complications
E08.6	Diabetes mellitus due to underlying condition with other specified complications
E08.61	Diabetes mellitus due to underlying condition with diabetic arthropathy
E08.610	Diabetes mellitus due to underlying condition with diabetic neuropathic arthropathy
E08.618	Diiabetes mellitus due to underlying condition with other diabetic arthropathy
E08.62	Diabetes mellitus due to underlying condition with skin complications
E08.620	Diabetes mellitus due to underlying condition with diabetic dermatitis
E08.621	Diabetes mellitus due to underlying condition with foot ulcer

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E08.622	Diabetes mellitus due to underlying condition with other skin ulcer
E08.628	Diabetes mellitus due to underlying condition with other skin complications
E08.63	Diabetes mellitus due to underlying condition with oral complications
E08.630	Diabetes mellitus due to underlying condition with periodontal disease
E08.638	Diabetes mellitus due to underlying condition with other oral complications
E08.64	Diabetes mellitus due to underlying condition with hypoglycemia
E08.641	Diabetes mellitus due to underlying condition with hypoglycemia with coma
E08.649	Diabetes mellitus due to underlying condition with hypoglycemia without coma
E08.65	Diabetes mellitus due to underlying condition with hyperglycemia
E08.69	Diabetes mellitus due to underlying condition with other specified complication
E08.8	Diabetes mellitus due to underlying condition with unspecified complications
E08.9	Diabetes mellitus due to underlying condition without complications
E09	Drug or chemical induced diabetes mellitus
E09.0	Drug or chemical induced diabetes mellitus with hyperosmolarity
E09.00	Drug or chemical induced diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E09.01	Drug or chemical induced diabetes mellitus with hyperosmolarity with coma
E09.1	Drug or chemical induced diabetes mellitus with ketoacidosis
E09.10	Drug or chemical induced diabetes mellitus with ketoacidosis without coma
E09.11	Drug or chemical induced diabetes mellitus with ketoacidosis with coma
E09.2	Drug or chemical induced diabetes mellitus with kidney complications
E09.21	Drug or chemical induced diabetes mellitus with diabetic nephropathy
E09.22	Drug or chemical induced diabetes mellitus with diabetic chronic kidney disease

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E09.29	Drug or chemical induced diabetes mellitus with other diabetic kidney complication
E09.3	Drug or chemical induced diabetes mellitus with ophthalmic complications
E09.31	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy
E09.311	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy with macular edema
E09.319	Drug or chemical induced diabetes mellitus with unspecified diabetic retinopathy without macular edema
E09.32	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy
E09.321	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E09.329	Drug or chemical induced diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E09.33	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy
E09.331	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E09.339	Drug or chemical induced diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E09.34	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy
E09.341	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E09.349	Drug or chemical induced diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E09.35	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy
E09.351	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with macular edema
E09.352	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E09.353	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E09.354	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E09.355	Drug or chemical induced diabetes mellitus with stable proliferative diabetic retinopathy
E09.359	Drug or chemical induced diabetes mellitus with proliferative diabetic retinopathy without macular edema
E09.36	Drug or chemical induced diabetes mellitus with diabetic cataract
E09.37	Drug or chemical induced diabetes mellitus with diabetic macular edema, resolved following treatment
E09.39	Drug or chemical induced diabetes mellitus with other diabetic ophthalmic complication
E09.4	Drug or chemical induced diabetes mellitus with neurological complications
E09.40	Drug or chemical induced diabetes mellitus with neurological complications with diabetic neuropathy, unspecified
E09.41	Drug or chemical induced diabetes mellitus with neurological complications with diabetic mononeuropathy
E09.42	Drug or chemical induced diabetes mellitus with neurological complications with diabetic polyneuropathy

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E09.43	Drug or chemical induced diabetes mellitus with neurological complications with diabetic autonomic (poly)neuropathy
E09.44	Drug or chemical induced diabetes mellitus with neurological complications with diabetic amyotrophy
E09.49	Drug or chemical induced diabetes mellitus with neurological complications with other diabetic neurological complication
E09.5	Drug or chemical induced diabetes mellitus with circulatory complications
E09.51	Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy without gangrene
E09.52	Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy with gangrene
E09.59	Drug or chemical induced diabetes mellitus with other circulatory complications
E09.6	Drug or chemical induced diabetes mellitus with other specified complications
E09.61	Drug or chemical induced diabetes mellitus with diabetic arthropathy
E09.610	Drug or chemical induced diabetes mellitus with diabetic neuropathic arthropathy
E09.618	Drug or chemical induced diabetes mellitus with other diabetic arthropathy
E09.62	Drug or chemical induced diabetes mellitus with skin complications
E09.620	Drug or chemical induced diabetes mellitus with diabetic dermatitis
E09.621	Drug or chemical induced diabetes mellitus with foot ulcer
E09.622	Drug or chemical induced diabetes mellitus with other skin ulcer
E09.628	Drug or chemical induced diabetes mellitus with other skin complications
E09.63	Drug or chemical induced diabetes mellitus with oral complications
E09.630	Drug or chemical induced diabetes mellitus with periodontal disease
E09.638	Drug or chemical induced diabetes mellitus with other oral complications

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E09.64	Drug or chemical induced diabetes mellitus with hypoglycemia
E09.641	Drug or chemical induced diabetes mellitus with hypoglycemia with coma
E09.649	Drug or chemical induced diabetes mellitus with hypoglycemia without coma
E09.65	Drug or chemical induced diabetes mellitus with hyperglycemia
E09.69	Drug or chemical induced diabetes mellitus with other specified complication
E09.8	Drug or chemical induced diabetes mellitus with unspecified complications
E09.9	Drug or chemical induced diabetes mellitus without complications
E10	Type 1 diabetes mellitus
E10.1	Type 1 diabetes mellitus with ketoacidosis
E10.10	Type 1 diabetes mellitus with ketoacidosis without coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma
E10.2	Type 1 diabetes mellitus with kidney complications
E10.21	Type 1 diabetes mellitus with diabetic nephropathy
E10.22	Type 1 diabetes mellitus with diabetic chronic kidney disease
E10.29	Type 1 diabetes mellitus with other diabetic kidney complication
E10.3	Type 1 diabetes mellitus with ophthalmic complications
E10.31	Type 1 diabetes mellitus with unspecified diabetic retinopathy
E10.311	Type 1 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E10.319	Type 1 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E10.32	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy
E10.321	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E10.329	Type 1 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E10.33	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy
E10.331	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E10.339	Type 1 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E10.34	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy
E10.341	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E10.349	Type 1 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E10.35	Type 1 diabetes mellitus with proliferative diabetic retinopathy
E10.351	Type 1 diabetes mellitus with proliferative diabetic retinopathy with macular edema
E10.352	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E10.353	Type 1 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E10.354	Type 1 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E10.355	Type 1 diabetes mellitus with stable proliferative diabetic retinopathy
E10.359	Type 1 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E10.36	Type 1 diabetes mellitus with diabetic cataract
E10.37	Type 1 diabetes mellitus with diabetic macular edema, resolved following treatment

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E10.39	Type 1 diabetes mellitus with other diabetic ophthalmic complication
E10.4	Type 1 diabetes mellitus with neurological complications
E10.40	Type 1 diabetes mellitus with diabetic neuropathy, unspecified
E10.41	Type 1 diabetes mellitus with diabetic mononeuropathy
E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy
E10.43	Type 1 diabetes mellitus with diabetic autonomic (poly)neuropathy
E10.44	Type 1 diabetes mellitus with diabetic amyotrophy
E10.49	Type 1 diabetes mellitus with other diabetic neurological complication
E10.5	Type 1 diabetes mellitus with circulatory complications
E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E10.59	Type 1 diabetes mellitus with other circulatory complications
E10.6	Type 1 diabetes mellitus with other specified complications
E10.61	Type 1 diabetes mellitus with diabetic arthropathy
E10.610	Type 1 diabetes mellitus with diabetic neuropathic arthropathy
E10.618	Type 1 diabetes mellitus with other diabetic arthropathy
E10.62	Type 1 diabetes mellitus with skin complications
E10.620	Type 1 diabetes mellitus with diabetic dermatitis
E10.621	Type 1 diabetes mellitus with foot ulcer
E10.622	Type 1 diabetes mellitus with other skin ulcer
E10.628	Type 1 diabetes mellitus with other skin complications
E10.63	Type 1 diabetes mellitus with oral complications
E10.630	Type 1 diabetes mellitus with periodontal disease

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E10.638	Type 1 diabetes mellitus with other oral complications
E10.64	Type 1 diabetes mellitus with hypoglycemia
E10.641	Type 1 diabetes mellitus with hypoglycemia with coma
E10.649	Type 1 diabetes mellitus with hypoglycemia without coma
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.69	Type 1 diabetes mellitus with other specified complication
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus without complications
E10.A	Type 1 diabetes mellitus, presymptomatic
E10.A0	Type 1 diabetes mellitus, presymptomatic, unspecified
E10.A1	Type 1 diabetes mellitus, presymptomatic, Stage 1
E10.A2	Type 1 diabetes mellitus, presymptomatic, Stage 2
E11	Type 2 diabetes mellitus
E11.0	Type 2 diabetes mellitus with hyperosmolarity
E11.00	Type 2 diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)
E11.01	Type 2 diabetes mellitus with hyperosmolarity with coma
E11.1	Type 2 diabetes mellitus with ketoacidosis
E11.10	Type 2 diabetes mellitus with ketoacidosis without coma
E11.11	Type 2 diabetes mellitus with ketoacidosis with coma
E11.2	Type 2 diabetes mellitus with kidney complications
E11.21	Type 2 diabetes mellitus with diabetic nephropathy
E11.22	Type 2 diabetes mellitus with diabetic chronic kidney disease

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E11.29	Type 2 diabetes mellitus with other diabetic kidney complication
E11.3	Type 2 diabetes mellitus with ophthalmic complications
E11.31	Type 2 diabetes mellitus with unspecified diabetic retinopathy
E11.311	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy without macular edema
E11.32	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy
E11.321	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E11.329	Type 2 diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E11.33	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy
E11.331	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E11.339	Type 2 diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema
E11.34	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy
E11.341	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E11.349	Type 2 diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E11.35	Type 2 diabetes mellitus with proliferative diabetic retinopathy
E11.351	Type 2 diabetes mellitus with proliferative diabetic retinopathy with macular edema

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E11.352	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E11.353	Type 2 diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E11.354	Type 2 diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E11.355	Type 2 diabetes mellitus with stable proliferative diabetic retinopathy
E11.359	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema
E11.36	Type 2 diabetes mellitus with diabetic cataract
E11.37	Type 2 diabetes mellitus with diabetic macular edema, resolved following treatment
E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication
E11.4	Type 2 diabetes mellitus with neurological complications
E11.40	Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41	Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43	Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44	Type 2 diabetes mellitus with diabetic amyotrophy
E11.49	Type 2 diabetes mellitus with other diabetic neurological complication
E11.5	Type 2 diabetes mellitus with circulatory complications
E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene
E11.52	Type 2 diabetes mellitus with diabetic peripheral angiopathy with gangrene
E11.59	Type 2 diabetes mellitus with other circulatory complications

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E11.6	Type 2 diabetes mellitus with other specified complications
E11.61	Type 2 diabetes mellitus with diabetic arthropathy
E11.610	Type 2 diabetes mellitus with diabetic neuropathic arthropathy
E11.618	Type 2 diabetes mellitus with other diabetic arthropathy
E11.62	Type 2 diabetes mellitus with skin complications
E11.620	Type 2 diabetes mellitus with diabetic dermatitis
E11.621	Type 2 diabetes mellitus with foot ulcer
E11.622	Type 2 diabetes mellitus with other skin ulcer
E11.628	Type 2 diabetes mellitus with other skin complications
E11.63	Type 2 diabetes mellitus with oral complications
E11.630	Type 2 diabetes mellitus with periodontal disease
E11.638	Type 2 diabetes mellitus with other oral complications
E11.64	Type 2 diabetes mellitus with hypoglycemia
E11.641	Type 2 diabetes mellitus with hypoglycemia with coma
E11.649	Type 2 diabetes mellitus with hypoglycemia without coma
E11.65	Type 2 diabetes mellitus with hyperglycemia
E11.69	Type 2 diabetes mellitus with other specified complication
E11.8	Type 2 diabetes mellitus with unspecified complications
E11.9	Type 2 diabetes mellitus without complications
E13	Other specified diabetes mellitus
E13.0	Other specified diabetes mellitus with hyperosmolarity
E13.00	Other specified diabetes mellitus with hyperosmolarity without nonketotic hyperglycemic-hyperosmolar coma (NKHHC)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E13.01	Other specified diabetes mellitus with hyperosmolarity with coma
E13.1	Other specified diabetes mellitus with ketoacidosis
E13.10	Other specified diabetes mellitus with ketoacidosis without coma
E13.11	Other specified diabetes mellitus with ketoacidosis with coma
E13.2	Other specified diabetes mellitus with kidney complications
E13.21	Other specified diabetes mellitus with diabetic nephropathy
E13.22	Other specified diabetes mellitus with diabetic chronic kidney disease
E13.29	Other specified diabetes mellitus with other diabetic kidney complication
E13.3	Other specified diabetes mellitus with ophthalmic complications
E13.31	Other specified diabetes mellitus with unspecified diabetic retinopathy
E13.311	Other specified diabetes mellitus with unspecified diabetic retinopathy with macular edema
E13.319	Other specified diabetes mellitus with unspecified diabetic retinopathy without macular edema
E13.32	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy
E13.321	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy with macular edema
E13.329	Other specified diabetes mellitus with mild nonproliferative diabetic retinopathy without macular edema
E13.33	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy
E13.331	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy with macular edema
E13.339	Other specified diabetes mellitus with moderate nonproliferative diabetic retinopathy without macular edema

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E13.34	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy
E13.341	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy with macular edema
E13.349	Other specified diabetes mellitus with severe nonproliferative diabetic retinopathy without macular edema
E13.35	Other specified diabetes mellitus with proliferative diabetic retinopathy
E13.351	Other specified diabetes mellitus with proliferative diabetic retinopathy with macular edema
E13.352	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment involving the macula
E13.353	Other specified diabetes mellitus with proliferative diabetic retinopathy with traction retinal detachment not involving the macula
E13.354	Other specified diabetes mellitus with proliferative diabetic retinopathy with combined traction retinal detachment and rhegmatogenous retinal detachment
E13.355	Other specified diabetes mellitus with stable proliferative diabetic retinopathy
E13.359	Other specified diabetes mellitus with proliferative diabetic retinopathy without macular edema
E13.36	Other specified diabetes mellitus with diabetic cataract
E13.37	Other specified diabetes mellitus with diabetic macular edema, resolved following treatment
E13.39	Other specified diabetes mellitus with other diabetic ophthalmic complication
E13.4	Other specified diabetes mellitus with neurological complications
E13.40	Other specified diabetes mellitus with diabetic neuropathy, unspecified
E13.41	Other specified diabetes mellitus with diabetic mononeuropathy
E13.42	Other specified diabetes mellitus with diabetic polyneuropathy

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E13.43	Other specified diabetes mellitus with diabetic autonomic (poly)neuropathy
E13.44	Other specified diabetes mellitus with diabetic amyotrophy
E13.49	Other specified diabetes mellitus with other diabetic neurological complication
E13.5	Other specified diabetes mellitus with circulatory complications
E13.51	Other specified diabetes mellitus with diabetic peripheral angiopathy without gangrene
E13.52	Other specified diabetes mellitus with diabetic peripheral angiopathy with gangrene
E13.59	Other specified diabetes mellitus with other circulatory complications
E13.6	Other specified diabetes mellitus with other specified complications
E13.61	Other specified diabetes mellitus with diabetic arthropathy
E13.610	Other specified diabetes mellitus with diabetic neuropathic arthropathy
E13.618	Other specified diabetes mellitus with other diabetic arthropathy
E13.62	Other specified diabetes mellitus with skin complications
E13.620	Other specified diabetes mellitus with diabetic dermatitis
E13.621	Other specified diabetes mellitus with foot ulcer
E13.622	Other specified diabetes mellitus with other skin ulcer
E13.628	Other specified diabetes mellitus with other skin complications
E13.63	Other specified diabetes mellitus with oral complications
E13.630	Other specified diabetes mellitus with periodontal disease
E13.638	Other specified diabetes mellitus with other oral complications
E13.64	Other specified diabetes mellitus with hypoglycemia
E13.641	Other specified diabetes mellitus with hypoglycemia with coma

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
E13.649	Other specified diabetes mellitus with hypoglycemia without coma
E13.65	Other specified diabetes mellitus with hyperglycemia
E13.69	Other specified diabetes mellitus with other specified complication
E13.8	Other specified diabetes mellitus with unspecified complications
E13.9	Other specified diabetes mellitus without complications
O24	Diabetes mellitus in pregnancy, childbirth, and the puerperium
O24.0	Pre-existing type 1 diabetes mellitus, in pregnancy, childbirth and the puerperium
O24.01	Pre-existing type 1 diabetes mellitus, in pregnancy
O24.011	Pre-existing type 1 diabetes mellitus, in pregnancy, first trimester
O24.012	Pre-existing type 1 diabetes mellitus, in pregnancy, second trimester
O24.013	Pre-existing type 1 diabetes mellitus, in pregnancy, third trimester
O24.019	Pre-existing type 1 diabetes mellitus, in pregnancy, unspecified trimester
O24.02	Pre-existing type 1 diabetes mellitus, in childbirth
O24.03	Pre-existing type 1 diabetes mellitus, in the puerperium
O24.1	Pre-existing type 2 diabetes mellitus, in pregnancy, childbirth and the puerperium
O24.11	Pre-existing type 2 diabetes mellitus, in pregnancy
O24.111	Pre-existing type 2 diabetes mellitus, in pregnancy, first trimester
O24.112	Pre-existing type 2 diabetes mellitus, in pregnancy, second trimester
O24.113	Pre-existing type 2 diabetes mellitus, in pregnancy, third trimester
O24.119	Pre-existing type 2 diabetes mellitus, in pregnancy, unspecified trimester
O24.12	Pre-existing type 2 diabetes mellitus, in childbirth

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
O24.13	Pre-existing type 2 diabetes mellitus, in the puerperium
O24.3	Unspecified pre-existing diabetes mellitus in pregnancy, childbirth and the puerperium
O24.31	Unspecified pre-existing diabetes mellitus in pregnancy
O24.311	Unspecified pre-existing diabetes mellitus in pregnancy, first trimester
O24.312	Unspecified pre-existing diabetes mellitus in pregnancy, second trimester
O24.313	Unspecified pre-existing diabetes mellitus in pregnancy, third trimester
O24.319	Unspecified pre-existing diabetes mellitus in pregnancy, unspecified trimester
O24.32	Unspecified pre-existing diabetes mellitus in childbirth
O24.33	Unspecified pre-existing diabetes mellitus in the puerperium
O24.4	Gestational diabetes mellitus
O24.41	Gestational diabetes mellitus in pregnancy
O24.410	Gestational diabetes mellitus in pregnancy, diet controlled
O24.414	Gestational diabetes mellitus in pregnancy, insulin controlled
O24.415	Gestational diabetes mellitus in pregnancy, controlled by oral hypoglycemic drugs
O24.419	Gestational diabetes mellitus in pregnancy, unspecified control
O24.42	Gestational diabetes mellitus in childbirth
O24.420	Gestational diabetes mellitus in childbirth, diet controlled
O24.424	Gestational diabetes mellitus in childbirth, insulin controlled
O24.425	Gestational diabetes mellitus in childbirth, controlled by oral hypoglycemic drugs
O24.429	Gestational diabetes mellitus in childbirth, unspecified control
O24.43	Gestational diabetes mellitus in the puerperium

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
O24.430	Gestational diabetes mellitus in the puerperium, diet controlled
O24.434	Gestational diabetes mellitus in the puerperium, insulin controlled
O24.435	Gestational diabetes mellitus in puerperium, controlled by oral hypoglycemic drugs
O24.439	Gestational diabetes mellitus in the puerperium, unspecified control
O24.8	Other pre-existing diabetes mellitus in pregnancy, childbirth, and the puerperium
O24.81	Other pre-existing diabetes mellitus in pregnancy
O24.811	Other pre-existing diabetes mellitus in pregnancy, first trimester
O24.812	Other pre-existing diabetes mellitus in pregnancy, second trimester
O24.813	Other pre-existing diabetes mellitus in pregnancy, third trimester
O24.819	Other pre-existing diabetes mellitus in pregnancy, unspecified trimester
O24.82	Other pre-existing diabetes mellitus in childbirth
O24.83	Other pre-existing diabetes mellitus in the puerperium
O24.9	Unspecified diabetes mellitus in pregnancy, childbirth and the puerperium
O24.91	Unspecified diabetes mellitus in pregnancy
O24.911	Unspecified diabetes mellitus in pregnancy, first trimester
O24.912	Unspecified diabetes mellitus in pregnancy, second trimester
O24.913	Unspecified diabetes mellitus in pregnancy, third trimester
O24.919	Unspecified diabetes mellitus in pregnancy, unspecified trimester
O24.92	Unspecified diabetes mellitus in childbirth
O24.93	Unspecified diabetes mellitus in the puerperium
P70.2	Neonatal diabetes mellitus

CPT/HCPCS codes *not* considered medically necessary:	
Code	*Description*
A4257	Replacement lens shield cartridge for use with laser skin piercing device, each
A9280	Alert or alarm device, not otherwise classified [when billed as hypoglycemic wristband alarm (e.g., Sleep Sentry)]
E0620	Skin piercing device for collection of capillary blood, laser, each

CPT/HCPCS codes not covered under the Medical Benefit Plan:	
Code	*Description*
These transdermal insulin delivery systems (e.g., V-Go) are considered self-use and may be covered under the Pharmacy Benefit Plan	
A9274	External ambulatory insulin delivery system, disposable, each, includes all supplies and accessories [when billed as Non-Programmable Transdermal Insulin Delivery Systems (e.g., V-Go disposable insulin delivery device)]
Long-term CGMs and implantable glucose monitoring systems may be covered under the Pharmacy Benefit Plan	
A4238	Supply allowance for adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A4239	Supply allowance for non-adjunctive, non-implanted continuous glucose monitor (cgm), includes all supplies and accessories, 1 month supply = 1 unit of service
A9276	Sensor; invasive (e.g., subcutaneous), disposable, for use with non-durable medical equipment interstitial continuous glucose monitoring system, one unit = 1 day supply
A9277	Transmitter; external, for use with non-durable medical equipment interstitial continuous glucose monitoring system

CPT/HCPCS codes not covered under the Medical Benefit Plan:	
Code	*Description*
A9278	Receiver (monitor); external, for use with non-durable medical equipment interstitial continuous glucose monitoring system
E2102	Adjunctive, non-implanted continuous glucose monitor or receiver
E2103	Non-adjunctive, non-implanted continuous glucose monitor or receiver
0446T	Creation of subcutaneous pocket with insertion of implantable interstitial glucose sensor, including system activation and patient training
0447T	Removal of implantable interstitial glucose sensor from subcutaneous pocket via incision
0448T	Removal of implantable interstitial glucose sensor with creation of subcutaneous pocket at different anatomic site and insertion of new implantable sensor, including system activation

References

1. Abbott Freestyle Libre Pro For Healthcare Professionals. Available from: https://www.freestyle.abbott/in-en/products/freestyle-libre-pro.html. Accessed August 2022.
2. Ahmet A, Dagenais S, Barrowman NJ, et al. Prevalence of nocturnal hypoglycemia in pediatric type 1 diabetes: a pilot study using continuous glucose monitoring. J Pediatr. 2011 Aug; 159(2):297-302.e1.
3. American Diabetes Association Professional Practice Committee et al: 15. Management of diabetes in pregnancy: standards of medical care in diabetes-2022. Diabetes Care. 45(Supplement_1):S232-43, 2022
4. American Diabetes Association Professional Practice Committee et al: 15. Management of diabetes in pregnancy: standards of medical care in diabetes-2022. Diabetes Care. 45(Supplement_1):S232-43, 2022
5. American Diabetes Association. Addendum. 7. Diabetes Technology: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020 Aug;43(Suppl. 1):S77–S88. https://doi.org/10.2337/dc20-ad08c

6. American Diabetes Association. Diabetes Technology: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020 Jan; 43(Supplement 1): S77-S88. https://doi.org/10.2337/dc20-S007
7. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2004b Jan; 27 Suppl 1:S88-90.
8. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan; 44(Supplement 1): S1-S2. https://doi.org/10.2337/dc21-Sint
9. American Diabetes Association. Position Statement. Continuous subcutaneous insulin infusion. Diabetes Care 2004a; 27 (suppl 1):S110.
10. American Diabetes Association. Standards of medical care in diabetes - 2017. Available at: http://professional.diabetes.org/ResourcesForProfessionals.aspx?cid=84160. Accessed March 15, 2017.
11. American Diabetes Association. Standards of medical care in diabetes - 2018. Available at: http://care.diabetesjournals.org/content/diacare/suppl/2017/12/08/41.Supplement_1.DC1/DC_41_S1_Combined.pdf. Accessed October 10, 2018.
12. American Diabetes Association. Standards of medical care in diabetes - 2019. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed July 23, 2019.
13. American Diabetes Association. Standards of Medical Care in Diabetes—2020 Abridged for Primary Care Providers. Clinical Diabetes. 2020; 38(1):10-38.
14. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45(Suppl. 1):S97–S112.
15. American Medical Association (AMA). CPT Assistant. December 2009; 19(12):6-8. Updated February 2010; 20(2):13.
16. Amin R, Ross K, Acerini CL, et al. Hypoglycemia prevalence in prepubertal children with type 1 diabetes on standard insulin regimen: Use of continuous glucose monitoring system. Diabetes Care. 2003;26(3):662-667.
17. Arguello, Vanessa, Continuous Glucose Monitoring in Patients with Type 2 Diabetes Receiving Insulin Injections: Does this Mean Continuous Monitoring for Everyone, Ann Int Med; 2017, 167:436-437.
18. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383(9911):69-82.
19. Bergenstal RM, Klonoff DC, Garg SK, et al.; ASPIRE In-Home Study Group. Threshold-based insulin-pump interruption for reduction of hypoglycemia. N Engl J Med. 2013 Jul 18; 369(3):224-32.
20. Bergenstal RM, Tamborlane WV, Ahmann A, et al.; STAR 3 Study Group. Effectiveness of sensor-augmented insulinpump therapy in type 1 diabetes. N Engl J Med. 2010 Jul 22; 363(4):311-20. Erratum in: N Engl J Med. 2010 Sep 9; 363(11):1092.

21. Blevins T, Schwartz SL, Bode B, et al. A Study assessing an injection port for administration of insulin. Diabetes Spectr. 2008;21:197-202.
22. Blue Cross Blue Shield Association (BCBSA), Technology Evaluation Center (TEC). Artificial pancreas device systems. TEC Assessment Program. Chicago, IL: BCBSA; May 2014;28(14).
23. Bode B, Steed RD, Davidson PC. Reduction in severe hypoglycemia with long-term continuous subcutaneous insulin infusion in type I diabetes. Diabetes Care. 1996;19(4):324-327.
24. Boland E, Monsod T, Delucia M, et al. Limitations of conventional methods of self-monitoring of blood glucose: Lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001;24(11):1858-1862.
25. Boonin A, Balinski B, Sauter J, Martinez J, Abbott S. A Retrospective Chart Review of Two Different Insulin Administration Systems on Glycemic Control in Older Adults in Long-Term Care. J Gerontol Nurs. 2017;43(1):10-16.
26. Castle JR, El youssef J, Wilson LM, et al. Randomized Outpatient Trial of Single- and Dual-Hormone Closed-Loop Systems That Adapt to Exercise Using Wearable Sensors. Diabetes Care. 2018;41(7):1471-1477.
27. Chase HP, Beck R, Tamborlane W, et al. A randomized multicenter trial comparing the GlucoWatch Biographer with standard glucose monitoring in children with type 1 diabetes. Diabetes Care. 2005;28(5):1101-1106.
28. Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther. 2010 Jul;12(7):507-15.
29. Chase HP, Roberts MD, Wightman C, et al. Use of the GlucoWatch biographer in children with type 1 diabetes. Pediatrics. 2003;111(4 Pt 1):790-794.
30. Cheyne EH, Cavan DA, Kerr D. Performance of a continuous glucose monitoring system during controlled hypoglycaemia in healthy volunteers. Diabetes Technol Ther. 2002;4(5):607-613.
31. Chico A, Vidal-Rios P, Subira M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care. 2003;26(4):1153-1157.
32. Christiansen MP, Klaff LJ, Bailey TS, Brazg R, Carlson G, Tweden KS. A Prospective Multicenter Evaluation of the Accuracy and Safety of an Implanted Continuous Glucose Sensor: The PRECISION Study. Diabetes Technol Ther. 2019 May;21(5):231-237. doi: 10.1089/dia.2019.0020. Epub 2019 Mar 29. PMID: 30925083; PMCID: PMC6532543.
33. Christiansen MP, Klaff LJ, Brazg R, Chang AR, Levy CJ, Lam D, Denham DS, Atiee G, Bode BW, Walters SJ, Kelley L, Bailey TS. A Prospective Multicenter Evaluation of the Accuracy of a Novel

Implanted Continuous Glucose Sensor: PRECISE II. Diabetes Technol Ther. 2018 Mar;20(3):197-206. doi: 10.1089/dia.2017.0142. Epub 2018 Jan 30. PMID: 29381090; PMCID: PMC5867508.

34. ClinicalTrials.gov. Safety Evaluation of the Hybrid Closed Loop (HCL) system in pediatric subjects with Type 1 Diabetes. NCT NCT02660827. https://clinicaltrials.gov/ProvidedDocs/27/NCT02660827/Prot_000.pdf
35. Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1c in insulin-treated diabetes (MITRE Study). Diabet Med. 2009 May;26(5):540-7.
36. de Bock, M, et al., Exploration of the Performance of a Hybrid Closed Loop Insulin Delivery Algorithm That Includes Insulin Delivery Limits Designed to Protect Against Hypoglycemia. J Diabetes Sci Technol, 2017. 11(1): p. 68-73.
37. de Bock, M., et al., Exploration of the Performance of a Hybrid Closed Loop Insulin Delivery Algorithm That Includes Insulin Delivery Limits Designed to Protect Against Hypoglycemia. J Diabetes Sci Technol, 2017. 11(1): p. 68-73.
38. Dehennis A, Mortellaro MA, Ioacara S. Multisite study of an implanted continuous glucose sensor over 90 days in patients with diabetes mellitus. J Diabetes Sci Technol. 2015;9(5):951-956.
39. Deiss D, Szadkowska A, Gordon D, Mallipedhi A, Schütz-Fuhrmann I, Aguilera E, Ringsell C, De Block C, Irace C. Clinical Practice Recommendations on the Routine Use of Eversense, the First Long-Term Implantable Continuous Glucose Monitoring System. Diabetes Technol Ther. 2019 May;21(5):254-264. doi: 10.1089/dia.2018.0397. Epub 2019 Apr 25. PMID: 31021180; PMCID: PMC6532544.
40. Desouza C, Salazar H, Cheong B, et al. Association of hypoglycemia and cardiac ischemia: A study based on continuous monitoring. Diabetes Care. 2003;26(5):1485-1489.
41. Dexcom G6 Guide. Available from: https://provider.dexcom.com/education-research/cgm-education-use/product-information/using-your-dexcom-g6-guide. Accessed August 2022.
42. Dexcom G6 Pro Training & Resources. Available from: https://provider.dexcom.com/products/dexcom-g6-pro/training-resources. Accessed August 2022.
43. Diabetes Control and Complications Trial (DCCT) Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. N Engl J Med. 1993;329:977-86.
44. Diabetes Research in Children Network (DirecNet) Study Group, Buckingham B, Beck RW, Tamborlane WV, Xing D, Kollman C, Fiallo-Scharer R, Mauras N, Ruedy KJ, Tansey M, Weinzimer SA, Wysocki T. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr. 2007 Oct;151(4):388-93, 393.e1-2.

45. Diabetes Research in Children Network (DirecNet) Study Group. Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes. Pediatr Diabetes. 2006;7(1):32-38.
46. Diabetes Research in Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes. 2008 Apr;9(2):142-7.
47. Edelman SV. Watching your glucose with the GlucoWatch. Diabetes Technol Ther. 2001;3(2):283-284.
48. El-Khatib FH, Balliro C, Hillard MA, et al. Home use of a bihormonal bionic pancreas versus insulin pump therapy in adults with type 1 diabetes: a multicentre randomised crossover trial. Lancet 2017; 389:369.
49. El-Khatib FH, Russell SJ, Nathan DM, et al. A bihormonal closed-loop artificial pancreas for type 1 diabetes. Sci Transl Med 2010; 2:27ra27.
50. Farrar D, Tuffnell DJ, West J. Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. Cochrane Database Syst Rev. 2007;(3):CD005542.
51. Fatourechi MM, Kudva YC, Murad MH, Elamin MB, et al. Clinical review: Hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. J Clin Endocrinol Metab. 2009 Mar;94(3):729-40.
52. Feig DS, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. Lancet 2017;390(10110):2347-2359. DOI: 10.1016/S0140-6736(17)32400-5.
53. Fischer U. Continuous in vivo monitoring in diabetes: The subcutaneous glucose concentration. Acta Anaesthesiol Scand Suppl. 1995;104:21-29.
54. Floyd B, Chandra P, Hall S, et al. Comparative analysis of the efficacy of continuous glucose monitoring and selfmonitoring of blood glucose in type 1 diabetes mellitus. J Diabetes Sci Technol. 2012 Sep 1;6(5):1094-102.
55. FreeStyle Libre: Healthcare Professionals. Available from: https://provider.freestyle.abbott/ca-en/home.html. Accessed August 2022.
56. Garg, SK, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther, 2017. 19(3): p. 155-163.
57. Garg, SK, et al. Glucose Outcomes with the In-Home Use of a Hybrid Closed-Loop Insulin Delivery System in Adolescents and Adults with Type 1 Diabetes. Diabetes Technol Ther, 2017. 19(3): p. 155-163.

58. Golden SH, Brown T, Yeh HC, et al. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review No. 57. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 12-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012.
59. Guerci B, Floriot M, Bohme P, et al. Clinical performance of CGMS in type 1 diabetic patients treated by continuous subcutaneous insulin infusion using insulin analogs. Diabetes Care. 2003;26(3):582-589.
60. Haidar A, Legault L, Messier V, et al. Comparison of dual-hormone artificial pancreas, single-hormone artificial pancreas, and conventional insulin pump therapy for glycaemic control in patients with type 1 diabetes: an open-label randomised controlled crossover trial. Lancet Diabetes Endocrinol. 2015;3(1):17-26.
61. Hammond P. Continuous subcutaneous insulin infusion: Short-term benefits apparent, long-term benefits speculative. Br J Diabetes Vasc Dis. 2004;4(2):104-108.
62. Handelsman Y, Bloomgarden ZT, Grunberger G, et al.; American Association of Clinical Endocrinologists and American College of Endocrinology. Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
63. Hay LC, Wilmshurst EG, Fulcher G. Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: The results of continuous glucose monitoring. Diabetes Technol Ther. 2003;5(1):19-26.
64. Hayes, Inc. Health Technology Assessment. Artificial Pancreas with the MiniMed 670G for the Management of Diabetes Mellitus. Lansdale, PA: Hayes, Inc.; Nov 2020. https://evidence.hayesinc.com/report/htb.medtronic3863
65. Hayes, Inc. Health Technology Assessment. Eversense Continuous Glucose Monitor For Maintaining Glycemic Control In Adults With Diabetes Mellitus. Lansdale, PA: Hayes, Inc.; July 2020.
66. Hayes, Inc. Health Technology Brief. Eversense Continuous Glucose Monitor for Maintaining Glycemic Control in Adults with Diabetes Mellitus. http://www.hayesinc.com. Published September 14, 2018. Accessed July 23, 2019.
67. Hayes, Inc. Search & Summary. OmniPod insulin management system (Insulet Corporation). http://www.hayesinc.com. Published October 25, 2018. Accessed July 22, 2019
68. Hovorka R, et al. Overnight closed loop insulin delivery (artificial pancreas) in adults with type 1 diabetes: crossover randomised controlled studies. British Medical Journal 2011;342:d1855.
69. Institute for Clinical and Economic Review (ICER). Comparative Effectiveness Public Advisory Council (CEPAC). Controversies in the management of patients with type 2 diabetes. December

2014. Available at: http://www.icerreview.org/wp-content/uploads/2015/03/CEPAC-T2D-Final-Report-December-22.pdf. Accessed March 23, 2017.

70. International Consensus on Use of Continuous Glucose Monitoring, Diabetes Care, 2017, Dec; 40(12); 1631-1640. Available at http://care.diabetesjournals.org/content/40/12/1631.
71. Jafri RZ, Balliro CA, El-Khatib F, Maheno MM, Hillard MA, O'Donovan A, Selagamsetty R, Zheng H, Damiano ER, Russell SJ. A Three-Way Accuracy Comparison of the Dexcom G5, Abbott Freestyle Libre Pro, and Senseonics Eversense Continuous Glucose Monitoring Devices in a Home-Use Study of Subjects with Type 1 Diabetes. Diabetes Technol Ther. 2020 Nov;22(11):846-852. doi: 10.1089/dia.2019.0449. PMID: 32453604.
72. Jahn LG, Capurro JJ, Levy BL. Comparative dose accuracy of durable and patch insulin infusion pumps. J Diabetes Sci Technol. 2013;7(4):1011-1020.
73. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008 Jun;51(6):941-51.
74. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Buckingham B, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2009a Nov;32(11):1947-53.
75. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76.
76. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009b Aug;32(8):1378-83.
77. Juvenile Diabetes Research Foundation. Continuous Glucose Monitoring Study Group, Bode B, Beck RW, et al. Sustained benefit of continuous glucose monitoring on A1C, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care. 2009c Nov;32(11):2047-9.
78. Karhula T, Vuorinen AL, Rääpysjärvi K, et al. Telemonitoring and Mobile Phone-Based Health Coaching Among Finnish Diabetic and Heart Disease Patients: Randomized Controlled Trial. J Med Internet Res. 2015;17(6):e153.
79. Katalenich B, Shi L, Liu S, et al. Evaluation of a Remote Monitoring System for Diabetes Control. Clin Ther. 2015;37(6):1216-25.
80. Kaufman FR, Austin J, Neinstein A, et al. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. J Pediatr. 2002;141(5):625-630.

81. Kaufman FR, Gibson LC, Halvorson M, et al. A pilot study of the continuous glucose monitoring system: Clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care. 2001;24(12):2030-2034.
82. Klonoff DC, et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology and Metabolism 2011;96(10):2968-79. (Reaffirmed November 2015)
83. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the Accuracy of 18 Marketed Blood Glucose Monitors. Diabetes Care 2018 Aug; 41(8): 1681-1688.
84. Koivisto VA, Yki-Järvinen H, Helve E, et al. Pathogenesis and prevention of the dawn phenomenon in diabetic patients treated with CSII. Diabetes. 1986;35:78-82.
85. Kovatchev BP, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. Diabetes Care 2014;37(7):1789-96.
86. Kropff J, Choudhary P, Neupane S, Barnard K, Bain SC, Kapitza C, Forst T, Link M, Dehennis A, DeVries JH. Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial. Diabetes Care. 2017 Jan;40(1):63-68. doi: 10.2337/dc16-1525. Epub 2016 Nov 4. PMID: 27815290.
87. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE Study: A 180-day, prospective, multicenter, pivotal trial. Diabetes Care. 2017;40(1):63-68.
88. Kudva YC, Carter RE, Cobelli C, Basu R, Basu A. Closed-loop artificial pancreas systems: physiological input to enhance next-generation devices. Diabetes Care 2014;37(5): 1184-90.
89. Kumareswaran K, et al. Feasibility of closed-loop insulin delivery in type 2 diabetes: a randomized controlled study. Diabetes Care 2014;37(5):1198-203.
90. Langendam M, Luijf YM, Hooft L, et al. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008101.
91. Lee MK, Lee KH, Yoo SH, Park CY. Impact of initial active engagement in self-monitoring with a telemonitoring device on glycemic control among patients with type 2 diabetes. Sci Rep. 2017;7(1):3866.
92. Leelarathna L, et al. Day and night home closed-loop insulin delivery in adults with type 1 diabetes: three-center randomized crossover study. Diabetes Care 2014;37(7):1931-7.
93. Lorenz C, Sandoval W, Mortellaro M. Interference Assessment of Various Endogenous and Exogenous Substances on the Performance of the Eversense Long-Term Implantable Continuous Glucose Monitoring System. Diabetes Technol Ther. 2018 May;20(5):344-352. doi: 10.1089/dia.2018.0028. Epub 2018 Mar 30. PMID: 29600877; PMCID: PMC5963543.

94. Luijf YM, et al. Day and Night Closed-Loop Control in Adults With Type 1 Diabetes Mellitus: A comparison of two closed-loop algorithms driving continuous subcutaneous insulin infusion versus patient sel-f-management. Diabetes Care 2013;36(12):3882-7.
95. Maran A, Crepaldi C, Tiengo A, et al. Continuous subcutaneous glucose monitoring in diabetic patients: A multicenter analysis. Diabetes Care. 2002;25(2):347-352.
96. Marcus AO, Fernandez MP. Insulin pump therapy. Acceptable alternative to injection therapy. Postgrad Med. 1996;99(3):1-7.
97. Mastrototaro JJ, Gross TM. Reproducibility of the continuous glucose monitoring system matches previous reports and the intended use of the product. Diabetes Care. 2003;26(1):256.
98. Mauras N, et al. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care 2012;35(2):204-10.
99. McAdams BH, Rizvi AA. An Overview of Insulin Pumps and Glucose Sensors for the Generalist. J Clin Med. 2016;5(1):5. Published 2016 Jan 4. doi:10.3390/jcm5010005.
100. McCulloch DK. Blood glucose self-monitoring in management of adults with diabetes mellitus. UpToDate Inc., Waltham, MA. Last reviewed February 2017.
101. McCulloch DK. Management of blood glucose in adults with type 1 diabetes mellitus. UpToDate Inc., Waltham, MA. Last reviewed February 2017.
102. McCulloch DK. Patient Education: Diabetes Mellitus type 1: Overview (Beyond the Basics). UpToDate Inc., Waltham, MA. Last reviewed February 2017.
103. McCulloch DK. Patient Education: Diabetes Mellitus type 2: Overview (Beyond the Basics). UpToDate Inc., Waltham, MA. Last reviewed February 2017.
104. Meade LT. The use of continuous glucose monitoring in patients with type 2 diabetes. Diabetes Technology & Therapeutics 2012;14(2):190-5.
105. Medtronic Guardian Connect System User Guide. Available from: https://www.medtronicdiabetes.com/sites/default/files/library/download-library/user-guides/GuardianT%20Connect%20CGM%20System%20User%20Guide.PDF
106. Medtronic iPro 2 Professional CGM. Available from: https://www.medtronicdiabetes.com/download-library/ipro-2. Accessed August 2022.
107. Minimed 670G: a hybrid closed-loop insulin delivery system. Med Lett Drugs Ther, 2016. 58(1508): p. 147-148.
108. Minimed 670G: a hybrid closed-loop insulin delivery system. Med Lett Drugs Ther, 2016. 58(1508): p. 147-148.
109. Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: A systematic review and metaanalysis of randomized, controlled trials. Am J Obstet Gynecol. 2007;197(5):447-456.

110. National Institute for Health and Care Excellence (NICE). CG17. Type 1 diabetes in adults: diagnosis and management. August 2015. Updated July 2016. Available at: https://www.nice.org.uk/guidance/ng17. Accessed March 15, 2017.
111. National Institute for Health and Care Excellence (NICE). CG18. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. August 2015. Updated November 2016. Available at: https://www.nice.org.uk/guidance/ng18. Accessed March 15, 2017.
112. Newman SP, Hurel SJ, Cooke D, et al. A randomized control trial of continuous glucose monitoring devices on Hb A1c -- The MITRE study. American Diabetes Association 67th Scientific Sessions: Abstract 0115-OR. Presented June 23, 2007. Alexandria, VA: American Diabetes Association; 2007.
113. Nimri R, et al. The "Glucositter" overnight automated closed loop system for type 1 diabetes: a randomized crossover trial. Pediatric Diabetes 2013;14(3):15967. DOI: 10.1111/pedi.120-25.
114. Nuha A. ElSayed, Grazia Aleppo, Vanita R. Aroda, Raveendhara R. Bannuru, Florence M. Brown, Dennis Bruemmer, Billy S. Collins, Marisa E. Hilliard, Diana Isaacs, Eric L. Johnson, Scott Kahan, Kamlesh Khunti, Jose Leon, Sarah K. Lyons, Mary Lou Perry, Priya Prahalad, Richard E. Pratley, Jane Jeffrie Seley, Robert C. Stanton, Robert A. Gabbay; on behalf of the American Diabetes Association, 7. Diabetes Technology: Standards of Care in Diabetes—2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S111–S127. https://doi.org/10.2337/dc23-S007
115. Oppel E, Kamann S, Heinemann L, Reichl FX, Högg C. The implanted glucose monitoring system Eversense: An alternative for diabetes patients with isobornyl acrylate allergy. Contact Dermatitis. 2020 Feb;82(2):101-104. doi: 10.1111/cod.13392. Epub 2019 Sep 17. PMID: 31463958.
116. Petrovski G, Dimitrovski C, Bogoev M, Milenkovic T, Ahmeti I, Bitovska I. Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. Diabetes Technology and Therapeutics 2011;13(11):1109-13.
117. Phillip M, et al. Nocturnal glucose control with an artificial pancreas at a diabetes camp. New England Journal of Medicine 2013;368(9):824-33.
118. Pickup JC, Sutton AJ. Severe hypoglycaemia and glycaemic control in Type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. Diabet Med. 2008 Jul;25(7):765-74.
119. Poomalar GK. Changing trends in management of gestational diabetes mellitus. World Journal of Diabetes 2015;6(2):284-95.

120. Potts RO, Tamada JA, Tierney MJ. Glucose monitoring by reverse iontophoresis. Diabetes Metab Res Rev. 2002;18 Suppl 1:S49-S53.
121. Reznik Y, Cohen O, Aronson R, et al.; OpT2mise Study Group. Insulin pump treatment compared with multiple daily injections for treatment of type 2 diabetes (OpT2mise): a randomized open-label controlled trial. Lancet. 2014 Oct 4;384(9950):1265-72.
122. Robert JJ. Continuous monitoring of blood glucose. Horm Res. 2002;57 Suppl 1:81-84.
123. Rosenfeld CR, Bohannon NJ, Bode B, et al. TheV-Go insulin delivery device used in clinical practice: Patient perception and retrospective analysis of glycemic control. Endocr Pract. 2012;18(5):660-667.
124. Russell SJ, El-Khatib FH, Sinha M, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. N Engl J Med 2014; 371:313.
125. Russell SJ, et al. Outpatient glycemic control with a bionic pancreas in type 1 diabetes. New England Journal of Medicine 2014;371(4):3132-5.
126. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-World Data from the First U.S. Commercial Users of an Implantable Continuous Glucose Sensor. Diabetes Technol Ther. 2019 Dec;21(12):677-681. doi: 10.1089/dia.2019.0234. Epub 2019 Aug 28. PMID: 31385732.
127. Saudek CD, Duckworth WC, Giobbie-Hurder A, et al. Implantable insulin pump vs multiple-dose insulin for non-insulin-dependent diabetes mellitus: A randomized clinical trial. Department of Veterans Affairs Implantable Insulin Pump Study Group. JAMA. 1996;276(16):1322-1327.
128. Senseonics Eversense Health Care Provider Resources Library. Available from: https://www.ascensiadiabetes.com/eversense/health-care-professionals/eversense-system/. Accessed August 2022.
129. Sutton D, Higdon C, Carmon M, Abbott S. Regular Insulin Administered With the V-Go Disposable Insulin Delivery Device in a Clinical Diabetes Setting: A Retrospective Analysis of Efficacy and Cost. Clin Diabetes. 2016;34(4):201-205.
130. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Eur J Endocrinol. 2012 Apr;166(4):567-74.
131. Tanenberg R, Bode B, Lane W, et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: A randomized controlled trial. Mayo Clin Proc. 2004;79(12):1521-1526.
132. Thabit H, et al. Home use of closed-loop insulin delivery for overnight glucose control in adults with type 1 diabetes: a 4-week, multicentre, randomised crossover study. Lancet. Diabetes & Endocrinology 2014;2(9):7019. DOI: 10.1016/S22138587(14)70114-7.

133. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.
134. Tierney MJ, Tamada JA, Potts RO, et al. Clinical evaluation of the GlucoWatch biographer: A continual, non-invasive glucose monitor for patients with diabetes. Biosens Bioelectron. 2001;16(9-12):621-629.
135. Trajanoski Z, Wach P, Gfrerer R, et al. Portable device for continuous fractionated blood sampling and continuous ex vivo blood glucose monitoring. Biosens Bioelectron. 1996;11(5):479-487.
136. U.S. Food and Drug Administration (FDA). MiniMed 770G System. (Medtronic MiniMed, Inc. Northridge, CA). Summary of Safety and Effectiveness PMA Number: P160017/S076. Notice of Approval 8/31/2020. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S076B.pdf
137. US Food and Drug Administration (FDA). Eversense continuous glucose monitoring system. (Senseonics, Incorporated, Germantown, MD) PMA Number: P160048. Jun 21, 2018. Accessed August 19, 2021. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160048
138. Vague P, Lassmann-Vague V, Belicar P, Alessis C. The implantable insulin pump in the treatment of diabetes. Hopes and reality? Bull Acad Natl Med. 1996 ;180(4):831-841; discussion 841-843.
139. Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM. Short and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care 2012;35(1):32-8.
140. Wolpert HA. Continuous glucose monitoring--coming of age. N Engl J Med. 2010;363(4):383-384.
141. Zick R, Petersen B, Richter M, Haug C; SAFIR Study Group. Comparison of continuous blood glucose measurement with conventional documentation of hypoglycemia in patients with Type 2 diabetes on multiple daily insulin injection therapy. Diabetes Technol Ther. 2007;9(6):483-492.

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Oscar Clinical Guideline: Botulinum Toxin (CG033, Ver. 15)

Botulinum Toxin

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Botulinum toxins are a class of injectable medications that block the nerves responsible for controlling muscle function. The paralysis of targeted muscles typically occurs within 2 to 5 days after administration and can last for 2 to 3 months. There are seven different types (A-G) of Botulinum toxin, but only types A and B are approved for clinical use:

- There are currently five botulinum toxin preparations available in the US, including:
    - four type A preparations (abobotulinumtoxinA [Dysport®], daxibotulinumtoxinA-lanm [Daxxify®], incobotulinumtoxinA [Xeomin®], and onabotulinumtoxinA [Botox®, Botox® Cosmetic])
        - Two additional forms of botulinum toxin are available for cosmetic purposes only (Jeuveau® [prabotulinumtoxinA-xvfs], and Letybo® [letibotulinumtoxinA-wlbg]).
    - one type B preparation (rimabotulinumtoxinB [Myobloc®])
- Botulinum toxin preparations must be prescribed and administered by a licensed physician or medical provider.

Botulinum toxins have pharmacological uses in the treatment of various medical conditions characterized by muscle spasms or overactivity, such as cerebral palsy, stroke, and spinal cord disorders. In these conditions, Botulinum toxins are used to reduce muscle tone, relieve pain, and improve functional ability. Botulinum toxins are also used to treat other conditions, such as chronic migraine, hyperhidrosis, and strabismus.

Botulinum toxins can also be used for cosmetic purposes, such as decreasing wrinkles, but such use is not considered medically necessary by the Plan. In cosmetic applications, Botulinum toxins are used to reduce the appearance of wrinkles by relaxing the muscles responsible for facial expressions. The effects of cosmetic Botulinum toxin injections typically last for 3 to 4 months.

NOTE: The Plan may require the use of preferred medications as the first-line treatment. Please refer to the following applicable Plan Clinical Guideline for a comprehensive list of our preferred and non-preferred drugs on the medical benefit:

- Commercial Preferred Physician-Administered Specialty Drugs (CG052).
- Botulinum Toxins - Medical Benefit Preferred Physician-Administered Drug Exceptions Criteria (CG088).

Definitions

"Achalasia" is a failed relaxation of the lower esophageal sphincter resulting in painful spasms and/or regurgitation of food.

"Blepharospasm" refers to uncontrolled blinking or spasms of the eyelids.

"Botulinum Toxins" refer to the seven serologically distinct neurotoxins derived from the bacterium *Clostridium botulinum*. These agents differ in their synthesis and the specific bacterium strain from which they are isolated. Botulinum toxins function by inhibiting acetylcholine release at the neuromuscular junction to cause flaccid paralysis of muscles.

"Cervical Dystonia" (also known as **"Spasmodic Torticollis"**) refers to painful contraction of the neck muscles causing twisting or tilting of the head to one side.

"**Chronic anal fissure**" is a tear in the skin of the anus that persists for more than 8 weeks.

"**Chronic migraine"** is a type of migraine headache that occurs at least 15 days per month for more than three months.

"Detrusor Hyperactivity" (also known as **"Bladder Overactivity"**) refers to spasms of the bladder muscles resulting in pain or incontinence.

"**Detrusor sphincter dyssynergia (DSD)"** is a medical condition that affects the coordination between the bladder and the muscles around the urethra, which is called the external urinary sphincter.

"**Essential tremors"** is a neurological disorder characterized by involuntary shaking or trembling movements, usually affecting the arms and hands but sometimes involving the head and other parts of the body.

"Hyperhidrosis" refers to inappropriate, excessive sweating.

"**Hemifacial spasms"** is a neurological disorder characterized by involuntary contractions of the facial muscles on one side of the face.

"**Hyperhidrosis Disease Severity Scale (HDSS)**" is a tool used to assess the severity of hyperhidrosis, a condition characterized by excessive sweating beyond what is necessary for regulating body temperature. The HDSS is a simple and quick questionnaire that consists of only one question and is rated on a scale from 1 to 4:

1. No interference with daily activities
2. Noticeable but not causing interference with daily activities
3. Some interference with daily activities
4. Severe interference with daily activities

The HDSS is used by healthcare professionals to determine the impact of hyperhidrosis on a patient's quality of life and to guide treatment decisions. Patients with HDSS scores of 3 or 4 are considered to have severe hyperhidrosis and may require more aggressive treatment options, such as prescription antiperspirants, oral medications, or minimally invasive procedures like botulinum toxin injections or iontophoresis. Patients with HDSS scores of 1 or 2 may benefit from less invasive treatments like topical antiperspirants or lifestyle modifications.

"**Lower extremity**" Refers to the leg, knee, ankle, and foot.

"Muscle Spasms" refer to the involuntary contractions of one or more muscles.

"**Neurogenic"** refers to a condition or disorder that is caused by or related to problems with the nervous system.

"**Oromandibular dystonias (OMD)"** refer to a group of neurological movement disorders that affect the muscles of the jaw, mouth, and face. OMD can cause involuntary muscle contractions that result in abnormal movements and postures, such as jaw clenching, teeth grinding, lip pursing, or tongue protrusion. OMD can be classified into several types based on the location and pattern of muscle contractions, including jaw-opening, jaw-closing, or mixed OMD.

"**Overactive bladder**" is a condition in which the muscles in the bladder contract involuntarily and cause a sudden urge to urinate.

"**Prophylaxis**" is a preventative treatment intended to stop or reduce the recurrence of a disease or condition.

"Sialorrhea" (also known as **"Ptyalism"**) refers to excess salivation or drooling.

"**Spasmodic dysphonia**" is a neurological disorder that affects the muscles of the voice box, causing spasms and interruptions in speech.

"**Spasticity**" is a condition characterized by increased muscle tone, which can cause stiffness, spasms, or involuntary movements.

"**Strabismus**" is a vision disorder in which the eyes are not properly aligned and point in different directions.

"**Temporomandibular disorders (TMD)"** refer to a group of conditions that affect the temporomandibular joint (TMJ) and the muscles of the jaw and face.

"**Upper extremity**" refers to the arm, shoulder, and hand.

"**Urge incontinence**" is a type of urinary incontinence characterized by the sudden, strong urge to urinate that is followed by an involuntary loss of urine.

"**Urinary incontinence**" is a condition in which a person cannot control their bladder, leading to the involuntary loss of urine.

"**Urodynamic testing"** is a medical diagnostic procedure that evaluates how well the lower urinary tract (including the bladder and urethra) is functioning. The test measures various parameters, such as bladder pressure, urine flow rate, and capacity, to help diagnose conditions that affect the urinary system, such as incontinence, urinary tract obstruction, or nerve or muscle problems.

Clinical Indications

Medical Necessity Criteria for Initial Authorization

OnabotulinumtoxinA (Botox) (J0585)

The Plan deems **OnabotulinumtoxinA (Botox)** medically necessary for the following indications if the disease-specific criteria for initial requests are met (refer to **Continued Care** for reauthorization criteria or **Table 1** for standard initial/retreatment authorization durations):

A. Achalasia, when **BOTH** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., gastroenterologist, endoscopist, ENT)***; and***
    b. Documented evidence of **ALL** of the following
        i. Confirmed diagnosis with esophageal manometry; ***and***
        ii. Alternative causes of the symptoms (e.g., esophageal stricture, carcinoma, schatzki's ring, or extrinsic compression), have been ruled out by upper endoscopy and/or adequately treated***; and***
        iii. Presence of progressive dysphagia to solids and liquids; ***and***
        iv. **ONE** of the following:
            1. Pneumatic dilation or surgical myotomy (i.e., laparoscopic Heller myotomy, or peroral endoscopic myotomy (POEM)) has been attempted but was unsuccessful***; or***
            2. The member was not a good candidate for the procedure***; or***
            3. The member refused treatment/surgery.

B. Axillary hyperhidrosis or palmar hyperhidrosis, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., dermatologist, neurologist)**; *and***
    b. The member is 18 years of age or older**; *and***
    c. Documented evidence of **ALL** of the following:
        i. Severe hyperhidrosis, defined as **ONE** of the following:

1. a score of 3 or 4 on the Hyperhidrosis Disease Severity Scale**; *or***
2. The impact of excessive sweating on quality of life has been significant, causing interference with daily activities (e.g., social, professional) and leading to feelings of anxiety and embarrassment**; *and***

ii. Alternative causes of the symptoms (e.g., hyperthyroidism, lifestyle factors), have been ruled out or adequately treated**; *and***

iii. The member is unable to use, or has tried and failed first-line management with **BOTH** of the following:

1. lifestyle measures such as avoiding known triggers and tight clothing**; *and***
2. using antiperspirants (e.g., aluminum chloride hexahydrate).

C. Blepharospasm, when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., ophthalmologist, neurologist, movement disorder specialist); ***and***

b. Member is 12 years of age or older**; *and***

c. Documented evidence of **BOTH** of the following:

i. Diagnosis of **ONE** or more of the following:

1. Benign essential blepharospasm; ***or***
2. Blepharospasm associated with dystonia; ***or***
3. Blepharospasm associated with facial nerve disorders such as Bell palsy; ***and***

ii. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to neuromuscular diseases (e.g., myasthenia gravis).

D. Cervical dystonia (i.e., spasmodic torticollis), when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***

b. Member is 16 years of age or older**; *and***

c. Documented evidence of **ALL** of the following:

i. Symptoms (e.g., abnormal head positioning, neck pain, limited range of motion, muscle spasms) have been present for at least 6 months**; *and***

ii. Neck pain and abnormal head tilt/torsion adversely affects range of motion and daily functioning; ***and***

iii. Sustained involuntary contractions in the neck muscles (e.g splenius, trapezius, posterior cervical, or sternocleidomastoid); ***and***

iv. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to:

1. Neuromuscular disease (e.g., myasthenia gravis); ***or***
2. Chronic neuroleptic treatment; ***or***
3. Fixed muscle contractures.

E. Chronic anal fissure, when **ALL** of the following are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., gastroenterologist, colon or rectal surgeon); ***and***
   b. Documented evidence of **ALL** of the following:
      i. At least 2 months of symptoms, including **ONE** or more of the following:
         1. Nocturnal pain and bleeding; ***or***
         2. Post-defecation pain; ***and***
      ii. The member is unable to use **ALL**, or has tried and failed **ONE** of the following:
         1. topical nitrates (e.g., Nitroglycerin 0.2% or 0.4% rectal ointment)**; *or***
         2. topical calcium channel blockers (e.g., Diltiazem 2% rectal gel, nifedipine 0.2% or 0.5% rectal ointment)**; *and***
   c. The member does **NOT** have documented evidence of ANY of the following:
      i. Anal fistula; ***or***
      ii. Hemorrhoids; ***or***
      iii. HIV; ***or***
      iv. Inflammatory bowel disease; ***or***
      v. Perianal abscess; ***or***
      vi. Perianal cancer; ***or***
      vii. Prior perianal surgical intervention.

F. Chronic migraine prophylaxis, when **ALL** of the following are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, headache specialist); ***and***
   b. Member is 18 years of age or older; ***and***
   c. Documented evidence of **ALL** of the following:
      i. Diagnosis of migraine headache (with or without aura) per International Classification of Headache Disorders criteria, defined as meeting **ALL** of the following criteria:
         1. Headache is characterized by at least **TWO** of the following:
            a. Pulsating quality; ***and/or***
            b. Unilateral location; ***and/or***
            c. Moderate to severe pain/intensity; ***and/or***
            d. Aggravation by physical activity; ***and***
         2. Symptoms are associated with at least **ONE** of the following:

a. Nausea and/or vomiting; ***or***
b. Photophobia (sensitivity to light) and phonophobia (sensitivity to sound); ***and***

3. Other potential causes of headache have been ruled out; ***and***

ii. The member has chronic migraines, defined as headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache**; *and***

iii. The member is unable to use **ALL**, or has adequately tried and failed an 8-week trial of at least **TWO** (2) preventative therapies, from at least **TWO** (2) of the following drug classes:

1. Anticonvulsants (such as topiramate, divalproex, sodium valproate); ***and/or***
2. Antidepressants (such as amitriptyline, nortriptyline, venlafaxine); ***and/or***
3. Beta blockers (such as propranolol, metoprolol); ***AND***

d. The member does **NOT** have documented evidence of ANY of the following:

i. Neuromuscular disease (e.g., myasthenia gravis); ***or***

ii. Botox (onabotulinumtoxinA) will be used concomitantly with a preventative calcitonin gene-related peptide (CGRP) antagonist for migraine headache prophylaxis.

- *i.e. the following CGRP antagonist products when used for preventive treatment of migraine include Aimovig (erenumab), Ajovy (fremanezumab), Emgality (galcanezumab), Nurtec (rimegepant), Qulipta (atogepant), Vyepti (eptinezumab).*
- *i.e. this restriction does not apply to the use of CGRP antagonists for acute/abortive treatment of migraine, such as Emgality (galcanezumab), Nurtec (rimegepant), or Ubrelvy (ubrogepant).*
- *<u>NOTE:</u> Please refer to the Plan's pharmacy benefit and Plan Clinical Guideline Anti-migraine Agents/ Calcitonin Gene-Related Peptide (CGRP) Antagonists and Serotonin Receptor 5-HT1F Agonists (PG008).*

G. Essential tremors, when **BOTH** of the following criteria are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist, otolaryngology); ***and***

b. Documented evidence of **BOTH** of the following:

i. ONE of the following diagnosis:

1. disabling head and neck tremor**; *or***
2. disabling essential hand tremor**; *and***

ii. The member is unable to use **ALL**, or has tried and failed **TWO** (2) of the following:
    1. Propranolol (immediate-release or extended-release)***; and/or***
    2. Primidone***; and/or***
    3. Gabapentin; ***and/or,***
    4. Topiramate.

H. Hemifacial spasm, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
    b. Member is 12 years of age or older; ***and***
    c. Documented evidence of **BOTH** of the following:
        i. Diagnosis of hemifacial spasm in muscles innervated by the facial nerve (cranial nerve VII); ***and***
        ii. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to neuromuscular diseases (e.g. myasthenia gravis).

I. Oromandibular dystonias (i.e., cranial dystonia), when **BOTH** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist, orofacial pain specialist, otolaryngologist)***; and***
    b. Documented evidence of **BOTH** of the following:
        i. characterized by continuous, bilateral, asynchronous muscle spasms in the face, jaw, pharynx, and tongue***; and***
        ii. causing difficulty in jaw closing or opening and interfering with fluid and food intake and speech.

J. Overactive bladder with urge incontinence, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., urologist); ***and***
    b. Member is 18 years of age or older; ***and***
    c. Documented evidence of **BOTH** of the following:
        i. Urodynamic testing confirms urinary incontinence with urgency***; and***
        ii. Symptoms had not been adequately managed with **BOTH** of the following:
            1. Behavioral therapies (such as bladder training and pelvic floor muscle therapy), for at least 8 weeks***; and***
            2. A minimum of **THREE (3)** pharmacologic therapies, with either inadequate response or intolerable side effects, each tried for at least 4 weeks:

a. Anticholinergic (i.e., antimuscarinics) therapy, such as darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin (Ditropan XL), solifenacin (Vesicare), tolterodine (Detrol/Detrol LA), or trospium (Sanctura/Sanctura XR)**; *and/or***
b. Beta-3 Adrenergic Agonists, such as Gemtesa (vibegron) or Myrbetriq (miraberon)**; *and***

d. The member does **NOT** have documented evidence of **ANY** of the following:
    i. acute urinary retention; ***or***
    ii. acute urinary tract infection.

K. Sialorrhea, when **BOTH** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, physical medicine and rehabilitation (PM&R), or ENT); ***and***
    b. Documented evidence of **ALL** of the following:
        i. Chronic sialorrhea resulting from a neurological condition (e.g., Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury); ***and***
        ii. Complications such as recurrent infection or chronic skin breakdown that have failed treatment with topical agents or lifestyle modifications**; *and***
        iii. The member is unable to use **ALL**, or has adequately tried and failed **two** (2) months of pharmacotherapy with **ONE** (1) of the following:
            1. Benztropine**; *and/or***
            2. Glycopyrrolate**; *and/or***
            3. Scopolamine.

L. Spasmodic dysphonia (i.e., laryngeal dystonia), when **BOTH** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., gastroenterologist, endoscopist, ENT); ***and***
    b. Documented evidence of **BOTH** of the following:
        i. Adductor-type spasmodic dysphonia confirmed by fiberoptic laryngoscopy**; *and***
        ii. Moderate to severe phonation difficulties.

M. Spasticity of the upper and/or lower extremity, when **ALL** of the following criteria are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R); ***and***
    b. The member is characterized by **ONE** of the following:
        i. Members greater than the age of 2 with spasticity due to cerebral palsy or stroke who are receiving ongoing rehabilitation; ***or***
        ii. Members 18 years of age or older with **ONE** of the following:

1. Spasticity secondary to multiple sclerosis or other demyelinating diseases of the central nervous system; ***or***
2. Spasticity secondary to spinal cord injury**; *or***
3. Post-stroke spasticity; ***and***

c. Documentation of **ALL** of the following:
   i. Joint is not affected by fixed contracture**; *and***
   ii. Abnormal muscle tone that interferes with daily functioning or is expected to result in joint contracture with further growth; ***and***
   iii. Treatment is expected to improve functioning and/or allow for further therapeutic rehabilitation**; *and***
   iv. Surgical intervention is the only alternative option; ***and***
   v. If the request is for the treatment of lower limb spasticity, the member has tried and failed appropriate non-surgical medical treatments (e.g., pharmacologic and physical therapies).

N. Strabismus, when **ALL** of the following are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., ophthalmologist); ***and***
   b. The member is 12 years of age or older; ***and***
   c. The member does **NOT** have documented evidence of **ANY** of the following:
      i. Duane's syndrome with lateral rectus weakness**; *or***
      ii. Likely to have a spontaneous recovery**; *or***
      iii. Restrictive strabismus**; *or***
      iv. Strabismus secondary to prior surgical overrecession of the ocular antagonist muscle.

O. Upper extremity focal dystonia (e.g., writer's cramp), when **ALL** of the following are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
   b. The member is 16 years of age or older; ***and***
   c. Documented evidence of **ALL** of the following:
      i. Significant pain and/or abnormal hand or forearm positioning that adversely affects daily functioning**; *and***
      ii. Failure of at least two months of conservative therapy and/or lifestyle modification.

P. Urinary incontinence due to detrusor overactivity (i.e., detrusor instability or detrusor hyperreflexia) or detrusor-sphincter dyssynergia, when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., urologist)**; *and***
b. The member is 5 years of age or older**; *and***
c. Documented evidence of **ALL** of the following:
    i. The condition is associated with a neurologic condition (e.g., spinal cord injury, multiple sclerosis, Parkinson's disease, cerebral palsy, stroke)**; *and***
    ii. Symptoms had not been adequately managed with **ALL** of the following:
        1. Behavioral therapies (such as bladder training and pelvic floor muscle therapy) for 8 to 12 weeks**; *and***
        2. The member is unable to use ALL or has tried and failed at least **ONE** of the following anticholinergic (i.e. antimuscarinics) therapies such as darifenacin (Enablex), fesoterodine (Toviaz), oxybutynin (Ditropan XL), solifenacin (Vesicare), tolterodine (Detrol/Detrol LA), or trospium (Sanctura/Sanctura XR) for 4 to 8 weeks (inadequate response or intolerable adverse effects)**; *and***
        3. **The member meets ONE** of the following:
            a. Balloon sphincter dilation or surgical treatment has been attempted but was unsuccessful**; *or***
            b. The member was not a candidate due to comorbidities**; *or***
            c. The member refused surgery; ***and***
d. The member does **NOT** have documented evidence of **ANY** of the following:
    i. urinary tract infection (UTI)**; *or***
    ii. urinary retention or postvoid residuals (PVR) greater than 200 mL unless the patient is receiving intermittent catheterization as part of the overall treatment plan.

<u>AbobotulinumtoxinA (Dysport) (J0586)</u>

The Plan deems AbobotulinumtoxinA (Dysport) medically necessary for the following indications if the disease-specific criteria for initial requests are met (refer to **Continued Care** for reauthorization criteria or **Table 1** for standard initial/retreatment authorization durations):

A. Axillary hyperhidrosis, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., dermatologist, neurologist)**; *and***
    b. The member is 18 years of age or older**; *and***
    c. Documented evidence of **ALL** of the following:
        i. Severe primary axillary hyperhidrosis, defined as **ONE** of the following:

1. a score of 3 or 4 on the Hyperhidrosis Disease Severity Scale**; *or***
2. The impact of excessive sweating on quality of life has been significant, causing interference with daily activities (e.g., social, professional) and leading to feelings of anxiety and embarrassment**; *and***

ii. Alternative causes of the symptoms (e.g., hyperthyroidism, lifestyle factors), have been ruled out or adequately treated**; *and***

iii. The member is unable to use, or has tried and failed first-line management with **BOTH** of the following:

1. lifestyle measures such as avoiding known triggers and tight clothing**; *and***
2. using antiperspirants (e.g., aluminum chloride hexahydrate)

B. Blepharospasm or hemifacial spasms, when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., ophthalmologist, neurologist, movement disorder specialist); ***and***

b. Member is 18 years of age or older; ***and***

c. Documented evidence of **BOTH** of the following:

i. Diagnosis of **ONE** or more of the following:

1. Benign essential blepharospasm; ***or***
2. Blepharospasm associated with dystonia; ***or***
3. Blepharospasm associated with facial nerve disorders such as Bell palsy; **or**
4. Hemifacial spasm involving the orbicularis oculi muscle; ***and***

ii. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to neuromuscular diseases (e.g., myasthenia gravis).

C. Cervical dystonia (i.e., spasmodic torticollis), when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***

b. Member is 16 years of age or older**; *and***

c. Documented evidence of **ALL** of the following:

i. Symptoms (e.g., abnormal head positioning, neck pain, limited range of motion, muscle spasms) have been present for at least 6 months**; *and***

ii. Neck pain and abnormal head tilt/torsion adversely affects range of motion and daily functioning; ***and***

iii. Sustained involuntary contractions in the neck muscles (e.g splenius, trapezius, posterior cervical, or sternocleidomastoid); ***and***

iv. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to:
    1. Neuromuscular disease (e.g., myasthenia gravis); ***or***
    2. Chronic neuroleptic treatment; ***or***
    3. Fixed muscle contractures.

D. Chronic anal fissure, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., gastroenterologist, colon or rectal surgeon); ***and***
    b. Documented evidence of **ALL** of the following:
        i. At least 2 months of symptoms, including **ONE** or more of the following:
            1. Nocturnal pain and bleeding; ***or***
            2. Post-defecation pain; ***and***
        ii. The member is unable to use **ALL**, or has tried and failed **ONE** of the following:
            1. topical nitrates (e.g., Nitroglycerin 0.2% or 0.4% rectal ointment)**; *or***
            2. topical calcium channel blockers (e.g., Diltiazem 2% rectal ointment, nifedipine 0.2% or 0.5% rectal ointment)**; *and***
    c. The member does **NOT** have documented evidence of **ANY** of the following:
        i. Anal fistula; ***or***
        ii. Hemorrhoids; ***or***
        iii. HIV; ***or***
        iv. Inflammatory bowel disease; ***or***
        v. Perianal abscess; ***or***
        vi. Perianal cancer; ***or***
        vii. Prior perianal surgical intervention.

E. Sialorrhea, when **BOTH** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R, or ENT); ***and***
    b. Documented evidence of **ALL** of the following:
        i. Chronic sialorrhea resulting from a neurological condition (e.g., Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury); ***and***
        ii. Complications such as recurrent infection or chronic skin breakdown that have failed treatment with topical agents or lifestyle modifications**; *and***
        iii. The member is unable to use **ALL**, or has adequately tried and failed **TWO** (2) months of pharmacotherapy with **ONE** (1) of the following:
            1. Benztropine**; *or***
            2. Glycopyrrolate**; *or***

3. Scopolamine.

F. Spasticity of the upper and/or lower extremity, when **ALL** of the following criteria are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R); ***and***
   b. The member is characterized by **ONE** of the following:
      i. Members greater than the age of 2 with spasticity due to cerebral palsy or stroke who are receiving ongoing rehabilitation; ***or***
      ii. Members 18 years of age or older with **ONE** of the following:
         1. Spasticity secondary to multiple sclerosis or other demyelinating diseases of the central nervous system; ***or***
         2. Spasticity secondary to spinal cord injury***; or***
         3. Post-stroke spasticity; ***and***
   c. Documentation of **ALL** of the following:
      i. Joint is not affected by fixed contracture***; and***
      ii. Abnormal muscle tone that interferes with daily functioning or is expected to result in joint contracture with further growth; ***and***
      iii. Treatment is expected to improve functioning and/or allow for further therapeutic rehabilitation***; and***
      iv. Surgical intervention is the only alternative option; ***and***
      v. If the request is for the treatment of lower limb spasticity, the member has tried and failed appropriate non-surgical medical treatments (e.g., pharmacologic and physical therapies).

G. Upper extremity focal dystonia (e.g., writer's cramp), when **ALL** of the following are met:
   a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
   b. The member is 16 years of age or older; ***and***
   c. Documented evidence of **ALL** of the following:
      i. Significant pain and/or abnormal hand or forearm positioning that adversely affects daily functioning***; and***
      ii. Failure of at least two months of conservative therapy and/or lifestyle modification.

<u>RimabotulinumtoxinB (Myobloc) (J0587)</u>

The Plan deems RimabotulinumtoxinB (Myobloc) medically necessary for the following indications if the disease-specific criteria for initial requests are met (refer to **Continued Care** for reauthorization criteria or **Table 1** for standard initial/retreatment authorization durations):

A. Cervical dystonia (i.e., spasmodic torticollis), when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
    b. Member is 18 years of age or older; ***and***
    c. Documented evidence of **ALL** of the following:
        i. Symptoms (e.g., abnormal head positioning, neck pain, limited range of motion, muscle spasms) have been present for at least 6 months**; *and***
        ii. Neck pain and abnormal head tilt/torsion adversely affects range of motion and daily functioning; ***and***
        iii. Sustained involuntary contractions in the neck muscles (e.g splenius, trapezius, posterior cervical, or sternocleidomastoid); ***and***
        iv. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to:
            1. Neuromuscular disease (e.g., myasthenia gravis); ***or***
            2. Chronic neuroleptic treatment; ***or***
            3. Fixed muscle contractures.

B. Sialorrhea, when **ALL** of the following are met:
    a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R, or ENT); ***and***
    b. Member is 18 years of age or older**; *and***
    c. Documented evidence of **ALL** of the following:
        i. Chronic sialorrhea resulting from a neurological condition (e.g., Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury); ***and***
        ii. Complications such as recurrent infection or chronic skin breakdown that have failed treatment with topical agents or lifestyle modifications**; *and***
        iii. The member is unable to use **ALL**, or has adequately tried and failed **two** (2) months of pharmacotherapy with **ONE** (1) of the following:
            1. Benztropine**; *or***
            2. Glycopyrrolate**; *or***
            3. Scopolamine.

IncobotulinumtoxinA (Xeomin) (J0588)

The Plan deems **IncobotulinumtoxinA (Xeomin)** medically necessary for the following indications if the disease-specific criteria for initial requests are met (refer to **Continued Care** for reauthorization criteria or **Table 1** for standard initial/retreatment authorization durations):

A. Blepharospasm or hemifacial spasms, when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., ophthalmologist, neurologist, movement disorder specialist); ***and***
b. Member is 18 years of age or older; ***and***
c. Documented evidence of **BOTH** of the following:
    i. Diagnosis of **ONE** or more of the following:
        1. Benign essential blepharospasm; ***or***
        2. Blepharospasm associated with dystonia; ***or***
        3. Blepharospasm associated with facial nerve disorders such as Bell palsy; or
        4. Hemifacial spasm involving the orbicularis oculi muscle; ***and***
    ii. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to neuromuscular diseases (e.g., myasthenia gravis).

B. Cervical dystonia (i.e., spasmodic torticollis), when **ALL** of the following are met:
a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
b. Member is 18 years of age or older; ***and***
c. Documented evidence of **ALL** of the following:
    i. Symptoms (e.g., abnormal head positioning, neck pain, limited range of motion, muscle spasms) have been present for at least 6 months***; and***
    ii. Neck pain and abnormal head tilt/torsion adversely affects range of motion and daily functioning; ***and***
    iii. Sustained involuntary contractions in the neck muscles (e.g splenius, trapezius, posterior cervical, or sternocleidomastoid); ***and***
    iv. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to:
        1. Neuromuscular disease (e.g., myasthenia gravis); ***or***
        2. Chronic neuroleptic treatment; ***or***
        3. Fixed muscle contractures.

C. Sialorrhea, when **ALL** of the following are met:
a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R, or ENT); ***and***
b. Member is 2 years of age or older***; and***
c. Documented evidence of **ALL** of the following:
    i. Chronic sialorrhea resulting from a neurological condition (e.g., Parkinson's disease, atypical parkinsonism, stroke, or traumatic brain injury); ***and***

ii. Complications such as recurrent infection or chronic skin breakdown that have failed treatment with topical agents or lifestyle modifications**; *and***

iii. The member is unable to use **ALL**, or has adequately tried and failed **two** (2) months of pharmacotherapy with **ONE (1)** of the following:

1. Benztropine**; *or***
2. Glycopyrrolate**; *or***
3. Scopolamine.

D. Spasticity of the upper limb, when **ALL** of the following criteria are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, PM&R); ***and***

b. The member is characterized by **ONE** of the following:

i. Members 2 to 17 years of age and **ONE** of the following:

1. the spasticity is not caused by cerebral palsy**; *or***
2. with spasticity due to cerebral palsy who are receiving ongoing rehabilitation; ***or***

ii. Members 18 years of age or older:

1. Spasticity secondary to multiple sclerosis or other demyelinating diseases of the central nervous system; ***or***
2. Spasticity secondary to spinal cord injury**; *or***
3. Post-stroke spasticity; ***and***

c. Documentation of **ALL** of the following:

i. Joint is not affected by fixed contracture**; *and***

ii. Abnormal muscle tone that interferes with daily functioning or is expected to result in joint contracture with further growth; ***and***

iii. Treatment is expected to improve functioning and/or allow for further therapeutic rehabilitation**; *and***

iv. Surgical intervention is the only alternative option**; *and***

v. If the request is for the treatment of lower limb spasticity, the member has tried and failed appropriate non-surgical medical treatments (e.g., pharmacologic and physical therapies).

DaxibotulinumtoxinA-lanm (Daxxify) (J0589)

The Plan deems **DaxibotulinumtoxinA-lanm (Daxxify)** medically necessary for the following indications if the disease-specific criteria for initial requests are met (refer to **Continued Care** for reauthorization criteria or **Table 1** for standard initial/retreatment authorization durations):

A. Cervical dystonia (i.e., spasmodic torticollis), when **ALL** of the following are met:

a. The request is by a provider specialist who will administer botulinum toxin (e.g., neurologist, movement disorder specialist); ***and***
b. Member is 18 years of age or older; ***and***
c. Documented evidence of **ALL** of the following:
    i. Symptoms (e.g., abnormal head positioning, neck pain, limited range of motion, muscle spasms) have been present for at least 6 months***; and***
    ii. Neck pain and abnormal head tilt/torsion adversely affects range of motion and daily functioning; ***and***
    iii. Sustained involuntary contractions in the neck muscles (e.g splenius, trapezius, posterior cervical, or sternocleidomastoid); ***and***
    iv. Alternative causes of the symptoms have been ruled out or adequately treated, including but not limited to:
        1. Neuromuscular disease (e.g., myasthenia gravis); ***or***
        2. Chronic neuroleptic treatment; ***or***
        3. Fixed muscle contractures.

Continued Care

Medical Necessity Criteria for Reauthorization

Except for specific conditions outlined elsewhere, the Plan considers continuing botulinum toxin treatment medically necessary if, at the end of the initial trial period:

A. A positive response is documented in the medical record, which should typically last for 3 months; ***and***
B. The member would continue to meet the clinical criteria for the specific botulinum toxin agent in the absence of further treatment; ***and***
C. The prescribing clinician provides an expected duration and frequency of ongoing treatment, which may require ongoing approval.
    NOTE: Treatment with botulinum toxin more frequently than every 3 months for a covered condition, regardless of diagnosis, is generally not considered medically necessary.
D. For chronic migraine prophylaxis with OnabotulinumtoxinA (Botox), after the initial trial period, which is defined as 6 months or a maximum of 2 treatments, the Plan considers continuing treatment medically necessary if the member experiences **ONE (1)** of the following:
    a. At least a 50% reduction in monthly migraine days; ***or***
    b. At least 2 fewer migraine days per month; ***or***
    c. At least a reduction of 7 headache days over a one-month period compared to the pre-treatment average; ***or***

d. A clinically meaningful improvement in ANY of the following validated migraine-specific patient-reported outcome measures:
    i. Migraine Disability Assessment (MIDAS)
        1. Reduction of ≥5 points when baseline score is 11-20; ***or***
        2. Reduction of ≥30% when baseline score is >20; ***or***
    ii. Migraine Physical Function Impact Diary (MPFID)
        1. Reduction of ≥5 points; ***or***
    iii. Headache Impact Test (HIT-6)
        1. Reduction of ≥5 points.

Criteria for Discontinuing Treatment

Botulinum toxin treatment is generally no longer considered medically necessary and should be discontinued, except as outlined for specific conditions elsewhere, when the following criteria are met:

A. Lack of documented clinical response after initial trial; ***or***
B. In cases where the initial trial was successful, lack of documented clinical response to two consecutive treatments precludes treatment at that site for a period of at least one year***; or***
C. For chronic migraine prophylaxis using OnabotulinumtoxinA (Botox), if the patient does not respond adequately after the initial trial period, defined as six months or a maximum of two treatments.

General Recommendations for Time to Retreatment and Dosing

Table 1 provides general recommendations for:

A. the time to retreatment with botulinum toxin agents, assuming that all other clinical criteria remain met. These recommendations may differ for individual members but should not occur more frequently than every three months. If requests for more frequent injection frequency are made, documentation of medical necessity should be provided.
B. the doses (in units) of botulinum toxin agents, assuming that all other clinical criteria are met. Although the recommended doses may vary by individual member and condition, they should not be exceeded regardless of indication. If injection dosages exceeding the recommended amounts are requested, further review and documentation of medical necessity may be required. The following table is provided for reference purposes only.

Table 1: Dosage and retreatment information for botulinum toxin regimens by indication

Botox (onabotulinumtoxinA)				
Indication	**Initial dose**	**Subsequent**	**Retreatment**	**Additional Considerations**

		Dose		
Unless otherwise noted in the indication-specific dosing, total maximum dose per 3 months are as follows: ● In pediatric patients <18 years, the maximum cumulative dose is 10 units/kg or 340 units, whichever is less. ● In adolescents & adults ≥18 years treated for 1 or more indications, the maximum cumulative dose should not exceed 400 units (i.e., ≤400 units per 3 months).				
Achalasia	20 to 25 units to each of the 4 quadrants in the lower esophageal sphincter		3 months	Maximum recommended dose is 100 units/course Residual lower esophageal sphincter tone of less than 18 mmHg after botulinum injection is a predictor of a good response
Blepharospasm	1.25–2.5 units per injection site	maximum dose per site: 5 units	3 months	Dose during subsequent treatment sessions may be increased by up to two-fold if initial response is insufficient (e.g., the duration of effect is <2 months) Cumulative dose: ≤200 units in 30-day period (i.e., maximum dose of 100 units per eye in a three-month period)
	Typically, 4-6 injection sites are used per affected eye.			
Cervical dystonia	50-200 units total	50-300 units total	3 months	Studies have documented a mean dose of 236 units divided among affected muscles (range: 198-300 units). Dose should be divided across all injected sites; Max 50 units/site The total dose injected into the sternocleidomastoid muscle should be limited to 100 units or less to decrease the risk of dysphagia.
Chronic anal fissure	5-100 units		2-4 months	Generally injected into the internal anal sphincter, with half on the right and the remainder into the left

Chronic migraine prophylaxis	155 units total		3 months	given as multiple injections divided among 7 head and neck muscles
Head/Neck Area Muscle(s)			**Total Dose Per Muscle**	**No. of Injection Sites per Muscle**
Frontalis			20 units	4 sites
Corrugator			10 units	2 sites
Procerus			5 units	1 site
Occipitalis			30 units	6 sites
Temporalis			40 units	8 sites
Trapezius			30 units	6 sites
Cervical paraspinal muscle group			20 units	4 sites
Total dose per treatment session			**155 units**	**31 sites**
Essential tremors, hand	50-100 units		3-4 months	Injected into the affected hand, divided among multiple injection sites
Essential tremors, head and neck	100-200 units		3-4 months	Injected into the affected muscles in the neck and/or head, divided among multiple injection sites
Hemifacial spasm	12–25 units administered into the inferior and superior orbicularis oculi, buccolabial, and/or platysma muscles. Typically, 20-30 injection sites are used on the affected side of the face, with a starting dosage of 2.5-5 units per injection site.		3 months	Cumulative dose: ≤200 units in 30-day period (i.e., maximum dose of 200 units per treatment session)
Hyperhidrosis, Axillary	50 units/axilla		4 months	Injections should be evenly distributed into multiple sites (10 to 15)
Hyperhidrosis, Palmar	100–120 units	100–165 units per palm	3 months	Inject among multiple (e.g., 50–60) sites in the hyperhidrotic area of

				each palm Studies have used doses of 200 units per palm
Laryngeal dysphonia	1-5 units/muscle	1-5 units/muscle	3 months	Typical doses range from 1-6 units in studies
Oromandibular dystonias (i.e., cranial dystonia)	10-50 units injected into each affected muscle		3-4 months	Total dose not to exceed 100 units per treatment session
Overactive bladder	100 units per treatment		3 months	Dose should divided across 20 injection sites
Sialorrhea	10-40 units/side	10-40 units/side	3 months	Total dose should be divided across parotid and submandibular if injecting both
Spasticity, Adult Upper Limb	75 Units to 400 Units divided among selected muscles; ≤50 units per site		3 months	Dose listed is total dose administered as divided separate intramuscular injection(s)
	● Adductor pollicis: 20 units (1 site). ● Biceps brachii: 60 to 200 units (divided into 2 to 4 sites). ● Brachialis: 30 to 50 units (divided into 1 to 2 sites). ● Brachioradialis: 45 to 75 units (divided into 1 to 2 sites). ● Flexor carpi radialis: 12.5 to 50 units (1 site). ● Flexor carpi ulnaris: 12.5 to 50 units (1 site). ● Flexor digitorum profundus: 30 to 50 units (1 site). ● Flexor digitorum sublimes: 30 to 50 units (1 site). ● Flexor pollicis brevis/opponens pollicis: 5 to 25 units (1 site). ● Flexor pollicis longus: 20 units (1 site). ● Lumbricals/interossei: 5 to 10 units (1 site). ● Pronator teres: 15 to 25 units (1 site). ● Pronator quadratus: 10 to 50 units (1 site). Stroke-related upper limb spasticity ● Adductor pollicis: 20 units (1 to 2 sites) ● Biceps brachii: 100 to 200 units (up to 4 sites) ● Flexor digitorum profundus: 15 to 50 units (1 to 2 sites)			

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<tr><td></td><td colspan="3">

Flexor digitorum sublimes: 15 to 50 units (1 to 2 sites)
Flexor carpi radialis: 15 to 60 units (1 to 2 sites)
Flexor carpi ulnaris: 10 to 50 units (1 to 2 sites)
Flexor pollicis longus: 20 units (1 to 2 sites)

</td></tr>
<tr><td rowspan="2">Spasticity, Adult Lower Limb</td><td>300 Units to 400 Units divided among 5 muscles; ≤50 units per site</td><td>3 months</td><td>Dose listed is total dose administered as divided separate intramuscular injection(s)</td></tr>
<tr><td colspan="3">

Flexor digitorum longus: 50 units (divided into 2 sites)
Flexor hallucis longus: 50 units (divided into 2 sites)
Gastrocnemius lateral head: 75 units (divided into 3 sites)
Gastrocnemius medial head: 75 units (divided into 3 sites)
Soleus: 75 units (divided into 3 sites)
Tibialis posterior: 75 units (divided into 3 sites)

</td></tr>
<tr><td rowspan="3">Spasticity, Associated with Cerebral Palsy in Pediatric Patients</td><td>Maximum dose per treatment session: 3–6 units/kg for large muscles, 1–2 units/kg for small muscles; maximum dose of 50 units per injection site</td><td>3 months</td><td>Maximum recommended total dose administered during a single treatment session should not exceed 12 units/kg or 400 units, whichever is less.</td></tr>
<tr><td colspan="3">Upper extremity: 3 to 6 units/kg total per session divided up amongst affected muscles; maximum dose per site: 50 units/site; maximum total dose per treatment session in the upper limb: 6 units/kg or 200 units total, whichever is less.

Biceps brachii: 1.5 to 3 units/kg divided in 4 sites
Brachialis: 1 to 2 units/kg divided in 2 sites
Brachioradialis: 0.5 to 1 unit/kg divided in 2 sites
Flexor carpi radialis: 1 to 2 units/kg divided in 2 sites
Flexor carpi ulnaris: 1 to 2 units/kg divided in 2 sites
Flexor digitorum profundus: 0.5 to 1 unit/kg divided in 2 sites
Flexor digitorum sublimis: 0.5 to 1 unit/kg divided in 2 sites

</td></tr>
<tr><td colspan="3">Lower extremity: 4 to 8 units/kg total per session divided up amongst affected muscles; maximum dose per site: 50 units/site; maximum total dose per treatment session in the lower limb or visit: 8 units/kg or 300 units total, whichever is less.

Gastrocnemius lateral head: 1 to 2 units/kg divided in 2 sites
Gastrocnemius medial head: 1 to 2 units/kg divided in 2 sites
Soleus: 1 to 2 units/kg divided in 2 sites
Tibialis posterior: 1 to 2 units/kg divided in 2 sites

</td></tr>
</table>

Strabismus	• Vertical muscles and for horizontal strabismus <20 prism diopters: 1.25 to 2.5 units in any one muscle • Horizontal strabismus of 20 to 50 prism diopters: 2.5 to 5 units in any one muscle • Persistent VI nerve palsy ≥1 month: 1.25 to 2.5 units in the medial rectus muscle		3 months	Max dose as a single injection for any one muscle is 25 units. Subsequent doses for patients experiencing incomplete paralysis of the target may be increased up to twice the previous administered dose.
Upper extremity focal dystonia	20-80 units/limb	20-200 units/limb	3 months	Total dose should be injected across affected muscles Studies have used doses of 200-360 units per treatment session.
Urinary incontinence due to detrusor overactivity secondary to neurologic condition	Adults: 200 units per treatment		3 months	given as 30 separate injections of approximately 6.7 units each into the detrusor muscle (avoiding the trigone)
	Children ≥5 years and <18 years, weight ≥34 kg: 200 units per treatment			administered as 20 injections
	Children ≥5 years and <18 years, weight <34 kg: 6 units/kg per treatment			administered as 20 injections
Dysport (abobotulinumtoxinA)				
Indication	**Initial dose**	**Subsequent Dose**	**Retreatment**	**Additional Considerations**
Axillary hyperhidrosis	100-200 units/axilla	100-500 units/axilla	3 months	Injections should be evenly distributed into multiple sites ~1 to 2 cm apart (10 to 20 injections)
Blepharospasm or hemifacial spasm	120 units subcutaneously per eye: 20-40 units/injection	80 units per eye: 20 units/injection	3 months	Cumulative dose: <60 units/eye or 120 units/both eyes per 3 month period after the initial dose
Cervical dystonia	250-500 units	250-1000 units	3 months	Dose should be divided among all treated muscles, retreatment should be no greater than 250 units

				more than prior treatment dose
Chronic anal fissure	90 to 150 units in 2 divided doses		2-4 months	injected into the internal anal sphincter on each side of the anterior midline Some studies have supported use of two injections of 90 units (180 units total)
Sialorrhea	15 to 75 units injected per gland (submandibular, parotid or both) either unilaterally or bilaterally		4-6 months	Injection should be into parotid and/or submandibular gland
Spasticity of upper/lower extremity (Adult)	Maximum recommended total dose (upper and lower limbs combined) is 1,500 units ● upper limb spasticity, total doses of 500 and 1,000 units divided among selected muscles ● lower limb spasticity, total doses of 1,000 and 1,500 units divided among selected muscles		3-5 months	Maximum total dose (including upper AND lower limbs combined) not to exceed 1500 units per 3 month period.
	Upper limbs: ● Brachialis: 200 to 400 units (1 to 2 injections per muscle). ● Brachioradialis: 100 to 200 units (1 to 2 injections per muscle). ● Biceps brachii: 200 to 400 units (1 to 2 injections per muscle). ● Flexor carpi radialis: 100 to 200 units (1 to 2 injections per muscle). ● Flexor carpi ulnaris: 100 to 200 units (1 to 2 injections per muscle). ● Flexor digitorum profundus: 100 to 200 units (1 to 2 injections per muscle). ● Flexor digitorum superficialis: 100 to 200 units (1 to 2 injections per muscle). ● Pronator teres: 100 to 200 units (1 injection per muscle).			
	Lower limbs: ● Flexor digitorum longus: 130 to 200 units (1 to 2 injections per muscle). ● Flexor hallucis longus: 70 to 200 units (1 injection per muscle). ● Gastrocnemius, medial head: 100 to 150 units (1 injection per muscle). ● Gastrocnemius, lateral head: 100 to 150 units (1 injection per muscle). ● Soleus: 330 to 500 units (3 injections per muscle). ● Tibialis posterior: 200 to 300 units (2 injections per muscle).			
Spasticity of upper/lower	Upper Limb: 8 Units/kg to 16 Units/kg per limb		3 months	Maximum total dose per treatment session = 30 Units/kg or 1000

extremity (Pediatric, Children ≥2 years and Adolescents <18 years)	• Maximum total dose per treatment session = 16 Units/kg or 640 Units, whichever is lower			Units, whichever is lower
	Lower Limb: 10 Units/kg to 15 Units/kg per limb • Maximum total dose per treatment session for unilateral limb injections = 15 Units/kg or 1000 Units, whichever is lower • Maximum total dose per treatment session for bilateral limb injections = 30 Units/kg or 1000 Units, whichever is lower			
	Upper extremity • Brachialis: 3 to 6 units/kg (up to 2 sites per muscle) • Brachioradialis: 1.5 to 3 units/kg (1 site per muscle) • Biceps brachii: 3 to 6 units/kg (up to 2 sites per muscle) • Flexor carpi radialis (FCR): 2 to 4 units/kg (up to 2 sites per muscle) • Flexor carpi ulnaris (FCU): 1.5 to 3 units/kg (1 site per muscle) • Flexor digitorum profundus (FDP): 1 to 2 units/kg (1 site per muscle) • Flexor digitorum superficialis (FDS): 1.5 to 3 units/kg (up to 4 sites per muscle) • Pronator quadratus: 0.5 to 1 units/kg (1 site per muscle) • Pronator teres: 1 to 2 units/kg (1 site per muscle) Total dose: 8 to 16 units/kg not to exceed 640 units			
	Lower extremity: • Gastrocnemius: 6 to 9 units/kg (1 to 4 sites per muscle) • Soleus: 4 to 6 units/kg (1 to 2 sites per muscle) Total: 10 to 15 units/kg divided across both muscles (1 to 6 sites per muscle)			
Upper extremity focal dystonia	15-150 units	15-150 units	3 months	Total dose should be injected across affected muscles
Myobloc (rimabotulinumtoxinB)				
Indication	**Initial dose**	**Subsequent Dose**	**Retreatment**	**Additional Considerations**
Cervical dystonia	2,500 to 5,000 units divided among		3-4 months	Toxin treatment-naive patients: Use

	the affected muscles in patients previously treated with botulinum toxin; initial dose in previously untreated patients should be lower.		a lower initial dose.
Sialorrhea	1,500 to 3,500 units divided among the parotid (500 to 1,500 units/gland) and submandibular (250 units/gland) glands (1 injection per side of face)	4-6 months	Injection should be into parotid and/or submandibular gland

Xeomin (incobotulinumtoxinA)

Indication	Initial dose	Subsequent Dose	Retreatment	Additional Considerations
Blepharospasm or hemifacial spasm	25 units per eye (50 units per treatment session)	maximum dose: 50 units per eye (100 units per treatment session)	3 months	
Cervical dystonia	120 units	120-400 units	3 months	Maximum cumulative dose per treatment session: 400 units. Initial doses >120 units not shown to provide additional efficacy and may be associated with increased incidence of adverse effects.
Sialorrhea	100 units divided among the parotid (30 units/gland) and submandibular (20 units/gland) glands on both sides (ie, 4 injection sites per treatment session)		4 months	divide dose with a ratio of 3:2 between parotid and submandibular glands.
Spasticity of the upper limb	See the below table for dose range for specific muscle group and maximum dose.		3 months	Maximum cumulative dose per treatment session: 400 units.

Dosing of IncobotulinumtoxinA for Upper Limb Spasticity in Adults

Clinical Pattern/Muscle	Recommended Dose per Muscle	Recommended No. of Injection Sites per Muscle
Clenched fist; flexor digitorum superficialis	25–100 units	2 sites

Clenched fist; flexor digitorum profundus	25–100 units	2 sites
Flexed wrist; flexor carpi radialis	25–100 units	1-2 sites
Flexed wrist; flexor carpi ulnaris	20–100 units	1-2 sites
Flexed elbow; brachioradialis	25–100 units	1-3 sites
Flexed elbow; biceps	50–200 units	1-4 sites
Flexed elbow; brachialis	25–100 units	1-2 sites
Pronated forearm; pronator quadratus	10–50 units	1 site
Pronated forearm; pronator teres	25–75 units	1-2 sites
Thumb-in-palm; flexor pollicis longus	10–50 units	1 site
Thumb-in-palm; adductor pollicis	5–30 units	1 site
Thumb-in-palm; flexor pollicis brevis/opponens pollicis	5–30 units	1 site

Dosing of IncobotulinumtoxinA for Upper Limb Spasticity in Children ≥2 years and Adolescents ≤17 years

NOTE: If a single upper extremity being treated, the total dose should not exceed 8 units/kg divided among affected muscles up to a maximum of 200 units per single upper limb; if both upper limbs are treated, total dose should not exceed 16 units/kg up to a maximum of 400 units.

Muscle	Dosage Range	Maximum Dose (units)	Number of Injection Sites Per Muscle
Adductor pollicis	0.5 units/kg	12.5	1
Biceps	2 to 3 units/kg	75	1 to 3
Brachialis	1 to 2 units/kg	50	1 to 2
Brachioradialis	1 to 2 units/kg	50	1 to 2
Flexor carpi radialis	1 unit/kg	25	1

Flexor carpi ulnaris	1 unit/kg	25	1
Flexor digitorum profundus	1 unit/kg	25	1
Flexor digitorum superficialis	1 unit/kg	25	1
Flexor pollicis brevis/Opponens pollicis	0.5 unit/kg	12.5	1
Flexor pollicis longus	1 unit/kg	25	1
Pronator quadratus	0.5 units/kg	12.5	1
Pronator teres	1 to 2 units/kg	50	1 to 2

Daxxify (daxibotulinumtoxinA-lanm)				
Indication	**Initial dose**	**Subsequent Dose**	**Retreatment**	**Additional Considerations**
Cervical dystonia	125 to 250 units divided among affected muscles		3 months	Total recommended dosage for a single treatment session: 125 to 250 units. Dose and number of injection sites should be personalized considering previous treatment, response, duration of effect, and any adverse events. The dosage can be modified by increments of 50 to 75 units depending on the individual's response.

Experimental or Investigational / Not Medically Necessary

1. **All botulinum toxin preparations (regardless of type)** are considered contraindicated, experimental, investigational, or unproven in the following cases:
    a. Infection at the proposed injection site***; or***
    b. Known hypersensitivity to any botulinum toxin preparation or the components in the formulation***; or***
    c. Retreatment of a condition with the same or different agent after a failed initial trial, regardless of if the member continues to meet clinical criteria***; or***

NOTE: If the member initially failed therapy due to an agent-specific intolerance or reaction, rather than a clinical feature, then this statement may not apply.

2. The Plan deems the use of botulinum toxin for **ALL** cosmetic purposes as not medically necessary. Such cosmetic purposes include, but are not limited to:
    a. chin dimpling; ***or***
    b. eyebrow elevation/shaping ("brow lift"); ***or***
    c. flaring nostrils (nasal flare); ***or***
    d. forehead lines; ***or***
    e. glabellar facial ("frown") lines; ***or***
    f. labiomandibular grooves; ***or***
    g. lateral brow lift; ***or***
    h. lateral canthal lines ("crow's feet"); ***or***
    i. lip lines; ***or***
    j. radial lines on the dorsum of the nose (bunny lines); ***or***
    k. to treat prominent platysma muscle bands (age-related neck degeneration).
3. **Botulinum toxin antibody assays** are considered experimental or investigational and are therefore not covered by the Plan.

<u>OnabotulinumtoxinA (Botox) (J0585)</u>

The use of OnabotulinumtoxinA (Botox) for any other indication not listed above is considered experimental, investigational, or unproven; these excluded indications include, but are not limited to, the following:

A. Acute and chronic back pain
B. Acute and chronic shoulder pain
C. Anal sphincter achalasia
    a. *Rationale:* A 2012 meta-analysis on 16 nonrandomized studies examining Botox for internal anal sphincter achalasia revealed significantly higher rates of non-response and adverse outcomes when compared to myectomy. Further evidence is required to determine a potential benefit of Botox therapy in this patient population.
D. benign prostatic hyperplasia (BPH, benign prostatic hypertrophy) with lower urinary tract symptoms (LUTS)
    a. *Rationale:* There is insufficient evidence to support the use of OnabotulinumtoxinA for men with lower urinary tract symptoms caused by benign prostatic hyperplasia. Currently, no guidelines in the field endorse OnabotulinumtoxinA as a potential treatment option. To fully evaluate the short- and long-term efficacy, including the need for repeated injections in patients with LUTS due to BPH, large-scale, placebo-controlled

randomized trials are necessary. Furthermore, given the availability of several effective treatments for BPH, the potential role of BoNT-A should be examined in further randomized trials that compare it to **α**-blockers, 5-**α** reductase inhibitors, minimally invasive treatments, and even traditional surgery.

E. Carpal tunnel syndrome
F. Chronic idiopathic constipation (CIC)
G. Chronic migraine prophylaxis, for the use of OnabotulinumtoxinA (Botox) in combination with calcitonin gene-related peptide (CGRP) monoclonal antibodies for the prevention of migraine: the Plan considers this approach experimental and investigational. While recent studies have shown potential benefits of this combination therapy in patients with difficult-to-treat chronic migraine, more research is needed to establish the long-term safety and efficacy of this approach.
H. Chronic pain, including, but not limited to: myofascial pain syndrome, inflammatory pain, knee osteoarthritis, musculoskeletal pain (including acute shoulder and back pain), neuropathic pain, postoperative pain, post-herpetic neuralgia, gynecologic pain syndromes, fibromyalgia.
    a. *Rationale:* Multiple systematic reviews and meta-analyses have concluded that the current evidence is inadequate to support the use of Botox in chronic pain syndromes.
I. Chronic paralytic strabismus, except when used in conjunction with surgical repair to reduce ocular antagonist muscle contracture.
J. Club foot (e.g. talipes equinovarus)
    a. *Rationale:* The existing evidence consists of a small (n=20) randomized trial showing no benefit with Botox in reducing cast time, need for further procedural intervention, or risk for relapse. A separate, larger study with 239 patients found some evidence of efficacy for Botox, however the study was designed as a retrospective case series. Further randomized, prospective evidence is needed to determine a potential benefit of Botox for this indication.
K. Cosmetic strabismus, defined as adults with congenital strabismus without binocular fusion.
L. Depression
M. First-bite syndrome, with or without pain that has failed traditional analgesics
N. Frey Syndrome (i.e. Gustatory sweating)
    a. *Rationale:* A 2013 evidence-based review concluded that the lack of randomized clinical evidence for Botox in Frey's syndrome limits the support for clinical use.
O. Gastroparesis
    a. *Rationale:* There is limited evidence to support the use of OnabotulinumtoxinA for gastroparesis. Some small studies have suggested potential benefit in reducing symptoms and improving gastric emptying, but larger randomized controlled trials are

needed to further evaluate its efficacy and safety for this condition. Therefore, more research is needed before making a definitive conclusion about the effectiveness of OnabotulinumtoxinA for gastroparesis.

P. Hyperhidrosis of the face/neck
    a. *Rationale:* more high-quality studies are needed to further evaluate the safety and efficacy of Botox in the treatment of craniofacial hyperhidrosis.

Q. Migraines or other headaches (e.g. tension, cluster, chronic daily) that do not meet the above criteria
    a. *Rationale:* OnabotulinumtoxinA has been used with varying degrees of success in a small number of patients suffering from headaches other than chronic migraine, including post-whiplash (cervicogenic) headache, tension-type headache, and cluster headache. The manufacturer cautions that the safety and effectiveness of onabotulinumtoxinA for prophylaxis of episodic migraine (less than or equal to 14 headache days per month) have not been established. The American Academy of Neurology (AAN) does not endorse the use of onabotulinumtoxinA as a treatment for headaches other than chronic migraine.

R. Motor tics / Tourette Syndrome
    a. *Rationale:*
        i. The American Academy of Neurology provides level C rating in 2019 practice guideline for prescribing botulinum toxin injections for the treatment of adolescents and adults with localized and bothersome simple motor tics when the benefits of treatment outweigh the risks. Furthermore, AAN provide level C rating for prescribing botulinum toxin injections for the treatment of older adolescents and adults with severely disabling or aggressive vocal tics when the benefits of treatment outweigh the risks. Therefore, Botox for Tourette Syndrome will be considered experimental or investigational.
        ii. A 2018 Cochrane Database analysis looked at the use of Botox in the treatment of motor tics. They found only a single randomized trial that met their selection criteria, and only 20 patients enrolled in the study, and that the quality of the evidence was "low-quality". In conclusion, the authors stated that they were "uncertain about botulinum toxin effects in the treatment of focal motor and phonic tics in select cases, as we assessed the quality of the evidence as very low. Additional randomised controlled studies are needed to demonstrate the benefits and harms of botulinum toxin therapy for the treatment of motor and phonic tics in patients with Tourette's syndrome."

S. Obesity

T. Painful bruxism
U. Palatal myoclonus
V. Phonic tics
W. Plantar fasciitis
X. Postnatal brachial plexus injury
Y. Post-radiation myokymia, including facial myokymia and trismus
Z. Raynaud's Phenomenon
    a. *Rationale*: Limited studies, including small non-controlled trials, case series, and retrospective reviews, have suggested some potential benefits of using onabotulinumtoxinA (botulinum toxin A) for severe symptoms associated with primary or secondary Raynaud phenomenon (RP). While a small randomized, double-blind, placebo-controlled trial in patients with scleroderma-associated RP also showed some positive effect in patient-reported clinical measures, it did not demonstrate significant improvements in blood flow as measured by laser Doppler imaging, which was the primary outcome. A systemic review found insufficient evidence to assess the efficacy of onabotulinumtoxinA in severe RP, and experts recommend reserving its use for patients who have not tolerated or have failed initial conventional therapy. Further trials may be necessary to determine the role of onabotulinumtoxinA in this condition.
AA. Refractory interstitial cystitis
BB. Tardive dyskinesia: Small noncontrolled trials suggest that botulinum toxin A may be beneficial for treating localized tardive dyskinesia, such as orofacial, head and neck, and cervical symptoms. However, the evaluation of the data is limited due to several studies not specifying the type of botulinum toxin A product used. Case reports primarily evaluating onabotulinumtoxinA have demonstrated benefits in most patients. However, the American Academy of Neurology clinical practice guidelines consider the data inadequate to support or refute the use of botulinum toxin type A for treating tardive dyskinesia.
CC. Temporomandibular Disorders (TMD): There is limited evidence supporting the use of botulinum toxin A (BTX-A) for the treatment of Temporomandibular Disorders (TMD). Some small randomized controlled trials and case reports have suggested that BTX-A injections may provide pain relief and improve jaw function in patients with TMD. However, the evidence is not conclusive and larger, more rigorous studies are needed to determine the effectiveness and safety of BTX-A in the treatment of TMD.
DD. Thoracic outlet syndrome
EE. Trigeminal neuralgia

a. *Rationale:* The current evidence is either uncontrolled or nonrandomized with small patient samples. Review articles have suggested there may be some efficacy for Botox in trigeminal neuralgia but indicate that further study is needed.

FF. Upper esophageal sphincter dysfunction

AbobotulinumtoxinA (Dysport) (J0586)

The use of AbobotulinumtoxinA (Dysport) for any other indication not listed above is considered experimental, investigational, or unproven; these excluded indications include, but are not limited to, the following:

A. AbobotulinumtoxinA (Dysport) is contraindicated in members with allergy to cow's milk protein, per FDA guidelines
B. Achalasia or upper esophageal sphincter dysfunction
C. Benign prostatic hypertrophy (BPH)
    a. *Rationale:* A 2011 review article on abobotulinumtoxinA for lower urinary tract symptoms related to BPH concluded that the level of evidence is low and further randomized controlled trials are necessary.
D. Carpal tunnel syndrome
E. Charcot-Marie-Tooth disease
F. Chronic musculoskeletal and myofascial pain
    a. *Rationale:* A systematic review of the available randomized trials found lack of efficacy for Dysport in myofascial pain syndromes.
G. Gastroparesis
    a. *Rationale:* There is currently insufficient evidence to support the use of AbobotulinumtoxinA (Dysport) for gastroparesis. While botulinum toxin type A has been studied in the treatment of gastroparesis, most studies have focused on the use of onabotulinumtoxinA (Botox) and there is limited research on the efficacy of abobotulinumtoxinA for this indication. More research is needed to determine the safety and effectiveness of abobotulinumtoxinA in the treatment of gastroparesis.
H. Headaches, including migraines, tension headaches, or headaches secondary to cranial neuralgia
    a. *Rationale:* A prospective, multi-center, randomized, double-blind placebo-controlled trial found no significant difference between placebo and Dysport in headache free days (primary outcome) among patients suffering from chronic migraine.[5-6]
I. Hyperhidrosis, other than axillary hyperhidrosis

a. *Rationale:* An expert review by the American Academy of Neurology concluded that the evidence for Dysport in palmar hyperhidrosis was inadequate to guide clinical decision making.

J. Lateral epicondylitis
K. Obesity
L. Plantar fasciitis
M. Postnatal brachial plexus injury
N. Raynaud's Phenomenon
    a. *Rationale*: There is limited evidence to support the use of Dysport (abobotulinumtoxinA) in the treatment of Raynaud's Phenomenon (RP). Some small studies and case reports have suggested that botulinum toxin A (BTX-A) injections, including Dysport, may have some benefit for the treatment of severe RP symptoms. However, the evidence is not yet strong enough to make definitive recommendations for the use of Dysport in RP treatment. More studies are needed to determine the optimal dose, injection sites, and duration of effect for BTX-A in the treatment of RP.
O. Refractory interstitial cystitis
P. Shoulder pain
Q. Strabismus
R. Tardive dyskinesia
    a. Rationale: AAN clinical practice guidelines consider the data insufficient to support or refute the use of botulinum toxin type A for treating tardive dyskinesia.
S. Temporomandibular Disorders (TMD)
    a. Rationale: There is limited evidence to support the use of Dysport (abobotulinumtoxinA) in the treatment of Temporomandibular Disorders (TMD). Some small studies and case reports have suggested that botulinum toxin A (BTX-A) injections, including Dysport, may have some benefit for the treatment of certain types of TMD, however, the evidence is not yet strong enough to make definitive recommendations for the use of Dysport in TMD treatment. More studies are needed to determine the optimal dose, injection sites, and duration of effect for BTX-A in the treatment of TMD.
T. Tourette Syndrome
    a. *Rationale:* There is currently insufficient evidence to support the use of Dysport (abobotulinumtoxinA) in the treatment of Tourette Syndrome. While some small studies and case reports have shown promise, larger, well-designed clinical trials are needed to fully evaluate the safety and efficacy of this treatment approach. The American Academy of Neurology's clinical practice guidelines currently do not recommend the use of botulinum toxin for the treatment of tics in Tourette Syndrome.

U. Trigeminal neuralgia

RimabotulinumtoxinB (Myobloc) (J0587)

The use of RimabotulinumtoxinB (Myobloc) for any other indication not listed above is considered experimental, investigational, or unproven; these excluded indications include, but are not limited to, the following:

A. Bladder dysfunction (e.g. overactive bladder, detrusor hyperreflexia)
    a. *Rationale:* The evidence has been contradictory or inconclusive, with some studies showing RimabotulinumtoxinB efficacy while others have demonstrated a lack of benefit. A 2011 Cochrane review (updating the previous 2007 review) identified 19 studies meeting inclusion criteria, and found that the efficacy of RimabotulinumtoxinB was inferior to that of type A toxins with a substantially shorter duration of benefit across randomized trials for bladder dysfunction.
B. Blepharospasm and Associated Facial Nerve Disorders (e.g., hemifacial spasm)
    a. *Rationale:* RimabotulinumtoxinB is limited in efficacy and experience, but has been used for blepharospasm or hemifacial spasm, mainly in patients who have responded to onabotulinumtoxinA. The American Academy of Neurology recommends onabotulinumtoxinA and incobotulinumtoxinA as treatment options, and abobotulinumtoxinA may be considered for blepharospasm, but does not make a recommendation for rimabotulinumtoxinB due to insufficient data.
C. Disabling headaches (e.g., migraine, cluster headache)
D. Gastroparesis
    a. *Rationale:* There is limited evidence to support the use of RimabotulinumtoxinB (Myobloc) in the treatment of gastroparesis. Some small studies have suggested potential benefit in improving symptoms such as nausea and vomiting, but more research is needed to establish the safety and effectiveness of this treatment for gastroparesis.
E. Hyperhidrosis (including primary axillary hyperhidrosis and focal palmar hyperhidrosis)
    a. *Rationale:* Although RimabotulinumtoxinB has been utilized for symptomatic management of primary axillary and focal palmar hyperhidrosis characterized by excessive glandular secretion, its efficacy evidence and experience are less extensive when compared to OnabotulinumtoxinA.
F. Incontinence after spinal cord injury
G. Involuntary (smooth) muscle overactivity (e.g., neurogenic voiding dysfunction, anal sphincter disorders)

H. Musculoskeletal pain disorders (e.g., myofascial pain syndrome, chronic low back pain, pain associated with brachial plexopathy)

I. Raynaud's Phenomenon

    a. *Rationale*: There is currently insufficient evidence to support the use of RimabotulinumtoxinB (Myobloc) in the treatment of Raynaud's Phenomenon.

J. Spasmodic dysphonia

K. Spasticity in adults, including post-stroke spasticity and spasticity of the upper and/or lower extremities associated with other neurological disorders

    a. *Rationale:* The clinical evidence for RimabotulinumtoxinB (type b agent) is substantially limited compared to type A agents. A single randomized trial on 24 patients showed possible improvements with RimabotulinumtoxinB but concluded that larger studies with long-term follow up were needed for further evidence. The US Pharmacopeial Convention has stated that off-label use of RimabotulinumtoxinB for spasticity secondary to stroke or brain injury may be indicated, however updated data has failed to demonstrated the statistically significant benefit seen in earlier studies. The American Academy of Neurology currently states (per 2016 guidelines), that the data is insufficient to determine the efficacy of Myobloc in lower limb spasticity, and the evidence is limited to a single Class I study for upper limb spasticity.

L. Spasticity in children with cerebral palsy (CP)

    a. *Rationale:* A review by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society concluded that the evidence was limited in children with CP, and that the existing evidence on RimabotulinumtoxinB showed inferior efficacy compared to type A toxins.

M. Temporomandibular Disorders (TMD)

    a. Rationale: There is currently insufficient evidence to support the use of RimabotulinumtoxinB (Myobloc) in the treatment of Temporomandibular Disorders (TMD). While there are some studies investigating the use of botulinum toxin in TMD, the evidence is limited and conflicting, with some studies reporting positive outcomes and others reporting no significant benefit. Further research is needed to determine the efficacy of RimabotulinumtoxinB in the treatment of TMD.

N. Tourette Syndrome

    a. *Rationale:* There is currently limited evidence on the use of RimabotulinumtoxinB (Myobloc) in the treatment of Tourette Syndrome. While some small studies have shown potential benefit, further research is needed to determine its efficacy and safety for this indication.

O. Upper esophageal dysfunction or achalasia

a. *Rationale:* A 2014 Cochrane review revealed no randomized clinical trials on RimabotulinumtoxinB for upper esophageal dysfunction.

<u>IncobotulinumtoxinA (Xeomin) (J0588)</u>

The use of IncobotulinumtoxinA (Xeomin) for any other indication not listed above is considered experimental, investigational, or unproven; these excluded indications include, but are not limited to, the following:

A. Atrial fibrillation
B. Detrusor hyperactivity (e.g. bladder overactivity)
    a. *Rationale:* There is limited evidence on Xeomin in patients with overactive bladder. Preliminary results on 95 patients from a double-blinded study on Xeomin and Botox in bladder overactivity were presented at the 27th Annual Congress of the European Association of Urology. However, further peer-reviewed randomized evidence is currently lacking, limiting guidance for clinical application.
C. Hyperhidrosis, including axillary, palmar, and craniofacial
    a. *Rationale:* Xeomin and Botox were compared in a double-blind trial in treating palmar hyperhidrosis. There were no significant differences in short- or long-term efficacy outcomes, however only 25 patients were included in the study. Given the small sample size and lack of confirmatory studies, further evidence is required. Similar limitations are present in comparable studies on axillary hyperhidrosis. Further evidence is needed to determine a potential benefit of Xeomin for this indication.
D. Gastroparesis
    a. *Rationale:* There is currently insufficient evidence to support the use of IncobotulinumtoxinA (Xeomin) for gastroparesis. While some small studies have shown promising results, larger randomized controlled trials are needed to establish its efficacy and safety in this condition. The use of botulinum toxin for gastroparesis is still considered investigational and not recommended for routine clinical use.
E. Migraine prophylaxis
    a. *Rationale:* The evidence for Xeomin in migraine prophylaxis comes from small, retrospective case series and poster presentations, indicating further prospective, randomized evidence is required to guide any potential clinical application.
F. Parkinson disease with tremor
    a. Rationale: There is insufficient, conflicting, or poor evidence regarding the use of incobotulinumtoxinA for Parkinson disease with tremor, and more research is needed.
G. Plantar fasciitis
    a. Rationale: There is a lack of sufficient, conflicting, or poor evidence regarding the use of incobotulinumtoxinA for plantar fasciitis.
H. Post-stroke lower limb spasticity

a. *Rationale:* A prospective, open label study on 71 patients demonstrated safety and efficacy of Xeomin in post-stroke lower limb spasticity, however further randomized studies are required to establish clinical use. Furthermore, the 2016 American Academy of Neurology Guidelines state that there "is insufficient evidence to support or refute the use of incoBoNT-A for the treatment of lower limb spasticity."

I. Raynaud's Phenomenon
   a. *Rationale*: There is currently insufficient evidence to support the use of IncobotulinumtoxinA (Xeomin) for Raynaud's Phenomenon.

J. Temporomandibular Disorders (TMD)
   a. *Rationale:* There is limited evidence to support the use of IncobotulinumtoxinA for the treatment of Temporomandibular Disorders (TMD). While some studies have shown potential benefits, more research is needed to establish its efficacy and safety in this context.

K. Tourette Syndrome
   a. *Rationale:* There is insufficient evidence to support the use of IncobotulinumtoxinA (Xeomin) for Tourette Syndrome.

DaxibotulinumtoxinA-lanm (Daxxify) (J0589)

The use of DaxibotulinumtoxinA-lanm (Daxxify) for any other indication not listed above is considered experimental, investigational, or unproven; these excluded indications include, but are not limited to, the following:

A. Pancreatic Carcinoma
B. Plantar fascial fibromatosis
C. Spasmodic Dysphonia

Applicable Billing Codes (CPT/HCPCS/ICD-10 Codes)

Codes considered medically necessary if clinical criteria are met:

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
J0585	Injection, onabotulinumtoxinA, 1 unit (Botox®)
J0586	Injection, abobotulinumtoxinA, 5 units (Dysport®)
J0587	Injection, rimabotulinumtoxinB, 100 units (Myobloc®)

J0588	Injection, incobotulinumtoxinA, 1 unit (Xeomin®)
C9160*	Daxxify (daxibotulinumtoxinA-lanm) Injection, daxibotulinumtoxina-lanm, 1 unit **Code Note: Code will be deleted effective 3/31/24 - see J0589*
J0589	Injection, daxibotulinumtoxina-lanm, 1 unit (Daxxify®)
ICD-10 codes considered medically necessary if criteria are met for onabotulinumtoxinA (J0585):	
G04.1	Tropical spastic paraplegia
G11.4	Hereditary spastic paraplegia
G12.21	Amyotrophic lateral sclerosis
G20	Parkinson's disease
G24.3	Spasmodic torticollis
G24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
G24.8	Other dystonia
G25.0	Essential tremor
G35	Multiple sclerosis
G36.0	Neuromyelitis optica
G36.1	Acute and subacute hemorrhagic leukoencephalitis
G36.8	Other specified acute disseminated demyelination
G36.9	Acute disseminated demyelination, unspecified
G37.0	Diffuse sclerosis of central nervous system
G37.1	Central demyelination of corpus callosum
G37.2	Central pontine myelinolysis
G37.3	Acute transverse myelitis in demyelinating disease of central nervous system
G37.4	Subacute necrotizing myelitis of central nervous system
G37.5	Concentric sclerosis [Balo] of central nervous system
G37.8	Other specified demyelinating diseases of central nervous system
G37.81	Myelin oligodendrocyte glycoprotein antibody disease
G37.89	Other specified demyelinating diseases of central nervous system
G37.9	Demyelinating disease of central nervous system, unspecified

G43.101	Migraine with aura, not intractable, with status migrainosus
G43.109	Migraine with aura, not intractable, without status migrainosus
G43.111	Migraine with aura, intractable, with status migrainosus
G43.119	Migraine with aura, intractable, without status migrainosus
G43.701	Chronic migraine without aura, not intractable with status migrainosus
G43.711	Chronic migraine without aura, intractable, with status migrainosus
G43.719	Chronic migraine without aura, intractable, without status migrainosus
G51.0	Bell's palsy
G51.1	Geniculate ganglionitis
G52.2	Melkersson's syndrome
G51.3	Clonic hemifacial spasm
G51.31	Clonic hemifacial spasm, right
G51.32	Clonic hemifacial spasm, left
G51.33	Clonic hemifacial spasm, bilateral
G51.39	Clonic hemifacial spasm, unspecified
G51.54	Facial myokymia
G51.58	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
G81.10	Spastic hemiplegia affecting unspecified side
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side
G81.14	Spastic hemiplegia affecting left nondominant side
G82.20	Paraplegia, unspecified
G82.21	Paraplegia, complete
G82.22	Paraplegia, incomplete

G82.50	Quadriplegia, unspecified
G82.51	Quadriplegia, C1-C4 complete
G82.52	Quadriplegia, C1-C4 incomplete
G82.53	Quadriplegia, C5-C7 complete
G82.84	Quadriplegia, C5-C7 incomplete
G83.10	Monoplegia of lower limb affecting unspecified side
G83.11	Monoplegia of lower limb affecting right dominant side
G83.12	Monoplegia of lower limb affecting left dominant side
G83.13	Monoplegia of lower limb affecting right nondominant side
G83.14	Monoplegia of lower limb affecting left nondominant side
G83.31	Monoplegia, unspecified affecting right dominant side
G83.32	Monoplegia, unspecified affecting left dominant side
G83.33	Monoplegia, unspecified affecting right nondominant side
G83.34	Monoplegia, unspecified affecting left nondominant side
H49.881	Other paralytic strabismus, right eye
H49.882	Other paralytic strabismus, left eye
H49.883	Other paralytic strabismus, bilateral
H49.889	Other paralytic strabismus, unspecified eye
H49.9	Unspecified paralytic strabismus
H50.21	Vertical strabismus, right eye
H50.22	Vertical strabismus, left eye
H50.60	Mechanical strabismus, unspecified
H50.69	Other mechanical strabismus
H50.89	Other specified strabismus
H50.9	Unspecified strabismus
I69.031	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.032	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.033	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right non-dominant side

I69.034	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left non-dominant side
I69.039	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.041	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.042	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.043	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.044	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting left non-dominant side
I69.049	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.051	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.052	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.053	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.054	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left non-dominant side
I69.059	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.131	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.132	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.133	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.134	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.139	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.141	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.142	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting left dominant side

I69.143	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.144	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.149	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.151	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.152	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.153	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.154	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.159	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.231	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right dominant side
I69.232	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left dominant side
I69.233	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.234	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.239	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.241	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting right dominant side
I69.242	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting left dominant side
I69.243	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.244	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.251	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhageaffecting right dominant side
I69.252	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting left dominant side

I69.253	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.254	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.259	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.331	Monoplegia of upper limb following cerebral infarction affecting right dominant side
I69.332	Monoplegia of upper limb following cerebral infarction affecting left dominant side
I69.333	Monoplegia of upper limb following cerebral infarction affecting right non-dominant side
I69.334	Monoplegia of upper limb following cerebral infarction affecting left non-dominant side
I69.339	Monoplegia of upper limb following cerebral infarction affecting unspecified side
I69.341	Monoplegia of lower limb following cerebral infarction affecting right dominant side
I69.342	Monoplegia of lower limb following cerebral infarction affecting left dominant side
I69.343	Monoplegia of lower limb following cerebral infarction affecting right non-dominant side
I69.344	Monoplegia of lower limb following cerebral infarction affecting left non-dominant side
I69.351	Hemiplegia and hemiparesis following cerebral infarction affecting right dominant side
I69.352	Hemiplegia and hemiparesis following cerebral infarction affecting left dominant side
I69.353	Hemiplegia and hemiparesis following cerebral infarction affecting right non-dominant side
I69.354	Hemiplegia and hemiparesis following cerebral infarction affecting left non-dominant side
I69.359	Hemiplegia and hemiparesis following cerebral infarction affecting unspecified side
I69.831	Monoplegia of upper limb following other cerebrovascular disease affecting right dominant side
I69.832	Monoplegia of upper limb following other cerebrovascular disease affecting left dominant side

I69.833	Monoplegia of upper limb following other cerebrovascular disease affecting right non-dominant side
I69.834	Monoplegia of upper limb following other cerebrovascular disease affecting left non-dominant side
I69.839	Monoplegia of upper limb following other cerebrovascular disease affecting unspecified side
I69.841	Monoplegia of lower limb following other cerebrovascular disease affecting right dominant side
I69.842	Monoplegia of lower limb following other cerebrovascular disease affecting left dominant side
I69.843	Monoplegia of lower limb following other cerebrovascular disease affecting right non-dominant side
I69.844	Monoplegia of lower limb following other cerebrovascular disease affecting left non- dominant side
I69.849	Monoplegia of lower limb following other cerebrovascular disease affecting unspecified side
I69.851	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right dominant side
I69.852	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left dominant side
I69.853	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right non-dominant side
I69.854	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left non-dominant side
I69.859	Hemiplegia and hemiparesis following other cerebrovascular disease affecting unspecified side
I69.861	Other paralytic syndrome following other cerebrovascular disease affecting right dominant side
I69.862	Other paralytic syndrome following other cerebrovascular disease affecting left dominant side
I69.863	Other paralytic syndrome following other cerebrovascular disease affecting right non-dominant side
I69.864	Other paralytic syndrome following other cerebrovascular disease affecting left non-dominant side
I69.865	Other paralytic syndrome following other cerebrovascular disease, bilateral
I69.869	Other paralytic syndrome following other cerebrovascular disease affecting unspecified side

I69.931	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right dominant side
I69.932	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left dominant side
I69.933	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right non-dominant side
I69.934	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left non-dominant side
I69.939	Monoplegia of upper limb following unspecified cerebrovascular disease affecting unspecified side
I69.941	Monoplegia of lower limb following unspecified cerebrovascular disease affecting right dominant side
I69.942	Monoplegia of lower limb following unspecified cerebrovascular disease affecting left dominant side
I69.943	Monoplegia of lower limb following unspecified cerebrovascular disease affecting right non-dominant side
I69.944	Monoplegia of lower limb following unspecified cerebrovascular disease affecting left non-dominant side
I69.949	Monoplegia of lower limb following unspecified cerebrovascular disease affecting unspecified side
I69.951	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right dominant side
I69.952	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left dominant side
I69.953	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right non-dominant side
I69.954	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left non-dominant side
I69.959	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting unspecified side
J38.5	Laryngeal spasm
K11.7	Disturbances of salivary secretion
K22.0	Achalasia of cardia
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla

L74.512	Primary focal hyperhidrosis, palms
L98.8	Other specified disorders of the skin and subcutaneous tissue
M62.40	Contracture of muscle, unspecified site
M62.411	Contracture of muscle, right shoulder
M62.412	Contracture of muscle, left shoulder
M62.419	Contracture of muscle, unspecified shoulder
M62.421	Contracture of muscle, right upper arm
M62.422	Contracture of muscle, left upper arm
M62.429	Contracture of muscle, unspecified upper arm
M62.431	Contracture of muscle, right forearm
M62.432	Contracture of muscle, left forearm
M62.439	Contracture of muscle, unspecified forearm
M62.441	Contracture of muscle, right hand
M62.442	Contracture of muscle, left hand
M62.449	Contracture of muscle, unspecified hand
M62.451	Contracture of muscle, right thigh
M62.452	Contracture of muscle, left thigh
M62.459	Contracture of muscle, unspecified thigh
M62.461	Contracture of muscle, right lower leg
M62.462	Contracture of muscle, left lower leg
M62.469	Contracture of muscle, unspecified lower leg
M62.471	Contracture of muscle, right ankle and foot
M62.472	Contracture of muscle, left ankle and foot
M62.479	Contracture of muscle, unspecified ankle and foot
M62.48	Contracture of muscle, other site
M62.49	Contracture of muscle, multiple sites
M62.830	Muscle spasm of back
M62.831	Muscle spasm of calf
M62.838	Other muscle spasm
N31.0	Uninhibited neuropathic bladder, not elsewhere classified
N31.1	Reflex neuropathic bladder, not elsewhere classified

N31.8	Other neuromuscular dysfunction of bladder
N31.9	Neuromuscular dysfunction of bladder, unspecified
N32.81	Overactive bladder
N36.44	Muscular disorders of urethra [bladder sphincter dyssynergy] [due to spinal cord injury, bladder-hyphensphincter dyssynergia]
N39.3	Stress incontinence (female) (male)
N39.41	Urge incontinence
N39.42	Incontinence without sensory awareness
N39.43	Post-void dribbling
N39.44	Nocturnal enuresis
N39.45	Continuous leakage
N39.46	Mixed incontinence
N39.490	Overflow incontinence
N39.491	Coital incontinence
N39.492	Postural (urinary) incontinence
N39.498	Other specified urinary incontinence
R13.10	Dysphagia, unspecified
R13.11	Dysphagia, oral phase
R13.12	Dysphagia, oropharyngeal phase
R13.13	Dysphagia, pharyngeal phase
R13.14	Dysphagia, pharynoesophageal phase
R13.19	Other dysphagia
R25.2	Cramp and spasm
R32	Unspecified urinary incontinence
R39.81	Functional urinary incontinence
R49.0	Dysphonia
R61	Generalized hyperhidrosis
ICD-10 codes considered medically necessary if criteria are met for abobotulinumtoxinA (J0586) :	
G11.4	Hereditary spastic paraplegia
G24.3	Spasmodic torticollis
G24.5	Blepharospasm
G24.8	Other dystonia

G35	Multiple sclerosis
G36.0	Neuromyelitis optica
G36.1	Acute and subacute hemorrhagic leukoencephalitis
G36.8	Other specified acute disseminated demyelination
G36.9	Acute disseminated demyelination, unspecified
G37.0	Diffuse sclerosis of central nervous system
G37.1	Central demyelination of corpus callosum
G37.2	Central pontine myelinolysis
G37.3	Acute transverse myelitis in demyelinating disease of central nervous system
G37.4	Subacute necrotizing myelitis of central nervous system
G37.5	Concentric sclerosis [Balo] of central nervous system
G37.8	Other specified demyelinating diseases of central nervous system
G37.81	Myelin oligodendrocyte glycoprotein antibody disease
G37.89	Other specified demyelinating diseases of central nervous system
G37.9	Demyelinating disease of central nervous system, unspecified
G51.3	Clonic hemifacial spasm
G51.31	Clonic hemifacial spasm, right
G51.32	Clonic hemifacial spasm, left
G51.33	Clonic hemifacial spasm, bilateral
G51.39	Clonic hemifacial spasm, unspecified
G51.8	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified
G81.10	Spastic hemiplegia affecting unspecified sideSpastic hemiplegia
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side

G81.14	Spastic hemiplegia affecting left nondominant side
G82.20	Paraplegia, unspecified
G82.21	Paraplegia, complete
G82.22	Paraplegia, incomplete
G82.50	Quadriplegia, unspecified
G82.51	Quadriplegia, C1-C4 complete
G82.52	Quadriplegia, C1-C4 incomplete
G82.53	Quadriplegia, C5-C7 complete
G82.84	Quadriplegia, C5-C7 incomplete
G83.10	Monoplegia of lower limb affecting unspecified side
G83.11	Monoplegia of lower limb affecting right dominant side
G83.12	Monoplegia of lower limb affecting left dominant side
G83.13	Monoplegia of lower limb affecting right nondominant side
G83.14	Monoplegia of lower limb affecting left nondominant side
G83.20	Monoplegia of upper limb affecting unspecified side
G83.21	Monoplegia of upper limb affecting right dominant side
G83.22	Monoplegia of upper limb affecting left dominant side
G83.23	Monoplegia of upper limb affecting right nondominant side
G83.24	Monoplegia of upper limb affecting left nondominant side
G83.30	Monoplegia, unspecified affecting unspecified side
G83.31	Monoplegia, unspecified affecting right dominant side
G83.32	Monoplegia, unspecified affecting left dominant side
G83.33	Monoplegia, unspecified affecting right nondominant side
G83.34	Monoplegia, unspecified affecting left nondominant side
I69.031	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.032	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.033	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.034	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left non-dominant side
I69.039	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting unspecified side

I69.041	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.042	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.043	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.044	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting left non-dominant side
I69.049	Monoplegia of lower limb following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.051	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.052	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.053	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.0541	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left non-dominant sideHemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage
I69.059	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.131	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.132	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.133	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.134	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.139	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.141	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.142	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.143	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting right non-dominant side

I69.144	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.149	Monoplegia of lower limb following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.098	Other sequelae following nontraumatic subarachnoid hemorrhage
I69.151	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting right dominant sideHemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage
I69.152	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.153	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.154	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.159	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.231	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right dominant side
I69.232	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left dominant side
I69.233	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.234	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.239	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.241	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting right dominant side
I69.242	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting left dominant side
I69.243	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.244	Monoplegia of lower limb following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.251	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhageaffecting right dominant side

I69.252	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhageaffecting left dominant sideHemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage
I69.253	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.254	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.259	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.331	Monoplegia of upper limb following cerebral infarction affecting right dominant side
I69.332	Monoplegia of upper limb following cerebral infarction affecting left dominant side
I69.333	Monoplegia of upper limb following cerebral infarction affecting right non-dominant side
I69.334	Monoplegia of upper limb following cerebral infarction affecting left non-dominant side
I69.339	Monoplegia of upper limb following cerebral infarction affecting unspecified side
I69.341	Monoplegia of lower limb following cerebral infarction affecting right dominant side
I69.342	Monoplegia of lower limb following cerebral infarction affecting left dominant side
I69.343	Monoplegia of lower limb following cerebral infarction affecting right non-dominant side
I69.344	Monoplegia of lower limb following cerebral infarction affecting left non-dominant side
I69.351	Hemiplegia and hemiparesis following cerebral infarction affecting right dominant side
I69.352	Hemiplegia and hemiparesis following cerebral infarction affecting left dominant side
I69.353	Hemiplegia and hemiparesis following cerebral infarction affecting right non-dominant side
I69.354	Hemiplegia and hemiparesis following cerebral infarction affecting left non-dominant side
I69.359	Hemiplegia and hemiparesis following cerebral infarction affecting unspecified side
I69.831	Monoplegia of upper limb following other cerebrovascular disease affecting right dominant side

I69.832	Monoplegia of upper limb following other cerebrovascular disease affecting left dominant side
I69.833	Monoplegia of upper limb following other cerebrovascular disease affecting right non-dominant side
I69.834	Monoplegia of upper limb following other cerebrovascular disease affecting left non-dominant side
I69.839	Monoplegia of upper limb following other cerebrovascular disease affecting unspecified side
I69.841	Monoplegia of lower limb following other cerebrovascular disease affecting right dominant side
I69.842	Monoplegia of lower limb following other cerebrovascular disease affecting left dominant side
I69.843	Monoplegia of lower limb following other cerebrovascular disease affecting right non-dominant side
I69.844	Monoplegia of lower limb following other cerebrovascular disease affecting left non- dominant side
I69.849	Monoplegia of lower limb following other cerebrovascular disease affecting unspecified side
I69.851	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right dominant sideHemiplegia and hemiparesis following other cerebrovascular disease
I69.852	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left dominant side
I69.853	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right non-dominant side
I69.854	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left non-dominant side
I69.859	Hemiplegia and hemiparesis following other cerebrovascular disease affecting unspecified side
I69.931	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right dominant side
I69.932	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left dominant side
I69.933	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right non-dominant side
I69.934	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left non-dominant side

I69.939	Monoplegia of upper limb following unspecified cerebrovascular disease affecting unspecified side
I69.941	Monoplegia of lower limb following unspecified cerebrovascular disease affecting right dominant side
I69.942	Monoplegia of lower limb following unspecified cerebrovascular disease affecting left dominant side
I69.943	Monoplegia of lower limb following unspecified cerebrovascular disease affecting right non-dominant side
I69.944	Monoplegia of lower limb following unspecified cerebrovascular disease affecting left non-dominant side
I69.949	Monoplegia of lower limb following unspecified cerebrovascular disease affecting unspecified side
I69.951	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right dominant sideHemiplegia and hemiparesis following unspecified cerebrovascular disease
I69.952	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left dominant side
I69.953	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right non-dominant side
I69.954	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left non-dominant side
I69.959	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting unspecified side
H49.9	Unspecified paralytic strabismus
K11.7	Disturbances of salivary secretion
K60.0	Acute anal fissure
K60.1	Chronic anal fissure
K60.2	Anal fissure, unspecified
L74.510	Primary focal hyperhidrosis, axilla
L98.8	Other specified disorders of the skin and subcutaneous tissue
M62.40	Contracture of muscle, unspecified site
M62.411	Contracture of muscle, right shoulder
M62.412	Contracture of muscle, left shoulder
M62.419	Contracture of muscle, unspecified shoulder
M62.421	Contracture of muscle, right upper arm
M62.422	Contracture of muscle, left upper arm

M62.429	Contracture of muscle, unspecified upper arm
M62.431	Contracture of muscle, right forearm
M62.432	Contracture of muscle, left forearm
M62.439	Contracture of muscle, unspecified forearm
M62.441	Contracture of muscle, right hand
M62.442	Contracture of muscle, left hand
M62.449	Contracture of muscle, unspecified hand
M62.451	Contracture of muscle, right thigh
M62.452	Contracture of muscle, left thigh
M62.459	Contracture of muscle, unspecified thigh
M62.461	Contracture of muscle, right lower leg
M62.462	Contracture of muscle, left lower leg
M62.469	Contracture of muscle, unspecified lower leg
M62.471	Contracture of muscle, right ankle and foot
M62.472	Contracture of muscle, left ankle and foot
M62.479	Contracture of muscle, unspecified ankle and foot
M62.48	Contracture of muscle, other site
M62.49	Contracture of muscle, multiple sites
M62.831	Muscle spasm of calf
M62.838	Other muscle spasm
R25.2	Cramp and spasm
ICD-10 codes considered medically necessary if criteria are met for rimabotulinumtoxinB (J0587):	
G12.21	Amyotrophic lateral sclerosis
G20	Parkinson's disease
G24.3	Spasmodic torticollis
G24.4	Idiopathic orofacial dystonia
G24.8	Other dystonia
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G80.8	Other cerebral palsy
G80.9	Cerebral palsy, unspecified

K11.7	Disturbances of salivary secretion
R25.2	Cramp and spasm
ICD-10 codes considered medically necessary if criteria are met for incobotulinumtoxinA (J0588):	
G24.3	Spasmodic torticollis
G24.4	Idiopathic orofacial dystonia
G24.5	Blepharospasm
G51.3	Clonic hemifacial spasm
G51.8	Other disorders of facial nerve
G51.9	Disorder of facial nerve, unspecified
G80.0	Spastic quadriplegic cerebral palsy
G80.1	Spastic diplegic cerebral palsy
G80.2	Spastic hemiplegic cerebral palsy
G81.10	Spastic hemiplegia affecting unspecified sideSpastic hemiplegia
G81.11	Spastic hemiplegia affecting right dominant side
G81.12	Spastic hemiplegia affecting left dominant side
G81.13	Spastic hemiplegia affecting right nondominant side
G81.14	Spastic hemiplegia affecting left nondominant side
G82.53	Quadriplegia, C5-C7 complete
G82.84	Quadriplegia, C5-C7 incomplete
G83.0	Diplegia of upper limbs
G83.20	Monoplegia of upper limb affecting unspecified side
G83.21	Monoplegia of upper limb affecting right dominant side
G83.22	Monoplegia of upper limb affecting left dominant side
G83.23	Monoplegia of upper limb affecting right nondominant side
G83.24	Monoplegia of upper limb affecting left nondominant side
I69.031	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.032	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.033	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.034	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting left non-dominant side

I69.039	Monoplegia of upper limb following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.051	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right dominant side
I69.052	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left dominant side
I69.053	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting right non-dominant side
I69.0541	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting left non-dominant sideHemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage
I69.059	Hemiplegia and hemiparesis following nontraumatic subarachnoid hemorrhage affecting unspecified side
I69.131	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right dominant side
I69.132	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.133	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.134	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.139	Monoplegia of upper limb following nontraumatic intracerebral hemorrhage affecting unspecified side
I69.151	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affectingright dominant sideHemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage
I69.152	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left dominant side
I69.153	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting right non-dominant side
I69.154	Hemiplegia and hemiparesis following nontraumatic intracerebral hemorrhage affecting left non-dominant side
I69.231	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right dominant side
I69.232	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left dominant side
I69.233	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting right non-dominant side

I69.234	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.239	Monoplegia of upper limb following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.251	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhageaffecting right dominant side
I69.252	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting left dominant sideHemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage
I69.253	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting right non-dominant side
I69.254	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting left non-dominant side
I69.259	Hemiplegia and hemiparesis following other nontraumatic intracranial hemorrhage affecting unspecified side
I69.331	Monoplegia of upper limb following cerebral infarction affecting right dominant side
I69.332	Monoplegia of upper limb following cerebral infarction affecting left dominant side
I69.333	Monoplegia of upper limb following cerebral infarction affecting right non-dominant side
I69.334	Monoplegia of upper limb following cerebral infarction affecting left non-dominant side
I69.339	Monoplegia of upper limb following cerebral infarction affecting unspecified side
I69.351	Hemiplegia and hemiparesis following cerebral infarction affecting right dominant side
I69.352	Hemiplegia and hemiparesis following cerebral infarction affecting left dominant side
I69.353	Hemiplegia and hemiparesis following cerebral infarction affecting right non-dominant side
I69.354	Hemiplegia and hemiparesis following cerebral infarction affecting left non-dominant side
I69.359	Hemiplegia and hemiparesis following cerebral infarction affecting unspecified side
I69.831	Monoplegia of upper limb following other cerebrovascular disease affecting right dominant side
I69.832	Monoplegia of upper limb following other cerebrovascular disease affecting left dominant side

I69.833	Monoplegia of upper limb following other cerebrovascular disease affecting right non-dominant side
I69.834	Monoplegia of upper limb following other cerebrovascular disease affecting left non-dominant side
I69.839	Monoplegia of upper limb following other cerebrovascular disease affecting unspecified side
I69.851	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right dominant sideHemiplegia and hemiparesis following other cerebrovascular disease
I69.852	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left dominant side
I69.853	Hemiplegia and hemiparesis following other cerebrovascular disease affecting right non-dominant side
I69.854	Hemiplegia and hemiparesis following other cerebrovascular disease affecting left non-dominant side
I69.859	Hemiplegia and hemiparesis following other cerebrovascular disease affecting unspecified side
I69.931	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right dominant side
I69.932	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left dominant side
I69.933	Monoplegia of upper limb following unspecified cerebrovascular disease affecting right non-dominant side
I69.934	Monoplegia of upper limb following unspecified cerebrovascular disease affecting left non-dominant side
I69.939	Monoplegia of upper limb following unspecified cerebrovascular disease affecting unspecified side
I69.951	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right dominant sideHemiplegia and hemiparesis following unspecified cerebrovascular disease
I69.952	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left dominant side
I69.953	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting right non-dominant side
I69.954	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting left non-dominant side
I69.959	Hemiplegia and hemiparesis following unspecified cerebrovascular disease affecting unspecified side

K11.7	Disturbances of salivary secretion
L98.8	Other specified disorders of the skin and subcutaneous tissue
M62.40	Contracture of muscle, unspecified siteContracture of muscle
M62.411	Contracture of muscle, right shoulder
M62.412	Contracture of muscle, left shoulder
M62.419	Contracture of muscle, unspecified shoulder
M62.421	Contracture of muscle, right upper arm
M62.422	Contracture of muscle, left upper arm
M62.429	Contracture of muscle, unspecified upper arm
M62.431	Contracture of muscle, right forearm
M62.432	Contracture of muscle, left forearm
M62.439	Contracture of muscle, unspecified forearm
M62.441	Contracture of muscle, right hand
M62.442	Contracture of muscle, left hand
M62.449	Contracture of muscle, unspecified hand
M62.451	Contracture of muscle, right thigh
M62.452	Contracture of muscle, left thigh
M62.459	Contracture of muscle, unspecified thigh
M62.461	Contracture of muscle, right lower leg
M62.462	Contracture of muscle, left lower leg
M62.469	Contracture of muscle, unspecified lower leg
M62.471	Contracture of muscle, right ankle and foot
M62.472	Contracture of muscle, left ankle and foot
M62.479	Contracture of muscle, unspecified ankle and foot
M62.48	Contracture of muscle, other site
M62.49	Contracture of muscle, multiple sites
ICD-10 codes considered medically necessary if criteria are met for daxibotulinumtoxinA-lanm (Daxxify) (J0589):	
G24.3	Spasmodic torticollis
L98.8	Other specified disorders of the skin and subcutaneous tissue

CPT/HCPCS Codes considered medically necessary but may be subject to medical necessity review:

Code	*Description*

31513	Laryngoscopy, indirect; with vocal cord injection
31570	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic;
31571	Laryngoscopy, direct, with injection into vocal cord(s), therapeutic; with operating microscope or telescope
31573	Laryngoscopy, flexible; with therapeutic injection(s) (eg, chemodenervation agent or corticosteroid, injected percutaneous, transoral, or via endoscope channel), unilateral
31574	Laryngoscopy, flexible; with injection(s) for augmentation (eg, percutaneous, transoral), unilateral
43192	Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance
43201	Esophagoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43236	Esophagogastroduodenoscopy, flexible, transoral; with directed submucosal injection(s), any substance
43253	Esophagoscopy, rigid, transoral; with directed submucosal injection(s), any substance
46505	Chemodenervation of internal anal sphincter [covered for anal fissure only]
52287	Cystourethroscopy, with injection(s) for chemodenervation of the bladder
64611	Chemodenervation of parotid and submandibular salivary glands, bilateral
64612	Chemodenervation of muscles(s); muscles(s) innervated by facial nerve, unilateral (eg, for blepharospasm, hemifacial spasm)
64615	Chemodenervation of muscle(s); muscle(s) innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)
64616	Chemodenervation of muscle(s); neck muscle(s), excluding muscles of the larynx, unilateral (eg, for cervical dystonia, spasmodic torticollis)
64617	Chemodenervation of muscle(s); larynx, unilateral, percutaneous (eg, for spasmodic dysphonia), includes guidance by needle electromyography, when performed
64642	Chemodenervation of one extremity; 1-4 muscle(s)

64643	Chemodenervation of one extremity; each additional extremity, 1-4 muscle(s) (List separately in addition to code for primary procedure)
64644	Chemodenervation of one extremity; 5 or more muscles
64645	Chemodenervation of one extremity; each additional extremity, 5 or more muscles (List separately in addition to code for primary procedure)
64646	Chemodenervation of trunk muscle(s); 1-5 muscle(s)
64647	Chemodenervation of trunk muscle(s); 6 or more muscles
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (e.g., scalp, face, neck), per day
67345	Chemodenervation of extraocular muscle
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
95873	Electrical stimulation for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)
95874	Needle electromyography for guidance in conjunction with chemodenervation (List separately in addition to code for primary procedure)
S2340	Chemodenervation of abductor muscle(s) of vocal cord
S2341	Chemodenervation of adductor muscle(s) of vocal cord

CPT/HCPCS codes considered experimental or investigational or *not* considered medically necessary

Code	*Description*
86609	Antibody; bacterium, not elsewhere specified [neutralizing antibodies to botulinum toxin]

References

AbobotulinumtoxinA (Dysport)

1. Franco I, Landau-Dyer L, Isom-Batz G, Collett T, Reda EF. The use of botulinum toxin A injection for the management of external sphincter dyssynergia in neurologically normal children. J Urol.

2007 Oct;178(4 Pt 2):1775-9; discussion 1779-80. doi: 10.1016/j.juro.2007.03.185. Epub 2007 Aug 17. PMID: 17707430.

2. Annese V, Bassotti G, Coccia G, et al. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. The Gismad Achalasia Study Group. Aliment Pharmacol Ther. 1999;13(10):1347-50.
3. Arts J, Holvoet L, Caenepeel P, Bisschops R, Sifrim D, Verbeke K, Janssens J, Tack J. Clinical trial: a randomized-controlled crossover study of intrapyloric injection of botulinum toxin in gastroparesis. Aliment Pharmacol Ther. 2007;26:1251-1258.
4. Bakheit AM, Thilmann AF, Ward AB, et al. A randomized, double-blind, placebo-controlled, dose-ranging study to compare the efficacy and safety of three doses of botulinum toxin type A (Dysport) with placebo in upper limb spasticity after stroke. Stroke. 2000;31(10):2402-2406.
5. Boyle MH, McGwin G Jr, Flanagan CE, et al. High versus low concentration botulinum toxin A for benign essential blepharospasm: Does dilution make a difference? Ophthal Plast Reconstr Surg. 2009;25(2):81-84
6. Brisinda G, Cadeddu F, Brandara F, et al,. Botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Br J Surg. 2008 Jun;95(6):774-8. doi: 10.1002/bjs.6080.
7. Brisinda G, Cadeddu F, Brandara F, Marniga G, Maria G. Randomized clinical trial comparing botulinum toxin injections with 0.2 per cent nitroglycerin ointment for chronic anal fissure. Br J Surg. 2007;94(2):162-7.
8. Burns J, Scheinberg A, Ryan MM, Rose KJ, Ouvrier RA. Randomized trial of botulinum toxin to prevent pes cavus progression in pediatric Charcot-Marie-Tooth disease type 1A. Muscle Nerve. 2010;42(2):262-7.
9. Chankrachang S, Arayawichanont A, Poungvarin N, et al. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache. 2011;51(1):52-63.
10. Chartier-kastler E, Mehnert U, Denys P, Giuliano F. Botulinum neurotoxin A for male lower urinary tract symptoms. Curr Opin Urol. 2011;21(1):13-21.
11. Cvach K, Rosamilia A. Review of intravesical therapies for bladder pain syndrome/interstitial cystitis. Transl Androl Urol. 2015;4(6):629-37.
12. Dashtipour K, Chen JJ, Walker HW, Lee MY. Systematic Literature Review of AbobotulinumtoxinA in Clinical Trials for Lower Limb Spasticity. Medicine (Baltimore). 2016;95(2):e2468.
13. Davids JS, Hawkins AT, Bhama AR, et al,. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. Dis Colon Rectum. 2023 Feb 1;66(2):190-199. doi: 10.1097/DCR.0000000000002664. Epub 2022 Nov 1.
14. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients with brachial plexus birth palsy. Pediatr Rehabil. 2001;4(1):29-36.

15. Duarte GS, Rodrigues FB, Castelão M, Marques RE, Ferreira J, Sampaio C, Moore AP, Costa J. Botulinum toxin type A therapy for hemifacial spasm. Cochrane Database Syst Rev. 2020 Nov 19;11:CD004899.
16. Dysport (abobotulinumtoxinA for injection) [prescribing information]. Ipsen Biopharmaceuticals, Inc.), Wrexham, UK. September 2023.

17. Ezzeddine D, Jit R, Katz N, Gopalswamy N, Bhutani MS. Pyloric injection of botulinum toxin for treatment of diabetic gastroparesis. Gastrointest Endosc. 2002;55:920-923.
18. Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. Am J Gastroenterol. 2008;103:416-423.
19. Goldman JG. Writer's cramp. Toxicon. 2015;107(Pt A):98-104
20. Gómez-Caravaca MT, Cáceres-Redondo MT, Huertas-Fernández I, Vargas-González L, Carrillo F, Carballo M, Mir P. The use of botulinum toxin in the treatment of sialorrhea in parkinsonian disorders. Neurol Sci. 2015;36:275-279.
21. Hayes, Inc. Health Technology Assessment. Botulinum Toxin for Treatment of Pain Associated with Temporomandibular Disorders. Lansdale, PA: Hayes, Inc.,; May 28 2021.
22. Heckmann M, Ceballos-Baumann AO, Plewig G; Hyperhidrosis Study Group. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med. 2001;344:488-93.
23. Herd CP, Tomlinson CL, Rick C, Scotton WJ, Edwards J, Ives NJ, Clarke CE, Sinclair AJ. Cochrane systematic review and meta-analysis of botulinum toxin for the prevention of migraine. BMJ Open. 2019 Jul 16;9(7):e027953. Jinnah HA. Medical and Surgical Treatments for Dystonia. Neurol Clin. 2020;38:325-348.
24. Hu GC, Chuang YC, Liu JP, et al. Botulinum toxin (Dysport) treatment of the spastic gastrocnemius muscle in children with cerebral palsy: A randomized trial comparing two injection volumes. Clin Rehabil. 2009;23(1):64-71.
25. Hyman N, Barnes M, Bhakta B, et al. Botulinum toxin (Dysport) treatment of hip adductor spasticity in multiple sclerosis: A prospective, randomised, double blind, placebo controlled, dose ranging study. J Neurol Neurosurg Psychiatry. 2000;68(6):707-712.
26. Ipsen announces FDA approval of Dysport (abobotulinumtoxinA) for injection for the treatment of lower limb spasticity in children aged two and older. Press Release. Paris, France: Ipsen; August 1, 2016.
27. Jochim A, Meindl T, Huber C, et al. Treatment of blepharospasm and Meige's syndrome with abo- and onabotulinumtoxinA: long-term safety and efficacy in daily clinical practice. J Neurol. 2020 Jan;267(1):267-275. doi: 10.1007/s00415-019-09581-w. Epub 2019 Oct 19.
28. Karp BI, Atler K. Muscle Selection for Focal Limb Dystonia. Toxins (Basel). 2018;10(1):20. doi: 10.3390/toxins10010020

29. Karsai S, Raulin C. Current evidence on the unit equivalence of different botulinum neurotoxin A formulations and recommendations for clinical practice in dermatology. Dermatol Surg. 2009;35(1):1-8.
30. Khan A, Frazer-Green L, Amin R, et al,. Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report. Chest. 2023 Aug;164(2):394-413. doi: 10.1016/j.chest.2023.03.011. Epub 2023 Mar 13.
31. Kruisdijk JJM, Koelman JHTM, Ongerboer de Visser BW, et al. Botulinum toxin for writer's cramp: a randomised, placebo-controlled trial and 1-year follow-up. J Neurol Neurosurg Psychiatry. 2007; 78(3): 264–270. doi:10.1136/jnnp.2005.083170
32. Li L, Liu QS, Liu WH, et al. Treatment of obesity by endoscopic gastric intramural injection of botulinum toxin A: a randomized clinical trial. Hepatogastroenterology. 2012;59(118):2003-7.
33. Minguini N, De carvalho KM, Bosso FL, Hirata FE, Kara-josé N. Surgery with intraoperative botulinum toxin-A injection for the treatment of large-angle horizontal strabismus: a pilot study. Clinics (Sao Paulo). 2012;67(3):279-82
34. Naumann M, So Y, Argoff CE, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008;70(19):1707-14.
35. Pandey S. A practical approach to management of focal hand dystonia. Ann Indian Acad Neurol. 2015 Apr-Jun; 18(2): 146–153. doi: 10.4103/0972-2327.156563
36. Peterlein CD, Funk JF, Hölscher A, Schuh A, Placzek R. Is botulinum toxin A effective for the treatment of plantar fasciitis?. Clin J Pain. 2012;28(6):527-33.
37. Pittock SJ, Moore AP, Hardiman O, et al. A double-blind randomised placebo-controlled evaluation of three doses of botulinum toxin type A (Dysport) in the treatment of spastic equinovarus deformity after stroke. Cerebrovasc Dis. 2003;15(4):289-300.
38. Reichenbach ZW, Stanek S, Patel S, Ward SJ, Malik Z, Parkman HP, Schey R. Botulinum Toxin A Improves Symptoms of Gastroparesis. Dig Dis Sci. 2020;65:1396-1404.
39. Rodwell K, Edwards P, Ware RS, Boyd R. Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review. Dev Med Child Neurol. 2012;54(11):977-87.
40. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Cochrane Database Syst Rev. 2009;(2):CD006499.
41. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Cochrane Database Syst Rev. 2017 Mar 2;3(3):CD006499.
42. Sekmen U, Paksoy M. The Efficacy of Botulinum Toxin Injection Site in Chronic Anal Fissure Healing. Niger J Clin Pract. 2020;23:1639-1642.

43. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016;86(19):1818-26.
44. Soares A, Andriolo RB, Atallah AN, Da silva EM. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database Syst Rev. 2014;(7):CD007533.
45. Sridharan K, Sivaramakrishnan G. Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials. J Clin Neurosci. 2018;51:12-17
46. Straube A, Empl M, Ceballos-Baumann A, et al. Pericranial injection of botulinum toxin type A (Dysport) for tension-type headache - a multicentre, double-blind, randomized, placebo-controlled study. Eur J Neurol. 2008;15(3):205-213.
47. Tercica Inc. Dysport for injection (abobotulinumtoxin A). Full Prescribing Information. Brisbane, CA: Tercica; revised November 2018. Available at: https://www.ipsen.com/websites/Ipsen_Online/wp-content/uploads/sites/9/2019/01/21084019/Dysport_Full_Prescribing_Information.pdf.
48. Truong D, Comella C, Fernandez HH, Ondo WG; Dysport Benign Essential Blepharospasm Study Group. Efficacy and safety of purified botulinum toxin type A (Dysport) for the treatment of benign essential blepharospasm: A randomized, placebo-controlled, phase II trial. Parkinsonism Relat Disord. 2008;14(5):407-414.
49. Truong D, Duane DD, Jankovic J, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: Results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005;20(7):783-791.
50. Tsai CP, Chiu MC, Yen DJ, et al. Quantitative assessment of efficacy of dysport (botulinum toxin type A) in the treatment of idiopathic blepharospasm and hemifacial spasm. Acta Neurol Taiwan. 2005;14(2):61-68.
51. Tsai CP, Liu CY, Lin KP, Wang KC. Efficacy of botulinum toxin type a in the relief of Carpal tunnel syndrome: A preliminary experience. Clin Drug Investig. 2006;26(9):511-5.
52. Walshe M, Smith M, Pennington L. Interventions for drooling in children with cerebral palsy. Cochrane Database Syst Rev. 2012;11:CD008624.
53. Wong SM, Hui AC, Tong PY, Poon DW, Yu E, Wong LK. Treatment of lateral epicondylitis with botulinum toxin: a randomized, double-blind, placebo-controlled trial. Ann Intern Med. 2005;143(11):793-7.
54. Zhang H, Lian Y, et al. Two doses of botulinum toxin type A for the treatment of trigeminal neuralgia: observation of therapeutic effect from a randomized, double-blind, placebo-controlled trial. J of Headache and Pain. 2014; 15:65.

DaxibotulinumtoxinA-lanm (Daxxify)

1. Daxxify (daxibotulinumtoxinA) [prescribing information]. Newark, CA: Revance Therapeutics Inc; August 2023.
2. Khan A, Frazer-Green L, Amin R, et al,. Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report. Chest. 2023 Aug;164(2):394-413. doi: 10.1016/j.chest.2023.03.011. Epub 2023 Mar 13.
3. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124[PubMed 33144515]
4. Solish N, Carruthers J, Kaufman J, Rubio RG, Gross TM, Gallagher CJ: Overview of DaxibotulinumtoxinA for Injection: A Novel Formulation of Botulinum Toxin Type A. Drugs. 2021 Dec;81(18):2091-2101. doi: 10.1007/s40265-021-01631-w. Epub 2021 Nov 17.

OnabotulinumtoxinA (Botox)

1. 2019 surveillance of lower urinary tract symptoms in men: management (NICE guideline CG97) [Internet]. London: National Institute for Health and Care Excellence (NICE); 2019 Nov 14.
2. 2019 surveillance of urinary incontinence in neurological disease: assessment and management (NICE guideline CG148) [Internet]. London: National Institute for Health and Care Excellence (NICE); 2019 Jan 31.
3. Abdel-Fattah M, Chapple C, Guerrero K, et al,. Female Urgency, Trial of Urodynamics as Routine Evaluation (FUTURE study): a superiority randomised clinical trial to evaluate the effectiveness and cost-effectiveness of invasive urodynamic investigations in management of women with refractory overactive bladder symptoms. Trials. 2021 Oct 26;22(1):745. doi: 10.1186/s13063-021-05661-3.
4. Adam B et al: Botulinum toxin injection for treatment of chronic anal fissure: is there any dose-dependent efficiency? A meta-analysis. World J Surg. 40(12):3064-72, 2016
5. Adler CH, Factor SA, Brin M et al. Secondary nonresponsiveness to in patients with oromandibular dystonia. Mov Disord. 2002; 17:158-61.
6. Agamia NF, Sobhy N, Abd-Elraouf A, Tawfik A. Fractional CO2 Laser for Transcutaneous Drug Delivery of Onabotulinum Toxin in Palmar Hyperhidrosis. Dermatol Surg. 2021 May 1;47(5):678-683. doi: 10.1097/DSS.0000000000002901.

7. Ahmadi J, Azary S, Ashjaei B, Paragomi P, Khalifeh-soltani A. Intrasphincteric botulinum toxin injection in treatment of chronic idiopathic constipation in children. Iran J Pediatr. 2013;23(5):574-8.
8. Ahn MS, Catten M, Maas CS. Temporal brow lift using botulinum toxin A. Plast Reconstr Surg. 2000; 105:1129-35; discussion 1136-9.
9. Ailani J., Burch R., & Robbins M.S. (2021). The American Headache Society Consensus Statement: Update on integrating new migraine treatments into clinical practice. The Journal of Head and Face Pain, 61 (7), 1021-1039. Doi: https://doi.org/10.1111/head.14153
10. AIMOVIG(R) subcutaneous injection, erenumab-aooe subcutaneous injection. Amgen Inc (per FDA), Thousand Oaks, CA, 2021.
11. AJOVY(TM) subcutaneous injection, fremanezumab-vfrm subcutaneous injection. Teva Pharmaceuticals USA Inc (per FDA), North Wales, PA, 2021.
12. Alam M, Dover JS, Arndt KA. Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative: a double-blind, randomized controlled trial. Arch Dermatol. 2002; 138:510-4.
13. Albanese A, et al. EFNS guidelines on diagnosis and treatment of primary dystonias. European Journal of Neurology 2011 18(1):5 18.
14. Albanese A. Terminology for preparations of botulinum neurotoxins: what a difference a name makes. JAMA. 2011; 305:89-90.
15. Allergan Inc. Botox (onabotulinumtoxin A). Full Prescribing Information. 72284US11B, Irvine, CA: Allergan; revised May 2018. Available at: https://www.allergan.com/assets/pdf/botox_pi.pdf.
16. Allergan. Botox® (onabotulinumtoxinA) for injection prescribing information. Irvine, CA; 2017 Apr.
17. Allergan. Botox® Cosmetic (onabotulinumtoxinA) for injection prescribing information. Irvine, CA; 2017 Oct.
18. American Academy of Neurology. (May 2019). Practice Guideline Recommendations Summary: Treatment of Tics in People with Tourette Syndrome and Chronic Tic Disorders. https://www.aan.com/Guidelines/home/GuidelineDetail/958
19. Annese V, Bassotti G, Coccia G, et al. Comparison of two different formulations of botulinum toxin A for the treatment of oesophageal achalasia. The Gismad Achalasia Study Group. Aliment Pharmacol Ther. 1999;13(10):1347-50.
20. Annese V, D'Onofrio V, Andriulli A. Botulinum toxin in long-term therapy for achalasia. Ann Intern Med. 1998; 128:696.
21. Anon. Assessment: the clinical usefulness of botulinum toxin-A in treating neurologic disorders. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 1990; 40:1332-6.

22. Anon. Botox for overactive bladder. Med Lett Drugs Ther. 2013; 55(Apr 15):31-2.
23. Anon. Botulinum toxin (Botox Cosmetic) for frown lines. Med Lett Drugs Ther. 2002; 44:47-8.
24. Anon. Botulinum toxin for cervical dystonia. Med Lett Drugs Ther. 2001; 43:63-4.
25. Anon. Clinical use of botulinum toxin. NIH Consensus Statement Online 1990 Nov 12-14
26. Anon. Cosmetic use of botulinum toxin. Med Lett Drugs Ther. 1999; 41:63-4.
27. Anon. FDA approves Botox to treat severe underarm sweating. FDA talk paper. Rockville, MD: Food and Drug Administration; 2004 Jul 20.
28. Aoki KR. Evidence for antinociceptive activity of botulinum toxin type A in pain management. Headache. 2003; 43 (Suppl 1):9-15.
29. Apalla Z, Sotiriou E, Lallas A, Lazaridou E, Ioannides D. Botulinum toxin A in postherpetic neuralgia: a parallel, randomized, double-blind, single dose, placebo controlled trial. Clinical Journal of Pain 2013 29(10):857 64.
30. Arad-Cohen A, Blitzer A. Botulinum toxin treatment for symptomatic Frey's syndrome. Otolaryngol Head Neck Surg. 2000; 122:237-40.
31. Arezzo JC, Litwak MS, Gasper CA et al. The spread of paralytic activity in juvenile monkeys: a comparison of and botulinum toxin type B. Paper presented at the World Congress of Neurological Rehabilitation, Venice, Italy: 2002 Apr 2-6.
32. Argoff CE. A focused review on the use of botulinum toxins for neuropathic pain. Clin J Pain. 2002; 18(Suppl):S177-S181.
33. Armanious, M., Khalil, N., Lu, Y., & Jimenez-Sanders, R. (2021). Erenumab and OnabotulinumtoxinA combination therapy for the prevention of intractable chronic migraine without aura: A retrospective analysis. Journal of Pain & Palliative Care Pharmacotherapy, 35(1), 1-6.
34. Arnon SS, Schechter R, Inglesby TV et al for the Working Group on Civilian Biodefense. Botulinum toxin as a biologic weapon: medical and public health management. JAMA. 2001; 285:1059-70.
35. Arthurs B, Flanders M, Codere F et al. Treatment of blepharospasm with medication, surgery and type A botulinum toxin. Can J Ophthalmol. 1987; 22:24-8.
36. Aurora SK, Dodick DW, Turkel CC et al, for the PREEMPT 1 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010 Jul; 30:793-803.
37. Aurora SK, Winner P, Freeman MC et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled results of the 56-week PREEMPT clinical program. Headache. 2010; 51:1358-73.
38. Bai Y, et al. A systematic review on intrapyloric botulinum toxin injection for gastroparesis. Digestion 2010 81(1):27 34

39. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases. J Neurol Neurosurg Psychiatry. 1997; 62:198.
40. Bang CS, Baik GH, Shin IS, et al. Effect of intragastric injection of botulinum toxin A for the treatment of obesity: a meta-analysis and meta-regression. Gastrointest Endosc. 2015;81(5):1141-9.e1-7.
41. Barbehenn E, Lurie P, Stark S et al. Petition to the FDA requesting regulatory action concerning the possible spread of botulinum toxin (Botox, Myobloc) from the site of injection to other parts of the body. Washington, DC: Public Citizen's Health Research Group; 2008 Jan.
42. Barwood S, Baillieu C, Boyd R et al. Analgesic effects of botulinum toxin A: a randomized, placebo-controlled clinical trial. Dev Med Child Neurol. 2000; 42:116-21.
43. Baumann L, Black L. Botulinum toxin type B (Myobloc). Dermatol Surg. 2003; 29:496-500.
44. Baumann L, Frankel S, Welsh E et al. Cryoanalgesia with dichlorotetrafluoroethane lessens the pain of botulinum toxin injections for the treatment of palmar hyperhidrosis. Dermatol Surg. 2003; 29:1057-60.
45. Beckmann Y, Çetin Üncü F, Kurt İncesu T, Türe S. Effectiveness, Safety, and Health-Related Quality of Life of Chronic Migraine Patients Treated with Onabotulinum Toxin A. Eur Neurol. 2020;83(5):517-522. doi: 10.1159/000509853. Epub 2020 Sep 23.
46. Bell MS, Vermeulen LC, Sperling KB. Pharmacotherapy with botulinum toxin: harnessing nature's most potent neurotoxin. Pharmacotherapy. 2000; 20:1079-91.
47. Benson RA, Palin R, Holt PJ, Loftus IM. Diagnosis and management of hyperhidrosis. British Medical Journal 2013 347:f6800.
48. Berardelli A, Abbruzzese G, Bertolasi L et al. Guidelines for the therapeutic use of botulinum toxin in movement disorders. Italian Study Group for Movement Disorders, Italian Society of Neurology. Ital J Neurol Sci. 1997; 18:261-9.
49. Bhakta BB, Cozens JA, Chamberlain MA. Use of botulinum toxin in stroke patients with severe upper limb spasticity. J Neurol Neurosurg Psychiatry. 1996; 61:30-5.
50. Bhatia KP, Munchau A, Thompson PD et al. Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. J Neurol Neurosurg Psychiatry. 1999; 67:90-3.
51. Bielamowicz S, Stager SV, Badillo A et al. Unilateral versus bilateral injections of botulinum toxin in patients adductor spasmodic dysphonia. J Voice. 2002; 16:117-23.
52. Binder WJ, Brin MF, Blitzer A et al. Botulinum toxin type A (Botox®) for treatment of migraine headaches: an open-label study. Otolaryngol Head Neck Surg. 2000; 123:669-76
53. Binder WJ, Brin MF, Blitzer A et al. Botulinum toxin type A (Botox®) for treatment of migraine. Semin Cutan Med Surg. 2001; 20:93-100.

54. Bjerkhoel A, Trobbe O. Frey's syndrome: treatment with botulinum toxin. J Laryngol Otol 1997; 111:839.
55. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. J Neurol Neurosurg Psychiatry. 1990; 53:640-3.
56. Bleday, R. Anal fissure: Medical management. UpToDate.com. https://www.uptodate.com/contents/anal-fissure-medical-management?search=chronic%20anal%20fissure%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H3548935 Last updated Feb. 2020.
57. Blitzer A, Binder WJ, Aviv JE et al. The management of hyperfunctional facial lines with botulinum toxin. A collaborative study of 210 injection sites in 162 patients. Arch Otolaryngol Head Neck Surg. 1997; 123:389-92.
58. Blitzer A, Binder WJ, Brin MF. Botulinum toxin injections for facial lines and wrinkles: technique. In: Blitzer A, Binder WJ, Boyd JB et al., eds. Management of facial lines and wrinkles. Lippincott Williams & Wilkins, Philadelphia, PA; 2000:303-13.
59. Blitzer A, Brin MF, Greene PE et al. Botulinum toxin injection for the treatment of oromandibular dystonia. Ann Otol Rhinol Laryngol. 1989; 98:93-7.
60. Blitzer A, Brin MF, Stewart C., et al. Abductor laryngeal dystonia: a series treated with botulinum toxin. Laryngoscope. 1992; 102:163-7.
61. Blitzer A, Brin MF, Stewart CF. Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): a 12-year experience in more than 900 patients. Laryngoscope. 1998; 108:1435-41.
62. Blitzer A, Brin MF. Laryngeal dystonia: a series with botulinum toxin therapy. Ann Otol Rhinol Laryngol. 1991; 100:85-9.
63. Blitzer A. Botulinum neurotoxin A for the management of lower facial lines and platysmal bands. In: Lowe N, ed. Textbook of facial rejuvenation. Martin Dunitz, London; 2002:171-177.
64. Blumenfeld , Andrew. "Real-World Evidence for Control of Chronic Migraine Patients Receiving CGRP Monoclonal Antibody Therapy Added to Onabotulinumtoxina: A Retrospective Chart Review." Pain and Therapy, U.S. National Library of Medicine, Dec. 2021, https://pubmed.ncbi.nlm.nih.gov/33880725/.
65. Blumenfeld A, Evans RW. OnabotulinumtoxinA for chronic migraine. Headache. 2012 Jan; 52:142-8.
66. Blumenfeld AM, Binder W, Silberstein SD. Procedures for administering for migraine and tension-type headache. Headache. 2003; 43:884-91.
67. Böger A, Herath H, Rompel R, Ferbert A. Botulinum toxin for treatment of craniofacial hyperhidrosis. J Neurol 2000; 247:857.
68. BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use. Accessdata.fda.gov.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103000s5309lbl.pdf Updated June 2019. Accessed March 23, 2020.

69. Botox (onabotulinumtoxinA) [prescribing information]. Madison, NJ: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc.; August 2023.
70. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. nice.org.uk. https://www.nice.org.uk/Guidance/ta260. Published 2012. Accessed March 23, 2020.
71. Brandt F, Swanson N, Baumann L et al. Randomized, placebo-controlled study of a new botulinum toxin type A for treatment of glabellar lines: efficacy and safety. Dermatol Surg. 2009; 35(12):1893-901.
72. Brashear A, Gordon MF, Elovic E for the Botox Post-Stroke Spasticity Study Group. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med. 2002; 347:395- 400.
73. Brashear A, Lew MF, Dykstra DD et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology. 1999; 53:1439-46.
74. Brashear A, McAfee AL, Kuhn ER et al. Treatment with botulinum toxin type B for upper-limb spasticity. Arch Phys Med Rehabil. 2003; 84:103-7.
75. Brin MF, Binder W, Blitzer A et al. Botulinum Toxin Type A Botox® for Pain and Headache. In: Brin MF, Hallett M, Jankovic J, ed. Scientific and Therapeutic Aspects of Botulinum Toxin. Lippincott Williams & Wilkins, Philadelphia, PA; 2002.
76. Brin MF, Blitzer A, Stewart C. Laryngeal dystonia (spasmodic dysphonia): observations of 901 patients and treatment with botulinum toxin. Adv Neurol. 1998; 78:237-52.
77. Brin MF, Fahn S, Moskowitz C et al. Localized injections of botulinum toxin for the treatment of focal dystonia and hemifacial spasm. Movement Dis. 1987; 2:237-54.
78. Brin MF, Vapnek JM. Treatment of vaginismus with botulinum toxin injections. Lancet. 1997; 349:252-3.
79. Brin MF. Botulinum toxin: chemistry, pharmacology, toxicity, and immunology. Muscle Nerve Suppl. 1997; 6:S146-68.
80. Brisinda G, Cadeddu F, Brandara F, et al,. Botulinum toxin for recurrent anal fissure following lateral internal sphincterotomy. Br J Surg. 2008 Jun;95(6):774-8. doi: 10.1002/bjs.6080.
81. Brisinda G, Civello IM, Albanese A et al. Gastrointestinal smooth muscles and sphincters spasms: treatment with botulinum neurotoxin. Curr Med Chem. 2003; 10:603-23.
82. Brisinda G, Maria G, Bentivoglio AR et al. A comparison of injections of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure. N Engl J Med. 1999; 341:65-9.

83. Brown EA, Schutz SG, Simpson DM. Botulinum toxin for neuropathic pain and spasticity: an overview. Pain Management 2014 4(2):129 51. DOI: 10.2217/pmt.13.75.
84. Brown M, Williamson PR, Sutton L, et al,. Onabotulinum toxin-A versus extended release tolterodine in the management of idiopathic overactive bladder in children: A pilot randomised controlled trial (OVERT trial). J Pediatr Urol. 2021 Feb;17(1):77.e1-77.e12. doi: 10.1016/j.jpurol.2020.10.012. Epub 2020 Oct 19.
85. Bushara KO, Park DM, Jones JC et al. Botulinum toxin—a possible new treatment for axillary hyperhidrosis. Clin Exp Dermatol. 1996; 21:276-8.
86. Cady RK, Schreiber CP, Porter JAH et al. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache. 2011; 51(1): 21-32.
87. Callaway JE, Arezzo JC, Grethlein AJ. Botulinum toxin type B: an overview of its biochemistry and preclinical pharmacology. Semin Cutan Med Surg. 2001; 20:127-36.
88. Campanati A, Giuliodori K, Martina E et al. Onabotulinumtoxin type A (Botox(®)) versus Incobotulinumtoxin type A (Xeomin(®)) in the treatment of focal idiopathic palmar hyperhidrosis: results of a comparative double-blind clinical trial. J Neural Transm. 2014 Jan; 121:21-6.
89. Cantarella G, Berlusconi A, Mele V, et al. Treatment of Frey's syndrome with botulinum toxin type B. Otolaryngol Head Neck Surg. 2010;143(2):214-218.
90. Carr LJ, Cosgrove AP, Gingras P et al. Position paper on the use of botulinum toxin in cerebral palsy. Arch Dis Child. 1998; 79:271-3.
91. Carruthers A, Carruthers J, Cohen J. A prospective, double-blind, randomized, parallel- group, dose-ranging study of botulinum toxin type a in female subjects with horizontal forehead rhytides. Dermatol Surg. 2003; 29:461-7.
92. Carruthers J, Carruthers A. Aesthetic botulinum A toxin in the mid and lower face and neck. Dermatol Surg. 2003; 29:468-76.
93. Carruthers JA, Lowe NJ, Menter MA et al. A multicenter, double-blind, randomized, placebo-controlled study of the efficacy and safety of botulinum toxin type A in the treatment of glabellar lines. J Am Acad Dermatol. 2002; 46:840-9.
94. Carruthers JD, Carruthers JA. Treatment of glabellar frown lines with C. botulinum-A exotoxin. J Dermatol Surg Oncol. 1992; 18:17-21.
95. Carruthers JDA, Carruthers A. Botulinum toxin and laser resurfacing for lines around the eyes. In: Blitzer A, Binder WJ, Boyd JB et al., eds. Management of facial lines and wrinkles. Lippincott Williams & Wilkins, Philadelphia, PA; 2000:315-32.
96. Carruthers JDA, Kennedy RA, Bagaric D. Botulinum vs adjustable suture surgery in the treatment of horizontal misalignment in adult patients lacking fusion. Arch Ophthalmol. 1990; 108:1432-5.

97. Carruthers JDA. Ophthalmologic use of botulinum A exotoxin. Can J Ophthalmol. 1985; 20:135-41.
98. Centeno RF, Boswell CB, Matarasso A. Botulinum toxin for managing focal hyperhidrosis. Aesthetic Surg J. 2003; 23:67-9.
99. Chancellor MB, et al. Evidence based review and assessment of botulinum neurotoxin for the treatment of urologic conditions. Toxicon 2013 67:129 40.
100. Chapman MA, Barron R, Tanis DC et al. Comparison of botulinum neurotoxin preparations for the treatment of cervical dystonia. Clin Ther. 2007; 29:1325-37.
101. Chapple C, Sievert KD, MacDiarmid S et al. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomised, double-blind, placebo-controlled trial. Eur Urol. 2013 Aug; 64:249-56.
102. Chartier-Kastler E, Mehnert U, Denys P, Giuliano F. Botulinum neurotoxin A for male lower urinary tract symptoms. Current Opinion in Urology 2011 21(1):13 21.
103. Chen HL, et al. Botulinum toxin injection versus lateral internal sphincterotomy for chronic anal fissure: a meta- analysis of randomized control trials. Techniques in Coloproctology 2014 18(8):693 8.
104. Chen RS, Lu CS, Tsai CH. Botulinum toxin A injection in the treatment of hemifacial spasm. Acta Neurol Scand. 1996; 94:207-11.
105. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: a review, part 1. Am J Health Syst Pharm. 2006; 63:145-52.
106. Chertow DS, Tan ET, Maslanka SE et al. Botulism in 4 adults following cosmetic injections with an unlicensed, highly concentrated botulinum preparation. JAMA. 2006; 296:2476-9.
107. Chhina H, Howren A, Simmonds A, Alvarez CM. Onabotulinumtoxin A injections: A safety review of children with clubfoot under 2 years of age at BC Children's Hospital. European Journal of Paediatric Neurology 2014 18(2):171 5
108. Childers MK, Brashear A, Jozefczyk P at al. Dose-dependent response to intramuscular botulinum toxin type A for upper-limb spasticity in patients after a stroke. Arch Phys Med Rehabil. 2004 Jul; 85:1063-9.
109. Ching J, Tinsley A, Rothrock J. Prognosis Following Discontinuation of OnabotulinumA Therapy in "Super-responding" Chronic Migraine Patients. Headache. 2019 Sep;59(8):1279-1285. doi: 10.1111/head.13630. Epub 2019 Sep 9.
110. Chiu SY, Patel B, Burns MR, et al,. High-dose Botulinum Toxin Therapy: Safety, Benefit, and Endurance of Efficacy. Tremor Other Hyperkinet Mov (N Y). 2020 Feb 27;10. doi: 10.7916/tohm.v0.749.

111. Chughtai B, et al. Randomized, double-blind, placebo controlled pilot study of intra-detrusor injections of onabotulinumtoxinA for the treatment of refractory overactive bladder persisting following surgical management of benign prostatic hyperplasia. Canadian Journal of Urology 2014;21(2):7217 21.
112. Cipullo LM, et al. Pharmacological approach to overactive bladder and urge urinary incontinence in women: an overview. European Journal of Obstetrics, Gynecology, and Reproductive Biology 2014;174:27 34.
113. Cobb DB, Watson WA, Fernandez MC. Botulism-like syndrome after injections of botulinum toxin. Vet Hum Toxicol. 2000 Jun; 42:163.
114. Cohen, F., Armand, C., Lipton, R. B., & Vollbracht, S. (2021). Efficacy and tolerability of calcitonin gene-related peptide-targeted monoclonal antibody medications as add-on therapy to onabotulinumtoxinA in patients with chronic migraine. Pain Medicine, 22(9), 1857-1863.
115. Cohen DA, Savino PJ, Stern MB et al. Botulinum injection therapy for blepharospasm: review and report of 75 patients. Clin Neuropharmacol. 1986; 9:415-29.
116. Cohen S, Parkman HP. Treatment of achalasia—from whalebone to botulinum toxin. N Engl J Med. 1995; 332:815-6.
117. Corry IS, Cosgrove AP, Duffy CM et al. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. J Pediatr Orthop. 1998; 18:304-11.
118. Corry IS, Cosgrove AP, Walsh EG et al. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. Dev Med Child Neurol. 1997; 39:185-93.
119. Costa J, Espirito-Santo CC, Borges AA et al. Botulinum toxin type A therapy for cervical dystonia (review). Cochrane Database of Systematic Reviews. 2005, Issue 1. Article No: CD003633.
120. Coté TR, Mohan AK, Polder JA et al. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J Am Acad Dermatol. 2005; 53:407-15.
121. Cox L, Cameron AP. OnabotulinumtoxinA for the treatment of overactive bladder. Research and Reports in Urology 2014;6:79 89.
122. Crawford ED, Hirst K, Kusek JW et al. Effects of 100 and 300 units of onabotulinum toxin A on lower urinary tract symptoms of benign prostatic hyperplasia: A phase II randomized clinical trial. J Urol. 2011 Sep; 186: 965–70.
123. Cruccu G, Truini A. Refractory trigeminal neuralgia. Non surgical treatment options. CNS Drugs 2013;27(2):91 6.

124. Cummings RJ. The effectiveness of botulinum A toxin as an adjunct to the treatment of clubfeet by the Ponseti method: a randomized, double blind, placebo controlled study. Journal of Pediatric Orthopedics 2009 29(6):564 9.
125. Cvach K, Rosamilia A. Review of intravesical therapies for bladder pain syndrome/interstitial cystitis. Transl Androl Urol. 2015;4(6):629-37.
126. Davids JS, Hawkins AT, et al,. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anal Fissures. Dis Colon Rectum. 2023 Feb 1;66(2):190-199. doi: 10.1097/DCR.0000000000002664. Epub 2022 Nov 1.
127. Davies J, Duffy D, Boyt N et al. Botulinum toxin (Botox) reduces pain after hemorrhoidectomy. Dis Colon Rectum. 2003; 46:1097-1102.
128. Demiryurek BE. Botulinum Toxin Monotherapy for the Treatment of Essential Tremor: Life Quality Effect. Clin Neuropharmacol. 2021 Jan-Feb 01;44(1):1-4. doi: 10.1097/WNF.0000000000000428.
129. de Seze M, Petit H, Gallien P et al. Botulinum A toxin and detrusor sphincter dyssynergia: a double-blind lidocaine-controlled study in 13 patients with spinal cord disease. Eur Urol. 2002; 42:56-62.
130. Desiato MT, Risina B. The role of botulinum toxin in the neuro-rehabilitation of young patients with brachial plexus birth palsy. Pediatr Rehabil. 2001 Jan-Mar;4(1):29-36. doi: 10.1080/13638490151068456.
131. Desloovere K, Molenaers G, Jonkers I et al. A randomized study of combined and casting in the ambulant child with cerebral palsy using objective outcome measures. Eur J Neurol. 2001; 8 Suppl 5:75-87.
132. Diener HC, Dodick DW, Aurora SK et al, for the PREEMPT 2 Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010; 30:804–14.
133. Dodick DW, Silberstein SD, Lipton RB, DeGryse RE, Adams AM, Diener HC. Early onset of effect of onabotulinumtoxinA for chronic migraine treatment: Analysis of PREEMPT data. Cephalalgia. 2019 Jul;39(8):945-956. doi: 10.1177/0333102418825382. Epub 2019 May 21.
134. Dodick DW, Turkel CC, Degryse RE et al. OnabotulinumtoxinA for treatment of chronic migraine: a response. Headache. 2011 Jun; 51(6):1005-8. Reply.
135. Donahue SP. Botulinum toxin treatment for esotropia. American Orthoptic Journal 2013 63:29 31.
136. Dressler D, Adib Saberi F, Benecke R. Botulinum toxin type B for treatment of axillar hyperhidrosis. J Neurol. 2002; 249:1729-32.
137. Dressler D, Benecke R. Autonomic side effects of botulinum toxin type B treatment of cervical dystonia and hyperhidrosis. Eur Neurol. 2003; 49:34- 8.

138. Dressler D, Bigalke H, Benecke R. Botulinum toxin type B in antibody-induced therapy failure. J Neurol. 2003; 250:967-9.
139. Dressler D. Routine use of Xeomin in patients previously treated with Botox: long term results. Eur J Neurol. 2009; 16 Suppl 2:2-5.
140. Drobik C, Laskawi R. Frey's syndrome: treatment with botulinum toxin. Acta Otolaryngol. 1995; 115:459-61.
141. Duarte A, Coutinho L, Germiniani FMB, Teive HAG. Effects of onabotulinum toxin type A injections in patients with Meige's syndrome. Arq Neuropsiquiatr. 2024 Apr;82(4):1-7. doi: 10.1055/s-0044-1785691. Epub 2024 Apr 19.
142. Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database of Systematic Reviews 2011, Issue 12. Art. No.: CD005493.
143. Elia AE, Filippini G, Calandrella D et al. Botulinum neurotoxins for post-stroke spasticity in adults: a systematic review. Movement Disorders. 2009; 24(6):801-l2.
144. Elston JS, Russell RWR. Effect of treatment with botulinum toxin on neurogenic blepharospasm. BMJ. 1985; 290:1857-9.
145. EMGALITY(TM) subcutaneous injection, galcanezumab-gnlm subcutaneous injection. Eli Lilly and Company (per manufacturer), Indianapolis, IN, 2021.
146. Eslamian F, Dolatkhah N, Fallah L, Jahanjoo F, Toopchizadeh V, Talebi M. Effectiveness of Botulinum Toxin on Hand Tremor Intensity and Upper Limb Function in Patients with Parkinson's Disease: Results of a Systematic Review. Tremor Other Hyperkinet Mov (N Y). 2023 Aug 24;13:27. doi: 10.5334/tohm.773.
147. EAU Guidelines. Edn. presented at the EAU Annual Congress Paris 2024. ISBN 978-94-92671-23-3.
148. Evers S, Rahmann A, Vollmer-Haase J et al. Treatment of headache with botulinum toxin A--a review according to evidence-based medicine criteria. Cephalalgia. 2002; 22:699-710.
149. Fagien S, Cohen JL, Coleman W et al. Forehead line treatment with onabotulinumtoxinA in subjects with forehead and glabellar facial rhytids: a phase 3 study. Dermatol Surg. 2017; 43:S274-S284.
150. Fehlings D, et al. Botulinum toxin assessment, intervention and follow-up for paediatric upper limb hypertonicity: international consensus statement. European Journal of Neurology 2010 17 Suppl 2:38 56.
151. Fehlings D, Rang M, Glazier J et al. An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. J Pediatr. 2000; 137:331-7.
152. Ferreira JJ, Costa J, Coelho M et al. The management of cervical dystonia. Expert Opin Pharmacother. 2007; 8:129-40.

153. Ferreira JJ, Mestre TA, Lyons KE, et al,. MDS evidence-based review of treatments for essential tremor. Mov Disord. 2019 Jul;34(7):950-958. doi: 10.1002/mds.27700. Epub 2019 May 2.
154. Figgit DP, Noble S. Botulinum toxin B: A review of its therapeutic potential in the management of cervical dystonia. Drugs. 2002; 62:705-2.
155. Fishman VM, Parkman HP, Schiano TD et al. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. Am J Gastroenterol. 1996; 91:1724-30.
156. Flett PJ, Stern LM, Waddy H et al. Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. J Paediatr Child Health. 1999; 35:71-7.
157. Foster L, Clapp L, Erickson M, Jabbari B. Botulinum toxin A and chronic low back pain. Neurology. 2001;56:1290-1293.
158. Fowler CJ, et al. OnabotulinumtoxinA improves health- related quality of life in patients with urinary incontinence due to idiopathic overactive bladder: a 36 week, double =blind, placebo-controlled, randomized, dose- ranging trial. European Urology 2012 62(1):148 57.
159. Foxx-Orenstein AE et al: Common anorectal disorders. Gastroenterol Hepatol (N Y). 10(5):294-301, 2014
160. Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with botulinum toxin A: a pilot study. Headache. 2000; 40:231-6.
161. Freund BJ, Schwartz M. Use of botulinum toxin in chronic whiplash-associated disorder. Clin J Pain. 2002; 18:S163-8.
162. Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs: a help or a hindrance?. Biologics. 2010; 4:325-32.
163. Friedmacher F, Puri P. Comparison of posterior internal anal sphincter myectomy and intrasphincteric botulinum toxin injection for treatment of internal anal sphincter achalasia: a meta analysis. Pediatric Surgery International 2012 28(8):765 71.
164. Gallien P, Robineau S, Verin M et al. Treatment of detrusor sphincter dyssynergia by transperineal injection of botulinum toxin. Arch Phys Med Rehabi. 1998; 79:715-7.
165. Garcia A, Fulton JE Jr. Cosmetic denervation of the muscles of facial expression with botulinum toxin. A dose-response study. Dermatol Surg. 1996; 22:39-43.
166. Gassner HG, Sherris DA. Addition of an anesthetic agent to enhance the predictability of the effects of injections: a randomized controlled study. Mayo Clin Proc. 2000; 75:701-4.
167. George SM, Atkinson LR, Farrant PB, Shergill BS. Botulinum toxin for focal hyperhidrosis of the face. Br J Dermatol 2014; 170:211.
168. Gerwin R. Botulinum toxin treatment of myofascial pain: a critical review of the literature. Current Pain and Headache Reports 2012 16(5):413 22.

169. Ginsberg D, Gousse A, Keppenne V et al. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. J Urol. 2012; 187:2131-9.
170. Giordano CN, Matarasso SL, Ozog DM. Injectable and topical neurotoxins in dermatology: Indications, adverse events, and controversies. J Am Acad Dermatol. 2017; 76:1027-1042.
171. Glogau RG. Botulinum A neurotoxin for axillary hyperhidrosis. No sweat Botox. Dermatol Surg. 1998; 24:817-9.
172. Glogau RG. Review of the use of botulinum toxin for hyperhidrosis and cosmetic purposes. Clin J Pain. 2002; 18(6 Suppl):S191-7.
173. Gordon JM, Eaker EY. Prospective study of esophageal botulinum toxin injection in high-risk achalasia patients. Am J Gastroenterol. 1997; 92:1812-7.
174. Gordon K, Cadera W, Hinton G. Successful treatment of hereditary trembling chin with botulinum toxin. J Child Neurol. 1993; 8:154-6.
175. Gordon MF, Brashear A, Elovic E et al. Repeated dosing of botulinum toxin type A for upper limb spasticity following stroke. Neurology. 2004; 63:1971-3.
176. Graham HK, Aoki KR, Autti-Ramo I et al. Recommendations for the use of in the management of cerebral palsy. Gait Posture. 2000; 11:67-79.
177. Grazzi L. Onabotulinum toxin A for treatment of chronic migraine with medication overuse. Neurol Sci. 2013 May;34 Suppl 1:S27-8. doi: 10.1007/s10072-013-1381-1.
178. Greene P, Fahn S, Diamond B. Development of resistance to in patients with torticollis. Mov Disord. 1994; 9:213-7.
179. Greene P, Kang U, Fahn S et al. Double-blind, placebo-controlled trial of botulinum toxin injections for the treatment of spasmodic torticollis. Neurology. 1990; 40:1213-8.
180. Grosse J, Kramer G, Stöhrer M. Success of repeat detrusor injections of botulinum A toxin in patients with severe neurogenic detrusor overactivity and incontinence. Eur Urol. 2005; 47:653–9.
181. Guerrissi JO. Intraoperative injection of botulinum toxin A into orbicularis oculi muscle for the treatment of crow's feet. Plast Reconstr Surg. 2000; 105:2219-25; discussion 2226-8.
182. Guyuron B, Huddleston SW. Aesthetic indications for botulinum toxin injection. Plast Reconstr Surg. 1994; 93:913-8.
183. Hallett M, et al. Evidence based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon 2013 67:94 114.
184. Hallett M. One man's poison—clinical applications of botulinum toxin. N Engl J Med. 1999; 341:118-20.
185. Hartmann A, Worbe Y. Pharmacological treatment of Gilles de la Tourette syndrome. Neuroscience and Bio-behavioral Reviews 2013 37(6):1157 61.

186. Heckmann M, Heyer GH, Brunner B et al. Botulinum toxin type A injection in the treatment of lichen simplex: an open pilot study. J Am Acad Dermatol. 2002; 46:617-9.
187. Hellman A, Torres -Russotto D. Botulinum toxin in the management of blepharospasm: current evidence and recent developments. Therapeutic Advances in Neurological Disorders 2015 8(2):82 91.
188. Hermanowicz N, Truong DD. Treatment of oromandibular dystonia with botulinum toxin. Laryngoscope. 1991; 101:1216-8.
189. Herzig DO, Lu KC. Anal fissure. Surgical Clinics of North America 2010 90(1):33 44, Table of Contents
190. Hesse S, Krajnik J, Luecke D et al. Ankle muscle activity before and after botulinum toxin therapy for lower limb extensor spasticity in chronic hemiparetic patients. Stroke. 1996; 27:455-60.
191. Hesse S, Reiter F, Konrad M et al. Botulinum toxin type A and short-term electrical stimulation in the treatment of upper limb flexor spasticity after stroke: a randomized, double-blind, placebo-controlled trial. Clin Rehabil. 1998; 12:381-8.
192. Hexsel DM, Trindade de Almeida T, Rutowitsch M et al. Multicenter, double-blind study of the efficacy of injections of reconstituted up to six weeks before application. Dermatol Surg. 2003; 29:523-9.
193. Higuero T: Update on the management of anal fissure. J Visc Surg. 152(2 suppl):S37-43, 2015
194. Hoare BJ, Wallen MA, Imms C, Villanueva E, Rawicki HB, Carey L. Botulinum toxin A as an adjunct to treatment in the management of the upper limb in children with spastic cerebral palsy (UPDATE). Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD003469
195. Hosp C, Naumann MK, Hamm H. Botulinum toxin treatment of autonomic disorders: Focal hyperhidrosis and sialorrhea. Seminars in Neurology 2016 36(1):20 8.
196. Houltram J, Noble I, Boyd RN et al. Botulinum toxin type A in the management of equinus in children with cerebral palsy: an evidence-based economic evaluation. Eur J Neurol. 2001; 8 Suppl 5:194-202.
197. Huang W, Foster JA, Rogachefsky AS. Pharmacology of botulinum toxin. J Am Acad Dermatol. 2000; 43:249-59.
198. Ipsen Biopharmaceuticals, Inc. Dysport® for injection (abobotulinumtoxinA) prescribing information. Basking Ridge, NJ; 2017 Sep.
199. Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta analysis. Journal of the American Medical Association 2012 307(16):1736-45.
200. Jankovic J, Brin MF. Botulinum toxin: historical perspective and potential new indications. Muscle Nerve Suppl. 1997; 6:129-45.

201. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med. 1991; 324:1186-94.
202. Jankovic J, et al. Primary results from the Cervical Dystonia Patient Registry for Observation of OnabotulinumtoxinA Efficacy (CD PROBE). Journal of the Neurological Sciences 2015;349(1 2):84 93.
203. Jankovic J, Orman J. Botulinum A toxin for cranial-cervical dystonia: double-blind, placebo-controlled study. Neurology. 1987; 37:616-23.
204. Jankovic J, Schwartz K, Clemence W et al. A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Mov Disord. 1996; 11:250-256.
205. Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. J Neurol Neurosurg Psychiatry. 1990; 53:633-9.
206. Jankovic J, Schwartz K. Botulinum toxin injections for cervical dystonia. Neurology. 1990; 40:277-80.
207. Jankovic J, Schwartz K. Botulinum toxin treatment of tremors. Neurology. 1991; 41:1185-8.
208. Jankovic J, Schwartz K. Response and immunoresistance to botulinum toxin injections. Neurology. 1995; 45:1743-6.
209. Jankovic J, Schwartz K. Response and immunoresistance to botulinum toxin injections. Neurology. Sep; 45:1743-6.
210. Jankovic J, Schwartz KS. Clinical correlates of response to botulinum toxin injections. Arch Neurol. 1991; 48:1253-6.
211. Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. Neurology. 2003; 60:1186-8.
212. Jesitus J. Bogus Botox sounds wake-up call. Cosm Surg Times
213. Jochim A, Meindl T, Huber C, et al. Treatment of blepharospasm and Meige's syndrome with abo- and onabotulinumtoxinA: long-term safety and efficacy in daily clinical practice. J Neurol. 2020 Jan;267(1):267-275. doi: 10.1007/s00415-019-09581-w. Epub 2019 Oct 19.
214. Johnson EA. Clostridial toxins as therapeutic agents: benefits of nature's most toxic proteins. Annu Rev Microbiol. 1999; 53:551-75.
215. Jost WH, Schimrigk K. Therapy of anal fissure using botulin toxin. Dis Colon Rectum. 1994; 37:1321-4.
216. Jost WH, Schrank B. Repeat botulin toxin injections in anal fissure: in patients with relapse and after insufficient effect of first treatment. Dig Dis Sci. 1999; 44:1588-9.
217. Joyce KE, Beyer F, Thomson RG, Clarke MP. A systematic review of the effectiveness of treatments in altering the natural history of intermittent exotropia. British Journal of Ophthalmology 2015;99(4):440 50

218. Kaji R, Osako Y, Suyama K et al. Botulinum toxin type A in post-stroke upper limb spasticity. Curr Med Res Opin. 2010; 26:1983-92.
219. Kaji R, Osako Y, Suyama K et al. Botulinum toxin type A in post-stroke upper limb spasticity. Curr Med Res Opin. 2010; 8:1983-92.
220. Kalra HK, Magoon EH. Side effects of the use of botulinum toxin for treatment of benign essential blepharospasm and hemifacial spasm. Ophthalmic Surg. 1990; 21:335-8.
221. Kane MA, Rohrich RJ, Narins RS et al. Evaluation of variable-dose treatment with a new U.S. botulinum toxin type A (Dysport) for correction of moderate to severe glabellar lines: results from a phase 3, randomized, double-blind, placebo-controlled study. Plast Reconstr Surg. 2009; 124(5):1619-29.
222. Karamfilov T, Konrad H, Karte K et al. Lower relapse rate of botulinum toxin A therapy for axillary hyperhidrosis by dose increase. Arch Dermatol. 2000; 136:487-90.
223. Kayikcioglu A, Erk Y, Mavili E. Botulinum toxin in the treatment of zygomatic fractures. Plast Reconstr Surg. 2003; 111:341-6.
224. Keen M, Blitzer A, Aviv J et al. Botulinum toxin A for hyperkinetic facial lines: results of a double-blind, placebo-controlled study. Plast Reconstr Surg. 1994; 94:94-9.
225. Keizer SB, Rutten HP, Pilot P et al. Botulinum toxin injection versus surgical treatment for tennis elbow: a randomized pilot study. Clin Orthop. 2002; 401:125-31.
226. Khan A, Frazer-Green L, Amin R, et al,. Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report. Chest. 2023 Aug;164(2):394-413. doi: 10.1016/j.chest.2023.03.011. Epub 2023 Mar 13.
227. Kirazli Y, On AY, Kismali B et al. Comparison of phenol block and botulinus toxin type A in the treatment of spastic foot after stroke. Am J Phys Med Rehabil. 1998; 77:510-5.
228. Khashab MA, Vela MF, Thosani N, et al. ASGE guideline on the management of achalasia. Gastrointest Endosc. 2020 Feb;91(2):213-227.e6. doi: 10.1016/j.gie.2019.04.231. Epub 2019 Dec 13.
229. Klein AW, Glogau RG. Botulinum toxin: beyond cosmesis. Arch Dermatol. 2000; 136:539-41.
230. Klein AW. Complications and adverse reactions with the use of botulinum toxin. Semin Cutan Med Surg. 2001; 20:109-20.
231. Klein AW. Dilution and storage of botulinum toxin. Dermatol Surg. 1998; 24:1179-80.
232. Klein AW. Treatment of wrinkles with Botox. Curr Probl Dermatol. 2002; 30:188-217.
233. Kolbasnik J, Waterfall WE, Fachnie B, Chen Y, Tougas G. Long-term efficacy of Botulinum toxin in classical achalasia: a prospective study. Am J Gastroenterol. 1999 Dec;94(12):3434-9. doi: 10.1111/j.1572-0241.1999.01605.x.

234. Kollewe K, Mohammadi B, Dengler R, Dressler D. Hemifacial spasm and reinnervation synkinesias: long-term treatment with either Botox or Dysport. Journal of Neural Transmission 2010;117(6):759 63.
235. Koman LA, Brashear A, Rosenfeld S et al. Botulinum toxin type A neuromuscular blockade in the treatment of equinus foot deformity in cerebral palsy: a multicenter, open-label clinical trial. Pediatrics. 2001 Nov; 108:1062-71.
236. Koman LA, Mooney JF III, Smith B et al. Management of cerebral palsy with botulinum-A toxin: preliminary investigation. J Pediatr Orthop. 1993; 13:489-95.
237. Koman LA, Mooney JF III, Smith BP et al. Botulinum toxin type A neuromuscular blockade in the treatment of lower extremity spasticity in cerebral palsy: a randomized, double-blind, placebo-controlled trial. BOTOX Study Group. J Pediatr Orthop. 2000; 20:108-15.
238. Koman LA, Mooney JF III, Smith BP et al. Management of spasticity in cerebral palsy with botulinum-A toxin: report of a preliminary, randomized, double-blind trial. J Pediatr Orthop. 1994; 14:299-303.
239. Koman LA, Smith BP, Balkrishnan R. Spasticity associated with cerebral palsy in children. Pediatr Drugs. 2003; 5:11-23.
240. Koog YH, Min BI. Effects of botulinum toxin A on calf muscles in children with cerebral palsy: a systematic review. Clinical Rehabilitation 2010;24(8):685 700
241. Krack P, Deuschl G, Benecke R et al. Dose standardization of botulinum toxin. Mov Disord. 1998; 13:749-51.
242. Kraft SP, Lang AE. Botulinum toxin injections in the treatment of blepharospasm, hemifacial spasm, and eyelid fasciculations. Can J Neurol Sci. 1988; 15:276-80.
243. Kuo HC. Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. J Urol. 2003; 170:1908-12.
244. Kuo HC. Effect of botulinum a toxin in the treatment of voiding dysfunction due to detrusor underactivity. Urology. 2003; 61:550-4.
245. L'Hommedieu C, Stough R, Brown L et al. Potentiation of neuromuscular weakness in infant botulism by aminoglycosides. J Pediatr. 1979; 95:1065–70.
246. Laccourreye O, Akl E, Gutierrez-Fonseca R et al. Recurrent gustatory sweating (Frey syndrome) after intracutaneous injection of botulinum toxin type A: incidence, management, and outcome. Arch Otolaryngol Head Neck Surg. 1999; 125:283-6.
247. Lakraj AA, Moghimi N, Jabbari B. Hyperhidrosis: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel) 2013;5(4):821 40.
248. Lakraj AA, Moghimi N, Jabbari B. Sialorrhea: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel) 2013;5(5):1010 31

249. Lang AM. Botulinum toxin therapy for myofascial pain disorders. Curr Pain Headache Rep. 2002; 6:355-60.
250. Lange DJ, Rubin M, Greene PE et al. Distant effects of locally injected botulinum toxin: a double-blind study of single fiber EMG changes. Muscle Nerve. 1991; 14:672-5.
251. Latimer PR, Hodgkins PR, Vakalis AN et al. Necrotising fasciitis as a complication of botulinum toxin injection. Eye. 1998; 12(Part 1):51-3.
252. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Cochrane Database of Systematic Reviews 2014, Issue 12. Art. No.: CD005046.
253. Linsenmeyer TA. Use of botulinum toxin in individuals with neurogenic detrusor overactivity: State of the art review. J Spinal Cord Med. 2013; 36:402-19.
254. Linsenmeyer TA. Use of botulinum toxin in individuals with neurogenic detrusor overactivity: state of the art review. Journal of Spinal Cord Medicine 2013 36(5):402 19.
255. Lipton RB. Varon SF, Grosberg B et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. Neurology. 2011; 77:1465-72.
256. Long H, Liao Z, Wang Y, Liao L, Lai W. Efficacy of botulinum toxins on bruxism: an evidence-based review. Int Dent J. 2012;62(1):1-5.
257. Love SC, et al. Botulinum toxin assessment, intervention and aftercare for lower limb spasticity in children with cerebral palsy: international consensus statement. European Journal of Neurology 2010 17 Suppl 2:9 37.
258. Love SC, Valentine JP, Blair EM et al. The effect of on the functional ability of the child with spastic hemiplegia: a randomized controlled trial. Eur J Neurol. 2001; 8 (Suppl 5):50-8.
259. Lowe NJ, Glaser DA, Eadie N, Daggett S, Kowalski JW, Lai PY. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52 week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. Journal of the American Academy of Dermatology 2007 56(4):604 11.
260. Lowe NJ, Lask G, Yamauchi P et al. Bilateral, double-blind, randomized comparison of 3 doses of and placebo in patients with crow's feet. J Am Acad Dermatol. 2002; 47:834-40.
261. Lowe NJ, Maxwell A, Harper H. Botulinum A exotoxin for glabellar folds: a double-blind, placebo-controlled study with an electromyographic injection technique. J Am Acad Dermatol. 1996; 35:569-72.
262. Lowe NJ, Yamauchi PS, Lask GP et al. Botulinum toxins types A and B for brow furrows: preliminary experiences with type B toxin dosing. J Cosmet Laser Ther. 2002; 4:15-8.
263. Lowe NJ, Yamauchi PS, Lask GP, et al. Efficacy and safety of botulinum toxin type a in the treatment of palmar hyperhidrosis: a double-blind, randomized, placebo-controlled study. Dermatol Surg 2002; 28:822.

264. Lyseng-Williamson KA, Frampton JE. OnabotulinumtoxinA (BOTOX®): A guide to its use in preventing headaches in adults with chronic migraine. CNS Drugs. 2012; 26(8):717-23.
265. MacDiarmid S, Glazier DB, McCrery RJ, et al,. Efficacy and safety of an alternative onabotulinumtoxinA injection paradigm for refractory overactive bladder. Neurourol Urodyn. 2024 Jan;43(1):31-43. doi: 10.1002/nau.25290. Epub 2023 Sep 25.
266. Madoff RD, Fleshman JW. AGA technical review on the diagnosis and care of patients with anal fissure. Gastroenterology. 2003; 124:235-45.
267. Madoff RD. Pharmacologic therapy for anal fissure. N Engl J Med. 1998; 338:257-9.
268. Magoon E, Dakoske C. Botulinum toxin injection for vertical strabismus. Am Orthop J. 1985; 35:48-52.
269. Magoon EH. Chemodenervation of strabismic children. Ophthalmology. 1989; 96:931-4.
270. Mall V, Glocker FX, Frankenschmidt A et al. Treatment of neuropathic bladder using botulinum toxin A in a 1-year-old child with myelomeningocele. Pediatr Nephrol. 2001; 16:1161-2.
271. Mangera A, et al. An updated systematic review and statistical comparison of standardised mean outcomes for the use of botulinum toxin in the management of lower urinary tract disorders. European Urology 2014 65(5):981 990.
272. Mangera A, et al. Contemporary management of lower urinary tract disease with botulinum toxin A: a systematic review of botox (onabotulinumtoxinA) and dysport (abobotulinumtoxinA). European Urology 2011 60(4):784 95
273. Marberger M, et al. A randomized double-blind placebo controlled phase 2 dose ranging study of onabotulinumtoxinA in men with benign prostatic hyperplasia. European Urology 2013 63(3):496-503
274. Marchal C, Perez JE, Herrera B, Machuca FJ, Redondo M. The use of botulinum toxin in benign prostatic hyperplasia. Neurourology and Urodynamics 2012 31(1):86 92
275. Maria G, Brisinda G, Civello IM et al. Relief by botulinum toxin of voiding dysfunction due to benign prostatic hyperplasia: results of a randomized, placebo-controlled study. Urology. 2003; 62:264-5. Reply.
276. Maria G, Cassetta E, Gui D et al. A comparison of botulinum toxin and saline for the treatment of chronic anal fissure. N Engl J Med. 1998; 338:217-20.
277. Markert RJ, Solomon GD. OnabotulinumtoxinA for treatment of chronic migraine. Headache. 2011; 51:1002-3. Letter.
278. Markey AC. Botulinum A exotoxin in cosmetic dermatology. Clin Exp Dermatol. 2000; 25:173-5.
279. Martinelli D, Arceri S, De Icco R, et al,. BoNT-A efficacy in high frequency migraine: an open label, single arm, exploratory study applying the PREEMPT paradigm. Cephalalgia. 2022 Feb;42(2):170-175. doi: 10.1177/03331024211034508. Epub 2021 Aug 18.
280. Matarasso A, Deva AK. Botulinum toxin. Plast Reconstr Surg. 2002; 109:1191-7.

281. Matarasso A, Matarasso SL, Brandt FS et al. Botulinum A exotoxin for the management of platysma bands. Plast Reconstr Surg. 2003; 112:127-34S.
282. Matarasso A, Matarasso SL. Botulinum A exotoxin for the management of platysma bands. Plast Reconstr Surg. 2003; 112:138-140S.
283. Matarasso SL, Matarasso A. Treatment guidelines for botulinum toxin type A for the periocular region and a report on partial upper lip ptosis following injections to the lateral canthal rhytids. Plast Reconstr Surg. 2001; 108:208-14,215-7.
284. Matarasso SL. Comparison of botulinum toxin types A and B: a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides. Dermatol Surg. 2003; 29:7-13.
285. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxinA (BOTOX®) and topiramate (TOPAMAX®) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009; 49: 1466-78.
286. Mauriello JA Jr, Coniaris H, Haupt EJ. Use of botulinum toxin in the treatment of one hundred patients with facial dyskinesias. Ophthalmology. 1987; 94:976-9.
287. McCann JD, Ugurbas SH, Goldberg RA. Benign essential blepharospasm. Int Ophthalmol Clin. 2002; 42:113-21.
288. Mehta S, et al. Meta- analysis of botulinum toxin A detrusor injections in the treatment of neurogenic detrusor overactivity after spinal cord injury. Archives of Physical Medicine and Rehabilitation 2013 94(8):1473 81.
289. Mentes BB, Irkorucu O, Akin M et al. Comparison of botulinum toxin injection and lateral internal sphincterotomy for the treatment of chronic anal fissure. Dis Colon Rectum. 2003; 46:232-7.
290. Merz Pharmaceuticals. Xeomin® (incobotulinumtoxinA) for injection, intramuscular use prescribing information. Raleigh, NC; 2015 Dec.
291. Minguez M, Melo F, Espi A et al. Therapeutic effects of different doses of botulinum toxin in chronic anal fissure. Dis Colon Rectum. 1999; 42:1016-21.
292. Modugno N, Priori A, Berardelli A et al. Botulinum toxin restores presynaptic inhibition of group Ia afferents in patients with essential tremor. Muscle Nerve. 1998; 21:1701-5.
293. Molenaers G, Desloovere K, Eyssen M et al. Botulinum toxin type A treatment of cerebral palsy: an integrated approach. Eur J Neurol. 1999; 6 Suppl 4:S51-7.
294. Molenaers G, Eyssen M, Desloovere K et al. A multilevel approach to treatment of the (ilio)psoas in spasticity in cerebral palsy. Eur J Neurol. 1999; 6(Suppl 4):S59-2.
295. Monheit GD, Cohen JL, the Reloxin Investigational Group. Long-term safety of repeated administrations of a new formulation of botulinum toxin type A in the treatment of glabellar lines: Interim analysis from an open-label extension study. J Am Acad Dermatol. 2009; 61(3):421-5.

296. Moonen AJ, Boeckxstaens GE. Management of achalasia. Gastroenterology Clinics of North America 2013;42(1):45 55.
297. Moore AP. Botulinum toxin A (BoNT-A) for spasticity in adults. What is the evidence? Eur J Neurol.2002; 9(Suppl 1):42-7.
298. Morre HH, Keizer SB, Os JJ. Treatment of chronic tennis elbow with botulinum toxin. Lancet. 1997; 349:1746.
299. Moy R, Maas C, Monheit G et al. Long-term safety and efficacy of a new botulinum toxin type A in treating glabellar lines. Arch Facial Plast Surg. 2009 Mar-Apr; 11:77-83.
300. Naumann M, Boo LM, Ackerman AH et al. Immunogenicity of botulinum toxins. J Neural Transm. 2013; 120(2):275-90.
301. Naumann M, et al. Assessment: Botulinum neurotoxin in the treatment of autonomic disorders and pain (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008;70(19):1707 14.
302. Naumann M, et al. Evidence- based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon 2013;67:141 52.
303. Naumann M, Flachenecker P, Brocker EB et al. Botulinum toxin for palmar hyperhidrosis. Lancet. 1997; 349:252.
304. Naumann M, Hofmann U, Bergmann I et al. Focal hyperhidrosis: effective treatment with intracutaneous botulinum toxin. Arch Dermatol. 1998; 134:301-4.
305. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ. 2001; 323:596-9.
306. Naver H, Swartling C, Aquilonius SM. Palmar and axillary hyperhidrosis treated with botulinum toxin: one-year clinical follow-up. Eur J Neuro. 2000; 7:55-62.
307. Nelson RL, Thomas K, Morgan J, Jones A. Non-surgical therapy for anal fissure. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD003431.
308. neuro-rehabilitation of young patients with brachial plexus birth palsy.
309. Niemann N, Jankovic J. Botulinum Toxin for the Treatment of Hand Tremor. Toxins (Basel). 2018 Jul 19;10(7):299. doi: 10.3390/toxins10070299.
310. Nitti VW, Dmochowski R, Herschorn S et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013; 189:2186-93.
311. Nitti V, Haag-Molkenteller C, Kennelly M, Chancellor M, Jenkins B, Schurch B. Treatment of neurogenic detrusor overactivity and overactive bladder with Botox (onabotulinumtoxinA): Development, insights, and impact. Medicine (Baltimore). 2023 Jul 1;102(S1):e32377. doi: 10.1097/MD.0000000000032377.

312. NURTEC(R) ODT orally disintegrating tablets, rimegepant orally disintegrating tablets. Biohaven Pharmaceuticals Inc (per FDA), New Haven, CT, 2021.
313. O'Brien CF. Treatment of spasticity with botulinum toxin. Clin J Pain. 2002; 18: S182-90.
314. Odderson IR. Hyperhidrosis treated by botulinum A exotoxin. Dermatol Surg 1998; 24:1237.
315. Odderson IR. Long-term quantitative benefits of in the treatment of axillary hyperhidrosis. Dermatol Surg. 2002; 28:480- 3.
316. Odergren T, Hjaltason H, Kaakkola S et al. A double blind, randomised, parallel group study to investigate the dose equivalence of Dysport and Botox in the treatment of cervical dystonia. J Neurol Neurosurg Psychiatry. 1998; 64:6-12.
317. Pacchetti C, Albani G, Martignoni E et al. "Off" painful dystonia in Parkinson's disease treated with botulinum toxin. Mov Disord. 1995; 10:333-6.
318. Pandey S, Srivanitchapoom P, Kirubakaran R, Berman BD. Botulinum toxin for motor and phonic tics in Tourette's syndrome. Cochrane Database of Systematic Reviews 2018, Issue 1. Art. No.: CD012285. DOI: 10.1002/14651858.CD012285.pub2.
319. Pasricha PJ, Rai R, Ravich WJ et al. Botulinum toxin for achalasia: long- term outcome and predictors of response. Gastroenterology. 1996; 110:1410-5.
320. Pasricha PJ, Ravich WJ, Hendrix TR et al. Intrasphincteric botulinum toxin for the treatment of achalasia. N Engl J Med. 1995; 332:774-8.
321. Patel PN, Kabagambe EK, Starkweather JC, et al,. Outcomes of Onabotulinum Toxin A Treatment for Adductor Spasmodic Dysphonia and Laryngeal Tremor. JAMA Otolaryngol Head Neck Surg. 2018 Apr 1;144(4):293-299. doi: 10.1001/jamaoto.2017.3088. Patel S, Martino D. Cervical dystonia: from pathophysiology to pharmacotherapy. Behavioural Neurology 2013;26(4):275 82.
322. Pearce LB, Borodic GE, Johnson EA et al. The median paralysis unit: a more pharmacologically relevant unit of biologic activity for botulinum toxin. Toxicon. 1995; 33:217-27.
323. Pediatr Rehabil. 2001;4(1):29-36.
324. Pero R, Coretti L, Lembo F. Botulinum Toxin A for Controlling Obesity. Toxins (Basel). 2016;8(10)
325. Perry WB et al: Practice parameters for the management of anal fissures (3rd revision). Dis Colon Rectum. 53(8):1110-5, 2010
326. Peterlein CD, Funk JF, Hölscher A, Schuh A, Placzek R. Is botulinum toxin A effective for the treatment of plantar fasciitis?. Clin J Pain. 2012;28(6):527-33.
327. Petracca M, et al. Botulinum Toxin A and B in sialorrhea: Long-term data and literature overview. Toxicon 2015;107(Pt A):129 40.
328. Phelan MW, Franks M, Somogyi GT et al. Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. J Urol. 2001; 165:1107-10.

329. Poewe W. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. Clinically appropriate conversion factor may be less than three. J Neurol Neurosurg Psychiatry. 2002; 72:430.
330. Porta M, Maggioni G, Ottaviani F, Schindler A. Treatment of phonic tics in patients with Tourette's syndrome using botulinum toxin type A. Neurol Sci. 2004;24(6):420-3.
331. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence -based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2010 (AAN reaffirmed 2013)74(4):336 43.
332. Pribitkin EA, Greco TM, Goode RL et al. Patient selection in the treatment of glabellar wrinkles with botulinum toxin type A injection. Arch Otolaryngol Head Neck Surg. 1997; 123:321-6.
333. Primary Focal Axillary Hyperhidrosis. Sweathelp.org https://sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-axillary.html Accessed March 23, 2020.
334. Pringsheim T, Davenport W, Mackie G, et al,. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci. 2012 Mar;39(2 Suppl 2):S1-59.
335. Qerama E, Fuglsang Frederiksen A, Jensen TS. The role of botulinum toxin in management of pain: an evidence based review. Current Opinion in Anaesthesiology 201023(5):602 10.
336. Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, Delgado MR, Hirtz D et al. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2010; 74:336-43.
337. QULIPTA(TM) oral tablets, atogepant oral tablets. AbbVie Inc (per FDA), North Chicago, IL, 2021.
338. Racette BA, Good L, Sagitto S et al. Botulinum toxin B reduces sialorrhea in parkinsonism. Mov Disord. 2003; 18:1059-61.
339. Racette BA, Lopate G, Good L et al. Ptosis as a remote effect of therapeutic botulinum toxin B injection. Neurology. 2002; 59:1445-7.
340. Racette BA, Stambuk M, Perlmutter JS. Secondary nonresponsiveness to new bulk botulinum toxin A (BCB2024). Mov Disord. 2002; 17:1098-100.
341. Raj PP. Botulinum toxin in the treatment of pain associated with musculoskeletal hyperactivity. Curr Rev Pain. 1997; 1:403- 16.
342. Ramirez -Castaneda J, Jankovic J. Long-term efficacy and safety of botulinum toxin injections in dystonia. Toxins (Basel) 20135(2):249 66.

343. Ramirez AL, Reeck J, Maas CS. Botulinum toxin type B (MyoBloc) in the management of hyperkinetic facial lines. Otolaryngol Head Neck Surg. 2002; 126:459-67.
344. Ramzan Z, Nassri AB. The role of Botulinum toxin injection in the management of achalasia. Current Opinion in Gastroenterology 2013 29(4):468 .
345. Ranoux D, Gury C, Fondarai J et al. Respective potencies of Botox and Dysport: a double blind, randomised, crossover study in cervical dystonia. J Neurol Neurosurg Psychiatry. 2002; 72:459-62.
346. Rawicki B, et al. Botulinum toxin assessment, intervention and aftercare for paediatric and adult niche indications including pain: international consensus statement. European Journal of Neurology 2010 17 Suppl 2:122 34.
347. Restivo DA, Lanza S, Patti F, et al. Improvement of diabetic autonomic gustatory sweating by botulinum toxin type A. Neurology 2002; 59:1971.
348. Roche N, Schnitzler A, Genet F F et al. Undesirable distant effects following injection. Clin Neuropharmacol 2008; 31:272-80.
349. Rodwell K, Edwards P, Ware RS, Boyd R. Salivary gland botulinum toxin injections for drooling in children with cerebral palsy and neurodevelopmental disability: a systematic review. Dev Med Child Neurol. 2012;54(11):977-87.
350. Ron T, Jankovic J. Botulinum Toxin Type A in the Management of Oromandibular Dystonia and Bruxism. In: Brin MF, Hallett M, Jankovic J, ed. Scientific and therapeutic aspects of botulinum toxin. Lippincott Williams & Wilkins, Philadelphia, PA; 2002.
351. Rosenstengel C, Matthes M, Baldauf J, Fleck S, Schroeder H. Hemifacial spasm: conservative and surgical treatment options. Deutsches Arzteblatt International 2012 109(41):667 73.
352. Rothrock JF, Adams AM, Lipton RB, et al,. FORWARD Study: Evaluating the Comparative Effectiveness of OnabotulinumtoxinA and Topiramate for Headache Prevention in Adults With Chronic Migraine. Headache. 2019 Nov;59(10):1700-1713. doi: 10.1111/head.13653. Epub 2019 Sep 26.
353. Rowe FJ, Noonan CP. Botulinum toxin for the treatment of strabismus. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD006499.
354. Rowland LP. Stroke, spasticity, and botulinum toxin. N Engl J Med. 2002; 347:382-3.
355. Royal MA. The use of botulinum toxins in the management of myofascial pain and other conditions associated with painful muscle spasm. Available from website.
356. Rubin MG, Dover J, Glogau RG et al. The efficacy and safety of a new U.S. botulinum toxin type A in the retreatment of glabellar lines following open-label treatment. J Drugs Dermatol. 2009; 8:439-44.

357. Rudzinska M, Wojcik M, Szczudlik A. Hemifacial spasm non -motor and motor -related symptoms and their response to botulinum toxin therapy. Journal of Neural Transmission 2010;117(6):765 72.
358. Russman BS, Tilton A, Gormley ME. Cerebral palsy: a rational approach to a treatment protocol, and the role of botulinum toxin in treatment. Muscle Nerve Suppl. 1997; 6:181-93S.
359. Ryll U, Bastiaenen C, De Bie R, Staal B. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity -related cerebral palsy: a systematic review. Developmental Medicine and Child Neurology 2011;53(3):210 6.
360. Sakzewski L, Ziviani J, Boyd RN. Efficacy of upper limb therapies for unilateral cerebral palsy: a meta -analysis. Pediatrics 2014;133(1):e175 204.
361. Sampaio C, Ferreira JJ, Simoes F. DYSBOT: a single-blind, randomized parallel study to determine whether any differences can be detected in the efficacy and tolerability of two formulations of botulinum toxin type A—Dysport and Botox—assuming a ratio of 4:1. Mov Disord. 1997; 12:1013-8.
362. Sandrini G, Perrotta A, Tassorelli C, et al,. Botulinum toxin type-A in the prophylactic treatment of medication-overuse headache: a multicenter, double-blind, randomized, placebo-controlled, parallel group study. J Headache Pain. 2011 Aug;12(4):427-33. doi: 10.1007/s10194-011-0339-z. Epub 2011 Apr 16.
363. Sato H, Watanabe T, Otsuka S, Tsukada S. Short-term Efficacy of Botulinum Toxin A for Refractory Overactive Bladder in Female Patients. In Vivo. 2025 Mar-Apr;39(2):942-950. doi: 10.21873/invivo.13899.
364. Sattler G, Callander MJ, Grablowitz D et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg. 2010; 36 Suppl 4:2146-54.
365. Schaffner R, Kreyden OP. Complications and side-effects of botulinum toxin A. Curr Probl Dermatol. 2002; 30:141-8.
366. Schnider P, Binder M, Auff E, et al. Double-blind trial of botulinum A toxin for the treatment of focal hyperhidrosis of the palms. Br J Dermatol 1997; 136:548.
367. Schulte-Baukloh H, Michael T, Schobert J et al. Efficacy of botulinum-A toxin in children with detrusor hyperreflexia due to myelomeningocele: preliminary results. Urology. 2002; 59:325-8.
368. Schulte-Baukloh H, Michael T. Botulinum-A toxin in the treatment of neurogenic bladder in children. Pediatrics. 2002; 110(2 Part 1):420-1.
369. Schurch B, de Sèze M, Denys P et al. Botulinum toxin type A is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005; 174:196-200.

370. Schurch B, Hauri D, Rodic B et al. Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: a prospective study in 24 spinal cord injury patients. J Urol. 1996; 155:1023-9.
371. Schurch B, Hodler J, Rodic B. Botulinum A toxin as a treatment of detrusor-sphincter dyssynergia in patients with spinal cord injury: MRI controlled transperineal injections. J Neurol Neurosurg Psychiatry. 1997; 63:474-6.
372. Schurch B, Schmid DM, Stohrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med. 2000; 342:665.
373. Schwartz M, Freund B. Treatment of temporomandibular disorders with botulinum toxin. Clin J Pain. 2002; 18(6 Suppl):S198-203.
374. Scott AB, Magoon EH, McNeer KW et al. Botulinum treatment of childhood strabismus. Ophthalmology. 1990; 97:1434-8.
375. Scott AB, Suzuki D. Systemic toxicity of botulinum toxin by intramuscular injection in the monkey. Move Dis. 1988; 3:333-5.
376. Scott AB. Antitoxin reduces botulinum side effects. Eye. 1988; 2:29- 32.
377. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. Ophthalmology. 1980; 87:1044-9.
378. Scott AB. Botulinum toxin treatment of strabismus. In: Focal points 1989: clinical modules for ophthalmologists. American Academy of Ophthalmology. Vol. VII, module 12. 1989:1-11.
379. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine. Edinburgh: SIGN; 2023. (SIGN publication no. 155). [March 2023]. Available from URL: http://www.sign.ac.uk
380. Setler PE. Therapeutic use of botulinum toxins: background and history. Clin J Pain. 2002; 18(Suppl):S119-24.
381. Sheean G. Botulinum toxin for the treatment of musculoskeletal pain and spasm. Curr Pain Headache Rep. 2002; 6:460-9.
382. Shelley WB, Talanin NY, Shelley ED. Botulinum toxin therapy for palmar hyperhidrosis. J Am Acad Dermatol 1998; 38:227.
383. Sievert K-D, Chapple C, Herschorn S et al. OnabotulinumtoxinA 100U provides significant improvements in overactive bladder symptoms in patients with urinary incontinence regardless of the number of anticholinergic therapies used or reason for inadequate management of overactive bladder. Int J Clin Pract. 2014 Oct; 68; 10:1246–56.
384. Silberstein SD, Diener HC, Dodick DW, Sommer K, Lipton RB. Sustained benefits of onabotulinumtoxinA treatment in chronic migraine: An analysis of the pooled Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) randomized controlled trials. Headache. 2024 Jul-Aug;64(7):838-848. doi: 10.1111/head.14743. Epub 2024 Jun 22.

385. Silberstein SD, Holland S, Freitag F, et al,. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology. 2012 Apr 24;78(17):1337-45. doi: 10.1212/WNL.0b013e3182535d20. Erratum in: Neurology. 2013 Feb 26;80(9):871.
386. Silberstein S, Mathew N, Saper J et al for the BOTOX Migraine Clinical Research Group. Botulinum toxin type A as a migraine preventive treatment. Headache. 2000; 40:445-50.
387. Silberstein S, Tfelt-Hansen P, Dodick DW et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008; 28:484-95.
388. Silberstein SD, Blumenfeld AM, Cady RK et al. OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci. 2013 Aug 15; 331(1-2):48-56.
389. Simonetta Moreau M, Cauhepe C, Magues JP, Senard JM. A double-blind, randomized, comparative study of Dysport vs. Botox in primary palmar hyperhidrosis. Br J Dermatol 2003; 149:1041.
390. Simpson DM, Alexander DN, O'Brien CF et al. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. Neurology. 1996; 46:1306-10.
391. Simpson DM, Blitzer A, Brashear A et al. Assessment: botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2008; 70:1699-706.
392. Simpson DM, Gracies JM, Yablon SA et al. Botulinum neurotoxin versus tizanidine in upper limb spasticity: a placebo-controlled study. J Neurol Neurosurg Psychiatry. 2009; 80:380–5.
393. Simpson DM, Hallett M, Ashman EJ et al. Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adults spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology. 2016. Available from American Academy of Neurology website.
394. Simpson DM. Clinical trials of botulinum toxin in the treatment of spasticity. Muscle Nerve Suppl. 1997; 6:S1-7.
395. Simpson LL. Kinetic studies on the interaction between botulinum toxin type A and the cholinergic junction. J Pharmacol Exp Ther. 1980; 212:16-21.
396. Singh S, Davis H, Wilson P. Axillary hyperhidrosis: A review of the extent of the problem and treatment modalities. Surgeon 2015 13(5):279 85.
397. Sloop RR, Cole BA, Escutin RO. Reconstituted does not lose potency in humans if it is refrozen or refrigerated for 2 weeks before use. Neurology. 1997; 48:249-53.

398. Soares A, Andriolo RB, Atallah AN, da Silva EM. Botulinum toxin for myofascial pain syndromes in adults. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD007533.
399. Solomon BA, Hayman R. Botulinum toxin type A therapy for palmar and digital hyperhidrosis. J Am Acad Dermatol 2000; 42:1026.
400. Solomon S. OnabotulinumtoxinA for treatment of chronic migraine: the unblinding problem. Headache. 2013: 53:824-6. Commentary.
401. Solstice Neurosciences. Myobloc® (rimabotulinumtoxinB) injection prescribing information. South San Francisco, CA; 2010 May.
402. Souayah N, Karim H, Kamin SS et al. Severe botulism after focal injection of botulinum toxin. Neurology. 2006; 67:1855-6.
403. Sposito MM. New indications for botulinum toxin type a in cosmetics: mouth and neck. Plast Reconstr Surg. 2003; 112:75-85S.
404. Stefanidis D, et al. SAGES guidelines for the surgical treatment of esophageal achalasia. Surgical Endoscopy 2012 26(2):296 311.
405. Stein E. Botulinum toxin and anal fissure. Curr Probl Dermatol. 2002; 30:218-26.
406. Steward D.B., Gaertner W., Glasgow S., Migaly J., Feingold D., & Steele S.R. Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons. (2017). Clinical Practice Guideline for the Management of Anal Fissures. Dis Colon Rectum, 2017, 60, 7-14. DOI: 10.1097/DCR.0000000000000735
407. Storr M, Allescher HD, Rosch T et al. Treatment of symptomatic diffuse esophageal spasm by endoscopic injection of botulinum toxin: a prospective study with long term follow-up. Gastrointest Endosc. 2001; 54:754-9.
408. Strobl W, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins (Basel) 2015 7(5):1629 48.
409. Sussman D, Patel V, Del Popolo G, Lam W, Globe D, Pommerville P. Treatment satisfaction and improvement in health -related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurourology and Urodynamics 2013 32(3):242 9
410. Sutherland DH, Kaufman KR, Wyatt MP et al. Double-blind study of botulinum A toxin injections into the gastrocnemius muscle in patients with cerebral palsy. Gait Posture. 1999; 10:1-9.
411. Teive HA, Troiano AR, Robert F, et al. Botulinum toxin for treatment of Frey's syndrome: report of two cases. Arq Neuropsiquiatr 2003; 61:256.
412. Thobois S, Broussolle E, Toureille L et al. Severe dysphagia after botulinum toxin injection for cervical dystonia in multiple system atrophy. Mov Disord. 2001 Jul; 16:764-5.

413. Tincello DG, et al. Botulinum toxin a versus placebo for refractory detrusor overactivity in women: a randomised blinded placebo -controlled trial of 240 women (the RELAX study). European Urology 2012;62(3):507 14
414. Tögel B, Greve B, Raulin C. Current therapeutic strategies for hyperhidrosis: a review. Eur J Dermatol. 2002; 12:219-23.
415. Tomsak RL, Remler BF, Averbuch-Heller L et al. Unsatisfactory treatment of acquired nystagmus with retrobulbar injection of botulinum toxin. Am J Ophthalmol. 1995; 119:489-96.
416. Toni, Tahlia. "Effectiveness of Dual Migraine Therapy with CGRP Inhibitors and ONABOTULINUMTOXINA Injections: Case Series." Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, U.S. National Library of Medicine, Dec. 2021, https://pubmed.ncbi.nlm.nih.gov/34409517/.
417. Toni, T., Tamanaha, R., Newman, B., Green, L., Katz, E., & Katz, P. (2021). Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: Case series. Neurological Sciences, 42(12), 5373-5377.
418. Triadafilopoulos G, et al. The Kagoshima consensus on esophageal achalasia. Diseases of the Esophagus 2012;25(4):337 48.
419. Truong D, Duane DD, Jankovic J et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005; 20:783-91.
420. Tsai CP, Liu CY, Lin KP, Wang KC. Efficacy of botulinum toxin type a in the relief of Carpal tunnel syndrome: A preliminary experience. Clin Drug Investig. 2006;26(9):511-5.
421. Tugnoli V, Eleopra R, Quatrale R et al. Botulism-like syndrome after injections for focal hyperhidrosis. Br J Dermatol. 2002; 147:808-9.
422. Turkel CC, Dru RM, Simon D et al. Neutralizing antibody formation is rare following repeated injections of a low protein formulation of botulinum toxin type a (BTX-A) in patients with poststroke spasticity. Neurology. 2002; 58(Suppl 3):A316.
423. Ubhi T, Bhakta BB, Ives HL et al. Randomised double blind placebo controlled trial of the effect of botulinum toxin on walking in cerebral palsy. Arch Dis Child. 2000; 83:481-7.
424. UBRELVY(TM) oral tablets, ubrogepant oral tablets. Allergan USA Inc (per FDA), Madison, NJ, 2021
425. Ukleja A, Tandon K, Shah K, Alvarez A. Endoscopic botox injections in therapy of refractory gastroparesis. World Journal of Gastrointestinal Endoscopy 2015;7(8):790 8. DOI: 10.4253/wjge.v7.i8.790.
426. Utomo E, Groen J, Blok BF. Surgical management of functional bladder outlet obstruction in adults with neurogenic bladder dysfunction. Cochrane Database of Systematic Reviews 2014, Issue 5. Art. No.: CD004927.

427. Vadoud-Seyedi J, Heenen M, Simonart T. Treatment of idiopathic palmar hyperhidrosis with botulinum toxin. Report of 23 cases and review of the literature. Dermatology. 2001; 203:318-21.
428. Vaezi MF, Pandolfino JE, Yadlapati RH, Greer KB, Kavitt RT. ACG Clinical Guidelines: Diagnosis and Management of Achalasia. Am J Gastroenterol. 2020 Sep;115(9):1393-1411. doi: 10.14309/ajg.0000000000000731.
429. Valizadeh N, et al. Botulinum toxin injection versus lateral internal sphincterotomy for the treatment of chronic anal fissure: randomized prospective controlled trial. Langenbecks Archives of Surgery 2012 397(7):1093 8.
430. Verma G. Role of botulinum toxin type A (BTX A) in the management of trigeminal neuralgia. Pain Research and Treatment 2013 2013:831094.
431. Visco AG, Brubaker L, Richter HE et al. Anticholinergic therapy vs. onabotulinumtoxinA for urgency urinary incontinence. N Engl J Med. 2012; 367:1803-13.
432. Visco AG, et al. Anticholinergic therapy vs. onabotulinumtoxina for urgency urinary incontinence. New England Journal of Medicine 2012 367(19):1803 13.
433. Vivancos-Matellano F, Rodríguez-Sanz A, Herrero-Infante Y, Mascías-Cadavid J. Efficacy and Safety of Long-Term Therapy with Type A Botulinum Toxin in Patients with Blepharospasm. Neuroophthalmology. 2018 Nov 26;43(5):277-283. doi: 10.1080/01658107.2018.1542009.
434. VYEPTI(TM) intravenous injection, eptinezumab-jjmr intravenous injection. Lundbeck Seattle BioPharmaceuticals Inc (per manufacturer), Bothell, WA, 2021.
435. Wald A et al: ACG clinical guideline: management of benign anorectal disorders. The American Journal of Gastroenterology: October 2021 - Volume 116 - Issue 10 - p 1987-2008 doi: 10.14309/ajg.0000000000001507
436. Walling HW, Swick BL. Treatment options for hyperhidrosis. American Journal of Clinical Dermatology 2011 12(5):285 95.
437. Walshe M, Smith M, Pennington L. Interventions for drooling in children with cerebral palsy. Cochrane Database Syst Rev. 2012;11:CD008624.
438. Wang CC, Chou EC, Chuang YC, et al,. Effectiveness and Safety of Intradetrusor OnabotulinumtoxinA Injection for Neurogenic Detrusor Overactivity and Overactive Bladder Patients in Taiwan-A Phase IV Prospective, Interventional, Multiple-Center Study (Restore Study). Toxins (Basel). 2021 Dec 20;13(12):911. doi: 10.3390/toxins13120911.
439. Waseem Z, Boulias C, Gordon A, Ismail F, Sheean G, Furlan AD. Botulinum toxin injections for low-back pain and sciatica. Cochrane Database of Systematic Reviews 2011, Issue 1. Art. No.: CD008257.
440. Weckx F, Tutolo M, De Ridder D, Van der Aa F. The role of botulinum toxin A in treating neurogenic bladder. Translational Andrology and Urology 2016 5(1):63 71

441. Wehrmann T, Kokabpick H, Jacobi V et al. Long-term results of endoscopic injection of botulinum toxin in elderly achalasic patients with tortuous megaesophagus or epiphrenic diverticulum. Endoscopy. 1999; 31:352-8.
442. Wein T, Esquenazi A, Jost WH et al. OnabotulinumtoxinA for the Treatment of Post-Stroke Distal Lower-Limb Spasticity: A Randomized Trial. PM R. 2018;
443. Wein T, Jog M, Bhogal M, Dhani S, Miller R, Ismail F, Beauchamp R, Trentin G. Long-term Safety and Dosing of OnabotulinumtoxinA: A Prospective, Observational Study. Can J Neurol Sci. 2019 Nov;46(6):742-752. doi: 10.1017/cjn.2019.238.
444. Wenzel R, Jones D, Borrego JA. Comparing two botulinum toxin type A formulations using manufacturers' product summaries. J Clin Pharm Ther. 2007; 32:387-402.
445. WH. One hundred cases of anal fissure treated with botulin toxin: early and long-term results. Dis Colon Rectum. 1997; 40:1029-32.
446. Wheeler AH, Goolkasian P, Gretz SS. A randomized, double-blind, prospective pilot study of botulinum toxin injection for refractory, unilateral, cervicothoracic, paraspinal, myofascial pain syndrome. Spine. 1998; 23:1662-6.
447. Wheeler AH, Goolkasian P, Gretz SS. Botulinum toxin A for the treatment of chronic neck pain. Pain. 2001; 94:255-60.
448. Wheeler AH, Goolkasian P. Open label assessment of botulinum toxin A for pain treatment in a private outpatient setting. J Musculoskeletal Pain. 2001; 9:67-82.
449. Wheeler AH. Botulinum toxin A, adjunctive therapy for refractory headaches associated with pericranial muscle tension. Headache. 1998; 38:468-71.
450. Wheeler AH. Botulinum toxin injection technique for treatment of headaches. Aesthetic Surg J. 2002; 22:65-8.
451. Wheeler AH. Therapeutic uses of botulinum toxin. Am Fam Physician. 1997; 55:541-5, 548.
452. Williams A. Consensus statement for the management of focal dystonias. Br J Hosp Med. 1993; 50:655-9.
453. Winner PK, Blumenfeld AM, Eross EJ, et al,. Long-Term Safety and Tolerability of OnabotulinumtoxinA Treatment in Patients with Chronic Migraine: Results of the COMPEL Study. Drug Saf. 2019 Aug;42(8):1013-1024. doi: 10.1007/s40264-019-00824-3.
454. Winner PK, Kabbouche M, Yonker M, Wangsadipura V, Lum A, Brin MF. A Randomized Trial to Evaluate OnabotulinumtoxinA for Prevention of Headaches in Adolescents With Chronic Migraine. Headache. 2020 Mar;60(3):564-575. doi: 10.1111/head.13754. Epub 2020 Feb 9.
455. Wollina U, Karamfilov T, Konrad H. High-dose therapy for axillary hyperhidrosis markedly prolongs the relapse-free interval. J Am Acad Dermatol. 2002; 46:536-40.

456. Woodcock J (US Food and Drug Administration). Response to Public Citizen's petition on botulinum toxin re: docket no: FDA-2008-P-0061. Rockville, MD; 2009 April 30. From FDA website.
457. Wyndaele JJ, Van Dromme SA. Muscular weakness as side effect of botulinum toxin injection for neurogenic detrusor overactivity. Spinal Cord. 2002; 40:599-600.
458. Xia JH, et al. Botulinum toxin A in the treatment of trigeminal neuralgia. International Journal of Neuroscience 2016126(4):348 53.
459. Yablon SA, Jackkson MS, Daggett S et al. Toxin neutralizing antibody formation with (BoNTA) treatment in neuromuscular disorders. Neurology. 2005; 64 (suppl 1); A72. Abstract.
460. Yablon SA. Botulinum neurotoxin intramuscular chemodenervation. Role in the management of spastic hypertonia and related motor disorders. Phys Med Rehab Clin NA. 2001; 12:833-74.
461. Yiannakopoulou E. Botulinum toxin and anal fissure: efficacy and safety systematic review. International Journal of Colorectal Disease 201227(1):1 9.
462. Yang D, Bechara R, Dunst CM, Konda VJA. AGA Clinical Practice Update on Advances in Per-Oral Endoscopic Myotomy (POEM) and Remaining Questions-What We Have Learned in the Past Decade: Expert Review. Gastroenterology. 2024 Dec;167(7):1483-1490. doi: 10.1053/j.gastro.2024.08.038. Epub 2024 Oct 16.
463. Yoshimura DM, Aminoff MJ, Tami TA et al. Treatment of hemifacial spasm with botulinum toxin. Muscle Nerve. 1992; 15:1045- 9.
464. Żebryk P, Puszczewicz MJ. Botulinum toxin A in the treatment of Raynaud's phenomenon: a systematic review. Arch Med Sci. 2016 Aug 1; 12(4): 864–870. doi: 10.5114/aoms.2015.48152
465. Zesiewicz TA, Elble RJ, Louis ED, et al,. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology. 2011 Nov 8;77(19):1752-5. doi: 10.1212/WNL.0b013e318236f0fd. Epub 2011 Oct 19.
466. Zesiewicz TA, Elble R, Louis ED, et al,. Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2005 Jun 28;64(12):2008-20. doi: 10.1212/01.WNL.0000163769.28552.CD. Epub 2005 Jun 22.
467. Zhang T, et al. The efficacy of botulinum toxin type A in managing chronic musculoskeletal pain: a systematic review and meta-analysis. Inflammopharmacology 201119(1):21 34
468. Zhou X, Yan HL, Cui YS, Zong HT, Zhang Y. Efficacy and safety of onabotulinumtoxinA in treating neurogenic detrusor overactivity: a systematic review and meta -analysis. Chinese Medical Journal 2015128(7):963 8.
469. Zimbler MS, Holds JB, Kokoska MS et al. Effect of botulinum toxin pretreatment on laser resurfacing results: a prospective, randomized, blinded trial. Arch Facial Plast Surg. 2001; 3:165-9.

IncobotulinumtoxinA (Xeomin)

1. Bakheit AM, Ward CD, McLellan DL. Generalised botulism-like syndrome after intramuscular injections of botulinum toxin type A: a report of two cases. J Neurol Neurosurg Psychiatry. 1997; 62:198.
2. Bell MS, Vermeulen LC, Sperling KB. Pharmacotherapy with botulinum toxin: harnessing nature's most potent neurotoxin. Pharmacotherapy. 2000; 20:1079-91.
3. Benecke R, Jost WH, Kanovsky P, Ruzicka E, Comes G, Grafe S. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology. 2005;64(11):1949-1951.
4. Benecke R. Xeomin in the treatment of cervical dystonia. Eur J Neurol. 2009; 16 Suppl 2:6-10.
5. Bhatia KP, Munchau A, Thompson PD et al. Generalised muscular weakness after botulinum toxin injections for dystonia: a report of three cases. J Neurol Neurosurg Psychiatry. 1999; 67:90-3.
6. Campanati A, Giuliodori K, Martina E, et al. Onabotulinumtoxin A (Botox) versus incobotulinum toxin A (Xeomin) in the treatment of focal idiopathic palmar hyperhidrosis: results of a comparative double-blind clinical trial. J Neural Transm 2014;121:21-6.
7. Carraro E, Trevisi E, Martinuzzi A. Safety profile of incobotulinum toxin A [Xeomin(®)] in gastrocnemius muscles injections in children with cerebral palsy: Randomized double-blind clinical trial. Eur J Paediatr Neurol. 2016;20(4):532-7.
8. Castelnovo G, Le Floch A, Campello C, Bouly S. IncobotulinumtoxinA (XEOMIN®) in chronic refractory migraine. Poster presented at the 23rd Meeting of the European Neurological Society (ENS), 8-11 June 2013, Barcelona, Spain [ENS 2013 Abstract]
9. Chapman MA, Barron R, Tanis DC et al. Comparison of botulinum neurotoxin preparations for the treatment of cervical dystonia. Clin Ther. 2007; 29:1325-37.
10. Cobb DB, Watson WA, Fernandez MC. Botulism-like syndrome after injections of botulinum toxin. Vet Hum Toxicol. 2000 Jun; 42:163.
11. Comella CL, Jankovic J, Truong DD, Hanschmann A, Grafe S; US XEOMIN Cervical Dystonia Study Group. Efficacy and safety of incobotulinumtoxinA (NT 201, XEOMIN®, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia. J Neurol Sci. 2011;308(1-2):103-109.
12. Contarino MF, Van Den Dool J, Balash Y, et al. Clinical practice: evidence-based recommendations for the treatment of cervical dystonia with botulinum toxin. Front Neurol. 2017;8:35. doi:10.3389/fneur.2017.00035[PubMed 28286494]

13. Costa J, Espirito-Santo CC, Borges AA et al. Botulinum toxin type A therapy for cervical dystonia (review). Cochrane Database of Systematic Reviews. 2005, Issue 1. Article No: CD003633. DOI: 10.1002/14651858.CD003633.pub2.
14. Dressler D, Rychlik R, Kreimendahl F, Schnur N, Lambert-baumann J. Long-term efficacy and safety of incobotulinumtoxinA and conventional treatment of post stroke arm spasticity: a prospective, non-interventional, open-label, parallel-group study. BMJ Open. 2015;5(12):e009358.
15. Dressler D. Comparing Botox and Xeomin for axillar hyperhidrosis. J Neural Transm 2010;117:317-19.
16. Dressler D. Routine use of Xeomin in patients previously treated with Botox: long term results. Eur J Neurol. 2009;16 (Suppl 2):2–5.
17. Elovic EP, Munin MC, Kaňovský P, Hanschmann A, Hiersemenzel R, Marciniak C. Randomized, placebo-controlled trial of incobotulinumtoxina for upper-limb post-stroke spasticity. Muscle Nerve. 2016;53(3):415-21
18. Fezza J, Burns J, Woodward J, Truong D, Hedges T, Verma A. A cross-sectional structured survey of patients receiving botulinum toxin type A treatment for blepharospasm. J Neurol Sci. 2016;367:56-62.
19. Frevert J, Dressler D. Complexing proteins in botulinum toxin type A drugs: a help or a hindrance?. Biologics. 2010; 4:325-32.
20. Hampel C, D'Andrea D, Gillitzer R, et al. Comparison of two different botulinum toxin A products (Xeomin, Botox) used for detrusor injection in patients with bladder overactivity (BO) – a prospective randomized double-blind study. 27th Annual Congress of the European Association of Urology, February 26th, 2012.
21. Jankovic J, Comella C, Hanschmann A, Grafe S. Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin) in the treatment of blepharospasm—a randomized trial. Mov Disord. 2011;26(8):1521-1528.
22. Jankovic J. Clinical efficacy and tolerability of Xeomin in the treatment of blepharospasm. Eur J Neurol. 2009; 16 Suppl 2:14-8.
23. Jost WH, Blümel J, Grafe S. Botulinum neurotoxin type A free of complexing proteins (XEOMIN) in focal dystonia. Drugs. 2007; 67:669-83.
24. Kanovský P, Slawek J, Denes Z et al. Efficacy and safety of botulinum neurotoxin NT 201 in poststroke upper limb spasticity. Clin Neuropharmacol. 2009 Sep-Oct; 32:259-65.
25. Kanovský P, Slawek J, Denes Z et al. Efficacy and safety of treatment with incobotulinum toxin A (botulinum neurotoxin type A free from complexing proteins; NT 201) in post-stroke upper limb spasticity. J Rehabil Med. 2011; 43:486-92.

26. Kanovsky P, Slawek J, Denes Z, et al. Efficacy and safety of treatment with incobotulinum toxin A (botulinum neurotoxin type A free from complexing proteins; NT 201) in poststroke upper limb spasticity. J Rehabil Med 2011;43:486-92.
27. Kazerooni R, Lim J, Ashley blake P, Lessig S. IncobotulinumtoxinA for Migraine: A Retrospective Case Series. Clin Ther. 2015;37(8):1860-4.
28. Khan A, Frazer-Green L, Amin R, et al,. Respiratory Management of Patients With Neuromuscular Weakness: An American College of Chest Physicians Clinical Practice Guideline and Expert Panel Report. Chest. 2023 Aug;164(2):394-413. doi: 10.1016/j.chest.2023.03.011. Epub 2023 Mar 13.
29. Lamb YN, Scott LJ. IncobotulinumtoxinA: A Review in Upper Limb Spasticity. Drugs. 2016;76(14):1373-9.
30. Matarasso A, Deva AK. Botulinum toxin. Plast Reconstr Surg. 2002; 109:1191-7.
31. Merz North America, Inc. FDA approves Xeomin (incobotulinumtoxinA) for adult patients with sialorrhea. Press Release. Raleigh, NC: Merz; July 3, 2018. Available at: https://www.merzusa.com/news/fda-approves-xeomin-incobotulinumtoxina-for-adult-patients-with-sialorrhea/.
32. Merz Pharmaceuticals, LLC. Xeomin (incobotulinumtoxinA) for injection, for intramuscular or intraglandular use. Prescribing Information. Raleigh, NC: Merz Pharmaceuticals; revised July 2018. Available at: http://www.xeomin.com/wp-content/uploads/xeomin-full-prescribing-information.pdf.
33. Merz Pharmaceuticals. Xeomin® incobotulinumtoxinA for injection, for intramuscular use prescribing information. Raleigh, NC; 2015 Dec.
34. Narayanaswami P, Geisbush T, Tarulli A, et al. Drooling in Parkinson's disease: A randomized controlled trial of incobotulinum toxin A and meta-analysis of Botulinum toxins. Parkinsonism Relat Disord. 2016;30:73-7.
35. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124
36. Park J, Lee MS, Harrison AR. Profile of Xeomin® (incobotulinumtoxinA) for the treatment of blepharospasm. Clin Ophthalmol. 2011; 5:725-32.
37. Pokushalov E, Kozlov B, Romanov A, et al. Long-term suppression of atrial fibrillation by botulinum toxin injection into epicardial fat pads in patients undergoing cardiac surgery: One year follow up of a randomized pilot study. Circ Arrhythm Electrophysiol. 2015;8(6):1334-1341.
38. Proietti S, Giovannozzi S, Lepri E, et al. Clinical and urodynamic efficacy of Xeomin in the treatment of neurogenic detrusor overactivity: preliminary results. Neurolurol Urodyn. 2011; 30 (suppl):45-46.

39. Roche N, Schnitzler A, Genet F F et al. Undesirable distant effects following botulinum toxin type A injection. Clin Neuropharmacol 2008; 31:272-80.
40. Roggenkämper P, Jost WH, Bihari K et al. Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm. 2006; 113:303-12.
41. Roggenkämper P, Jost WH, Bihari K, Comes G, Grafe S. Efficacy and safety of a new botulinum toxin type A free of complexing proteins in the treatment of blepharospasm. J Neural Transm. 2006;113(3):303-312.
42. Santamato A, Micello MF, Panza F, et al. Safety and efficacy of incobotulinum toxin type A (NT 201-Xeomin) for the treatment of post-stroke lower-limb spasticity: a prospective open-label study. Eur J Phys Rehabil Med 2013;49:483-9.
43. Sattler G, Callander MJ, Grablowitz D et al. Noninferiority of incobotulinumtoxinA, free from complexing proteins, compared with another botulinum toxin type A in the treatment of glabellar frown lines. Dermatol Surg. 2010; 36 Suppl 4:2146-54.
44. Simpson DM, Gracies JM, Graham K et al. Assessment: botulinum neurotoxin for the treatment of spasticity (an evidence-based review). Neurology. 2009; 73:736-7; author reply 737-8.
45. Simpson DM, Hallett M, Ashman EJ et al. Practice guideline update: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adults spasticity, and headache: report of the guideline development subcommittee of the American Academy of Neurology. 2016. Available at: https://www.neurology.org/doi/10.1212/wnl.0000000000002560
46. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:1-9.
47. Tugnoli V, Eleopra R, Quatrale R et al. Botulism-like syndrome after botulinum toxin type A injections for focal hyperhidrosis. Br J Dermatol. 2002; 147:808-9.
48. US Food and Drug Administration. Center for Drug Evaluation and Research: Application number 125360: Summary review for incobotulinumtoxinA. From FDA website.
49. Williams A. Consensus statement for the management of focal dystonias. Br J Hosp Med. 1993; 50:655-9.
50. Woodcock J (US Food and Drug Administration). Response to Public Citizen's petition on botulinum toxin re: docket no: FDA-2008-P-0061. Rockville, MD; 2009 April 30. From FDA website (https://www-fda-gov.libproxy.unm.edu/cder/drug/early_comm/botulinum_CP_response.pdf)/cder/drug/early_comm/botulinum_CP_response.pdf)

51. Xeomin (incobotulinumtoxinA) [prescribing information] Raleigh, NC: Merz Pharmaceuticals LLC; September 2023.
52. Zeuner KE, Deuschl G. Pharmacokinetics and pharmacodynamics of incobotulinumtoxinA influencing the clinical efficacy in post-stroke spasticity. Expert Opin Drug Metab Toxicol. 2016;12(4):457-66.

RimabotulinumtoxinB (Myobloc)

1. Adler CH, Bansberg SF, Krein-Jones K, Hentz JG. Safety and efficacy of botulinum toxin type B (Myobloc) in adductor spasmodic dysphonia. Mov Disord. 2004;19(9):1075-1079.
2. Albanese A. Terminology for preparations of botulinum neurotoxins: what a difference a name makes. JAMA. 2011; 305:89-90.
3. An JS, Hyun won C, Si han J, Park HS, Seo KK. Comparison of onabotulinumtoxinA and rimabotulinumtoxinB for the treatment of axillary hyperhidrosis. Dermatol Surg. 2015;41(8):960-7.
4. Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the Use of Botulinum Toxin in the Treatment of Lower Urinary Tract Disorders and Pelvic Floor Dysfunctions: A European Consensus Report. Eur Urol. 2009;55(1):100-20.
5. Arezzo JC, Litwak MS, Gasper CA et al. The spread of paralytic activity in juvenile monkeys: a comparison of and botulinum toxin type B. Paper presented at the World Congress of Neurological Rehabilitation, Venice, Italy: 2002 Apr 2-6.
6. Argoff CE. A focused review on the use of botulinum toxins for neuropathic pain. Clin J Pain. 2002; 18(Suppl):S177-S181.
7. Armanious M, Khalil N, Lu Y, Jimenez-Sanders R. Erenumab and OnabotulinumtoxinA Combination Therapy for the Prevention of Intractable Chronic Migraine without Aura: A Retrospective Analysis. J Pain Palliat Care Pharmacother 2021; 35:1.
8. Arnon SS, Schechter R, Inglesby TV et al for the Working Group on Civilian Biodefense. Botulinum toxin as a biologic weapon: medical and public health management. JAMA. 2001; 285:1059-70.
9. Barbehenn E, Lurie P, Stark S et al. Petition to the FDA requesting regulatory action concerning the possible spread of botulinum toxin (Botox, Myobloc) from the site of injection to other parts of the body. Washington, DC: Public Citizen's Health Research Group; 2008 Jan.
10. Baumann L, Black L. Botulinum toxin type B (Myobloc). Dermatol Surg. 2003; 29:496-500.
11. Baumann L, slezinger A, Halem M et al. Double-blind, randomized, placebo-controlled pilot study of the safety and efficacy of Myobloc (botulinum toxin type B) for the treatment of palmar hyperhidrosis. Dermatol Surg. 2005; 31:263-70.

12. Baumann L, Slezinger A, Halem M, et al. Pilot study of the safety and efficacy of Myobloc (botulinum toxin type B) for treatment of axillary hyperhidrosis. Int J Dermatol. 2005;44(5):418-424.
13. Baumann L, Slezinger A, Vujevich J et al. A double-blinded, randomized, placebo-controlled pilot study of the safety and efficacy of Myobloc (botulinum toxin type B)-purified neurotoxin complex for the treatment of crow's feet: a double-blinded, placebo-controlled trial. Dermatol Surg. 2003; 29:508-15.
14. Baumann LS, Helam ML. Botulinum toxin-B and the management of hyperhidrosis. Dermatology. 2004;22:60-65.
15. Bell MS, Vermeulen LC, Sperling KB. Pharmacotherapy with botulinum toxin: harnessing nature's most potent neurotoxin. Pharmacotherapy. 2000; 20:1079-91.
16. Benecke R, Jost WH, Kanovsky P et al. A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia. Neurology. 2005; 64(11):1949-51.
17. Berardelli A, Abbruzzese G, Bertolasi L et al. Guidelines for the therapeutic use of botulinum toxin in movement disorders. Italian Study Group for Movement Disorders, Italian Society of Neurology. Ital J Neurol Sci. 1997; 18:261-9.
18. Berman B, Seeberger L, Kumar R. Long-term safety, efficacy, dosing, and development of resistance with botulinum toxin type B in cervical dystonia. Mov Disord. 2005;20(2):233-237.
19. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. J Neurol Neurosurg Psychiatry. 1990; 53:640-3.
20. Brandenburg JE, Krach LE, Gormley ME Jr. Use of rimabotulinum toxin for focal hypertonicity management in children with cerebral palsy with non-response to onabotulinum toxin. Am J Phys Med Rehabil. 2013;92(10):898-904.
21. Brashear A, Lew MF, Dykstra DD, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-responsive cervical dystonia. Neurology. 1999;53(7):1439-1446.
22. Brashear A, Mcafee AL, Kuhn ER, Ambrosius WT. Treatment with botulinum toxin type B for upper-limb spasticity. Arch Phys Med Rehabil. 2003;84(1):103-7.
23. Brashear A, Mcafee AL, Kuhn ER, Fyffe J. Botulinum toxin type B in upper-limb poststroke spasticity: a double-blind, placebo-controlled trial. Arch Phys Med Rehabil. 2004;85(5):705-9.
24. Brin MF, Lew MF, Adler CH, et al. Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia. Neurology. 1999;53(7):1431-1438.
25. Callaway JE, Arezzo JC, Grethlein AJ. Botulinum toxin type B: an overview of its biochemistry and preclinical pharmacology. Semin Cutan Med Surg. 2001; 20:127-36.
26. Callaway JE, Oregozo P, Gore N et al. Long-term stability of a new liquid formulation of botulinum toxin type b (BoNT-B). Neurology. 2001; 56(suppl 3): A346.

27. Chapman MA, Barron R, Tanis DC et al. Comparison of botulinum neurotoxin preparations for the treatment of cervical dystonia. Clin Ther. 2007; 29:1325-37.
28. Cheng CM, Chen JS, Patel RP. Unlabeled uses of botulinum toxins: a review, part 1. Am J Health Syst Pharm. 2006; 63:145-52.
29. Cobb DB, Watson WA, Fernandez MC. Botulism-like syndrome after injections of botulinum toxin. Vet Hum Toxicol. 2000 Jun; 42:163.
30. Cohen F, Armand C, Lipton RB, Vollbracht S. Efficacy and Tolerability of Calcitonin Gene-Related Peptide-Targeted Monoclonal Antibody Medications as Add-on Therapy to OnabotulinumtoxinA in Patients with Chronic Migraine. Pain Med 2021; 22:1857.
31. Colosimo C, Chianese M, Giovannelli M et al. Botulinum toxin type B in blepharospasm and hemifacial spasm. J Neurol Neurosurg Psychiatry. 2003; 74:687-91.
32. Corry IS, Cosgrove AP, Duffy CM et al. Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. J Pediatr Orthop. 1998; 18:304-11.
33. Corry IS, Cosgrove AP, Walsh EG et al. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. Dev Med Child Neurol. 1997; 39:185-93.
34. Costa J, Borges A, Espírito-Santo C, et al. Botulinum toxin type A versus botulinum toxin type B for cervical dystonia. Cochrane Database Syst Rev. 2003;(3):CD004314.
35. Costa J, Espírito-Santo C, Borges A, et al. Botulinum toxin type B for cervical dystonia. Cochrane Database Syst Rev. 2004;(4):CD004315.
36. Costa J, Espirito-Santo CC, Borges AA et al. Botulinum toxin type A therapy for cervical dystonia (review). Cochrane Database of Systematic Reviews. 2005, Issue 1. Article No: CD003633.
37. Coté TR, Mohan AK, Polder JA et al. Botulinum toxin type A injections: adverse events reported to the US Food and Drug Administration in therapeutic and cosmetic cases. J Am Acad Dermatol. 2005; 53:407-15.
38. Cullis PA, O'Brien CF, Truong DD, et al. Botulinum toxin type B: An open-label, dose-escalation, safety and preliminary efficacy study in cervical dystonia patients. Adv Neurol. 1998;78:227-230.
39. Delgado MR, Hirtz D, Aisen M, et al. Practice parameter: pharmacologic treatment of spasticity in children and adolescents with cerebral palsy (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2010;74(4):336-43.
40. Dressler D, Adib Saberi F, Benecke R. Botulinum toxin type B for treatment of axillar hyperhidrosis. J Neurol. 2002; 249:1729-32.
41. Dressler D, Benecke R. Autonomic side effects of botulinum toxin type B treatment of cervical dystonia and hyperhidrosis. Eur Neurol. 2003; 49:34- 8.
42. Dressler D, Bigalke H, Benecke R. Botulinum toxin type B in antibody-induced therapy failure. J Neurol. 2003; 250:967-9.

43. Dressler D, Saberi FA, Benecke R. Botulinum toxin type B for treatment of axillary hyperhidrosis. J Neurol. 2002;249:1729-1732.
44. Duthie JB, Vincent M, Herbison GP, Wilson DI, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database Syst Rev. 2011;(12):CD005493.
45. Dutton JJ, White JJ, Richard MJ. Myobloc for the treatment of benign essential blepharospasm in patients refractory to botox. Ophthal Plast Reconstr Surg. 2006;22(3):173-7.
46. Dykstra DD, Pryor J, Goldish G. Use of botulinum toxin type B for the treatment of detrusor hyperreflexia in a patient with multiple sclerosis: a case report. Arch Phys Med Rehabil. 2003; 84:1399-400.
47. Elan Pharmaceuticals. South San Francisco, CA: Personal communication.
48. Elston JS, Russell RWR. Effect of treatment with botulinum toxin on neurogenic blepharospasm. BMJ. 1985; 290:1857-9.
49. Erbguth F, Claus D, Engelhardt A et al. Systemic effect of local botulinum toxin injections unmasks subclinical Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry. 1993; 56:1235- 6.
50. Evers S, Rahmann A, Vollmer-Haase J et al. Treatment of headache with botulinum toxin A--a review according to evidence-based medicine criteria. Cephalalgia. 2002; 22:699-710.
51. Fadeyi MO, Adams QM. Use of botulinum toxin type B for migraine and tension headaches. Am J Health-Syst Pharm. 2002;59:1860-1862.
52. Ferreira JJ, Costa J, Coelho M et al. The management of cervical dystonia. Expert Opin Pharmacother. 2007; 8:129-40.
53. Figgit DP, Noble S. Botulinum toxin B: A review of its therapeutic potential in the management of cervical dystonia. Drugs. 2002; 62:705-2.
54. Figgitt DP, Noble S. Botulinum toxin B: A review of its therapeutic potential in the management of cervical dystonia. Drugs. 2002;62(4):705-722.
55. Ghei M, Maraj BH, Miller R, et al. Effects of botulinum toxin B on refractory detrusor overactivity: a randomized, double-blind, placebo controlled, crossover trial. J Urol 2005;174(5):1873-7.
56. Glogau RG. Review of the use of botulinum toxin for hyperhidrosis and cosmetic purposes. Clin J Pain. 2002; 18(6 Suppl):S191-7.
57. Gracies JM, Bayle N, Goldberg S, Simpson DM. Botulinum toxin type B in the spastic arm: a randomized, double-blind, placebo-controlled, preliminary study. Arch Phys Med Rehabil. 2014;95(7):1303-11.
58. Guntinas-Lichius O. Injection of botulinum toxin type B for the treatment of otolaryngology patients with secondary treatment failure of. Laryngoscope. 2003 Apr; 113:743-5.
59. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med. 2001; 344:488-93.

60. Hirst GR, Watkins AJ, Guerrero K, et al. Botulinum toxin B is not an effective treatment of refractory overactive bladder. Urology. 2007;69(1):69-73.
61. Huang W, Foster JA, Rogachefsky AS. Pharmacology of botulinum toxin. J Am Acad Dermatol. 2000; 43:249-59.
62. Isaacson SH, Ondo W, Jackson CE, et al; MYSTICOL Study Group. Safety and efficacy of rimabotulinumtoxinB for treatment of sialorrhea in adults: a randomized clinical trial. JAMA Neurol. 2020;77(4):461-469. doi:10.1001/jamaneurol.2019.4565
63. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med. 1991; 324:1186-94.
64. Johnson EA. Clostridial toxins as therapeutic agents: benefits of nature's most toxic proteins. Annu Rev Microbiol. 1999; 53:551-75.
65. Jost WH. Botulinum toxin type B in the treatment of anal fissures: first preliminary results. Dis Colon Rectum. 2001; 44:1721-2.
66. Klein AW. Complications and adverse reactions with the use of botulinum toxin. Semin Cutan Med Surg. 2001; 20:109-20.
67. Koman LA, Smith BP, Balkrishnan R. Spasticity associated with cerebral palsy in children. Pediatr Drugs. 2003; 5:11-23.
68. Lew MF, Adornato BT, Duane DD et al. Botulinum toxin type B: a double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. Neurology. 1997; 49:701-7.
69. Lew MF. Botulinum toxin type B: an open-label, dose-escalation, safety and preliminary efficacy study in cervical dystonia patients. Adv Neurol. 1998; 78:227-30.
70. Lew MR, Brashear A, Factor S. The safety and efficacy of botulinum toxin type B in the treatment of patients with cervical dystonia: Summary of three controlled clinical trials. Neurology. 2000;55(12 Suppl 5):S29-S35.
71. Lowe NJ, Yamauchi PS, Lask GP et al. Botulinum toxins types A and B for brow furrows: preliminary experiences with type B toxin dosing. J Cosmet Laser Ther. 2002; 4:15-8.
72. Matarasso A, Deva AK. Botulinum toxin. Plast Reconstr Surg. 2002; 109:1191-7.
73. Matarasso SL. Comparison of botulinum toxin types A and B: a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides. Dermatol Surg. 2003; 29:7-13.
74. Moore AP. Botulinum toxin A (BoNT-A) for spasticity in adults. What is the evidence? Eur J Neurol.2002; 9(Suppl 1):42-7.
75. Myobloc (rimabotulinumtoxinB) [prescribing information]. Louisville, KY: Solstice Neurosciences; September 2020.
76. Myobloc(R) IM injection, rimabotulinumtoxinB IM injection. Solstice Neurosciences, LLC, Louisville, KY, Revised March 2021. https://www.myobloc.com/files/MYOBLOC_PI.pdf

77. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124
78. Nelson L, Bachoo P, Holmes J. Botulinum toxin type B: A new therapy for axillary hyperhidrosis. Br J Plast Surg. 2005;58(2):228-232.
79. O'Brien CF. Treatment of spasticity with botulinum toxin. Clin J Pain. 2002; 18: S182-90.
80. Ondo WG, Hunter C, Moore W. A double-blind placebo-controlled trial of botulinum toxin B for sialorrhea in Parkinson's disease. Neurology. 2004;62(1):37-40.
81. Pappert EJ, Germanson T; The Myobloc/Neurobloc European Cervical Dystonia Study Group. Botulinum toxin type B vs. type A in toxin-naïve patients with cervical dystonia: Randomized, double-blind, noninferiority trial. Mov Disord. 2007;23(4):510-517.
82. Park J, Lee MS, Harrison AR. Profile of Xeomin® (incobotulinumtoxinA) for the treatment of blepharospasm. Clin Ophthalmol. 2011; 5:725-32.
83. Racette BA, Good L, Sagitto S, Perlmutter JS. Botulinum toxin B reduces sialorrhea in Parkinsonism. Movement Disord. 2003;18(9):1059-1061.
84. Racette BA, Lopate G, Good L et al. Ptosis as a remote effect of therapeutic botulinum toxin B injection. Neurology. 2002; 59:1445-7.
85. Racette BA, Stambuk M, Perlmutter JS. Secondary nonresponsiveness to new bulk botulinum toxin A (BCB2024). Mov Disord. 2002; 17:1098-100.
86. Ramirez AL, Reeck J, Maas CS. Botulinum toxin type B (MyoBloc) in the management of hyperkinetic facial lines. Otolaryngol Head Neck Surg. 2002; 126:459-67.
87. Regan J, Murphy A, Chiang M, Mcmahon BP, Coughlan T, Walshe M. Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders. Cochrane Database Syst Rev. 2014;(5):CD009968
88. Sadick NS. Botulinum toxin type B for glabellar wrinkles: a prospective open-label response study. Dermatol Surg. 2002; 28:817-21.
89. Sadick NS. Prospective open-label study of botulinum toxin type B (Myobloc) at doses of 2,400 and 3,000 U for the treatment of glabellar wrinkles. Dermatol Surg. 2003; 29:501-7.
90. Sanger TD, Kukke SN, Sherman-Levine S. Botulinum toxin type B improves the speed of reaching in children with cerebral palsy and arm dystonia: An open-label, dose-escalation pilot study. J Child Neurol. 2007;22(1):116-122.
91. Sataloff RT, Heman-Ackah YD, Simpson LL et al. Botulinum toxin type B for treatment of spasmodic dysphonia: a case report. J Voice. 2002; 16:422-4.
92. Schwartz M, Freund B. Treatment of temporomandibular disorders with botulinum toxin. Clin J Pain. 2002; 18(6 Suppl):S198-203.

93. Schwerin A, Berweck S, Fietzek UM, Heinen F. Botulinum toxin B treatment in children with spastic movement disorders: A pilot study. Pediatr Neurol. 2004;31(2):109-113.
94. Setler PE. Therapeutic use of botulinum toxins: background and history. Clin J Pain. 2002; 18(Suppl):S119-24.
95. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:1-9.
96. Solstice Neurosciences, Inc. Myobloc® (rimabotulinumtoxinB) Injection. Prescribing Information. San Francisco, CA: Solstice Neurosciences; revised May 2010. Available at: https://www.myobloc.com/files/MYOBLOC_PI.pdf.
97. Stein E. Botulinum toxin and anal fissure. Curr Probl Dermatol. 2002; 30:218-26.
98. Terranova W, Breman JG, Locey RP et al. Botulism type B: epidemiologic aspects of an extensive outbreak. Am J Epidemiol. 1978; 108:150-6.
99. Toni T, Tamanaha R, Newman B, et al. Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. Neurol Sci 2021; 42:5373.
100. Trosch RM, Adler CH, Pappert EJ. Botulinum toxin type B (Myobloc(R)) in subjects with hemifacial spasm: Results from an open-label, dose-escalation safety study.
101. Truong D, Duane DD, Jankovic J et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005; 20:783-91.
102. Truong DD, Cullis PA, O'Brien CF et al. BotB (Botulinum toxin type B): evaluation of safety and tolerability in botulinum toxin type A-resistant cervical dystonia patients (preliminary study). Mov Disorders. 1997; 12:772-5.
103. Tsui JK. Botulinum toxin as a therapeutic agent. Pharmacol Ther. 1996; 72:13-24.
104. Tsui JKC, Hayward M, Mak EKM et al. Botulinum toxin type B in the treatment of cervical dystonia: a pilot study. Neurology. 1995; 45:2109-10.
105. van Laborde S, Dover JS, Moore M et al. Reduction in injection pain with botulinum toxin type B further diluted using saline with preservative: a double-blind, randomized controlled trial. J Am Acad Dermatol. 2003; 48:875-7.
106. Wenzel R, Jones D, Borrego JA. Comparing two botulinum toxin type A formulations using manufacturers' product summaries. J Clin Pharm Ther. 2007; 32:387-402.
107. Woodcock J (US Food and Drug Administration). Response to Public Citizen's petition on botulinum toxin re: docket no: FDA-2008-P-0061. Rockville, MD; 2009 April 30. From FDA website.

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Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Plaque psoriasis is a chronic autoimmune skin condition that affects approximately 2-3% of the global population. It is characterized by red, raised, scaly plaques on the skin, which can cause itching, pain, and significant psychological distress. Moderate to severe plaque psoriasis is typically defined as affecting more than 10% of the body surface area or having a significant impact on a patient's quality of life.

Drug treatment options for moderate to severe plaque psoriasis fall into several categories, including topical treatments, phototherapy, and systemic therapies.

- Topical treatments include treatment options such as vitamin D analogues, calcineurin inhibitors, keratolytics, and corticosteroids. These medications are applied directly to the skin and can help reduce inflammation and improve symptoms. However, they are generally only effective for mild to moderate psoriasis and may not be sufficient for patients with more severe disease, when a large portion of the body is affected, or those who may have difficulty applying the topical product to their own body.

- Phototherapy involves exposing the skin to ultraviolet (UV) light, which can help slow down the production of skin cells and reduce inflammation. This treatment can be effective for patients with moderate to severe plaque psoriasis, but it may require multiple sessions, can increase the risk of skin cancer, and may not be used on some sensitive affected areas (e.g., genitals, face).
- Systemic therapies include biologic agents, non-biologic agents, and oral medications. Biologic agents, such as tumor necrosis factor (TNF) inhibitors (e.g., adalimumab, certolizumab pegol, etanercept, infliximab) and interleukin (IL) inhibitors (e.g., bimekizumab, guselkumab, ixekizumab, risankizumab,secukinumab, tildrakizumab, ustekinumab), are targeted therapies that work by blocking specific molecules in the immune system that are involved in the development of psoriasis. Non-biologic agents, such as apremilast and tofacitinib, also work by targeting specific molecules in the immune system. Oral medications, such as methotrexate and acitretin, are systemic therapies that can help reduce inflammation and slow down the production of skin cells.

Ilumya (tildrakizumab-asmn)is FDA-approved for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Ilumya must be administered as a subcutaneous injection by a healthcare professional. The recommended dosage is 100 mg at Weeks 0, 4, and every 12 weeks thereafter. The medication works as an IgG1 kappa monoclonal antibody, inhibiting the effects of IL-23, to decrease the immune/inflammatory response that leads to the symptoms seen with plaque psoriasis.

Definitions

"Body surface area (BSA)" is a measure of the total area involved by plaques in relation to the total body surface area. There are a number of different methods, however most clinical trials on plaque psoriasis use the "handprint method", where the patient's actual palm/hand size is estimated as 1% of BSA. The head and neck, upper extremities, trunk, and lower extremities (including buttocks) typically correspond to approximately 10%, 20%, 30% and 40% of the BSA, respectively.

"Immune modulator" refers to the class of medications that function by inhibiting or activating various pathways of the immune system in an effort to reduce inflammatory/immune reactions.

"Monoclonal Antibody" is a type of drug that consists of a single clone of antibodies aimed against a specific target. Ilumya, for example, is a monoclonal antibody against IL-23.

"Plaque psoriasis" is a chronic skin disorder characterized by the formation of cutaneous plaques, which appear as scaly, raised lesions on the surface of the skin. These plaques can occur anywhere on the body and typically fluctuate in their location and severity.

"Systemic Therapy" refers to the broad category of agents infused for the treatment of plaque psoriasis.

"Phototherapy" is the use of ultraviolet light to treat the symptoms of plaque psoriasis. It can be performed as phototherapy alone with UVB or as photochemotherapy using UVA in combination with a photosensitizing drug (PUVA).

"PASI score" is the Psoriasis Area and Severity Index (PASI), which is the gold-standard for measurement of psoriasis severity. It combines a measure of the severity of lesions (erythema, or redness; induration, or hardening or thickening of tissue; and scaling) and the area affected into a single score, ranging from 0 (no disease) to 72 (maximal disease).

Medical Necessity Criteria for Initial Authorization

The Plan considers initial therapy for **Ilumya (tildrakizumab-asmn)** medically necessary when **ALL** of the following criteria are met:

1. The medication is being prescribed by or in consultation with a dermatologist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a diagnosis of moderate to severe plaque psoriasis as defined by **ONE** of the following:
    a. Psoriasis Area and Severity Index (PASI) score ≥12 or greater; ***or***
    b. Body Surface Area (BSA) is ≥10%; ***or***
    c. Body Surface Area (BSA) is ≥3% and plaques involve a sensitive region (e.g. face, head/neck/scalp, genitalia, hands, feet) or limit functional ability; ***AND***
4. The member is unable to use, or has adequately tried and failed **BOTH** of the following:
    a. phototherapy (e.g., UVB, PUVA) **OR** topical treatments (e.g., anthralin, calcipotriene, coal tars, corticosteroids, and/or tazarotene); ***and***
    b. at least 3 months of a conventional systemic therapy (e.g., methotrexate, cyclosporine, or acitretin) at maximally indicated doses; ***AND***
5. The member does **NOT** have documented evidence of **ANY** of the following:
    a. active serious infection; ***or***
    b. active TB infection; ***or***

c. concurrent use of a biologic or targeted synthetic disease-modifying antirheumatic drugs (DMARD) in combination with Ilumya; ***AND***

6. The member has a documented negative tuberculosis skin test within the last 12 months.

If the above prior authorization criteria are met, Ilumya will be approved for up to 12-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 12 months will be granted if **BOTH** of the following are met:

1. The member still meets the applicable initial criteria; ***AND***
2. chart documentation shows **ONE** of the following:
    a. At least 75% improvement in PASI score compared to baseline***; or***
    b. A reduction in body surface area (BSA) affected since starting treatment***; or***
    c. Chart documentation showing improvement or maintenance of disease activity.

Experimental or Investigational / Not Medically Necessary

Ilumya (tildrakizumab-asmn) for any other indication is *not* considered medically necessary by the Plan, or it is considered experimental or investigational and include, but are not limited to, the following:

- Use in pediatric populations (<18 years old), as the safety and efficacy of Ilumya has not been evaluated in this patient population***; or***
- In combination with any of the following medications, as there is limited evidence to support this:
    - Biologic Disease-modifying antirheumatic drugs (DMARDs)***; or***
    - Janus kinase inhibitors***; or***
    - Phosphodiesterase 4 (PDE4) inhibitors***; or***
- In patients needing or expected to receive a live vaccine***; or***
- In patients with latent or active TB***; or***
- In patients with a current active infection, including infections of the skin***; or***
- To treat any other condition besides chronic plaque psoriasis (e.g., acute graft-versus-host disease, vitiligo, bullous pemphigoid, alopecia, psoriatic arthritis, ankylosing spondylitis, and/or non-radiographic axial spondyloarthritis) .

Applicable Billing Codes (HCPCS/CPT Codes)

Ilumya (tildrakizumab-asmn)	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
J3245	Injection, tildrakizumab, 1 mg
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
L40.0	Psoriasis vulgaris

References

1. American Academy of Dermatology (AAD). (2018). Psoriasis clinical guidelines. Retrieved from: https://www.aad.org/practicecenter/quality/clinical-guidelines/psoriasis
2. Armstrong AW, Siegel MP, Bagel J, et al. From the Medical Board of the National Psoriasis Foundation: Treatment targets for plaque psoriasis. J Am Acad Dermatol 2017; 76:290.
3. Bartos, S., Hill, D., & Feldman, S. R. (2016). Review of maintenance of response to psoriasis treatments. Journal of Dermatological Treatment, 27(4), 293-297.
4. Bhatia N, Heim J, Vasquez JG, et al.,. Long-term quality of life outcomes from a phase 4 study of tildrakizumab in patients with moderate-to-severe plaque psoriasis in a real-world setting. J Dermatolog Treat. 2024 Dec;35(1):2310631. doi: 10.1080/09546634.2024.2310631. Epub 2024 Jul 22.
5. Bolognia J, Jorizzo JL, & Schaffer JV. (2017). Dermatology. Philadelphia: Elsevier
6. Brunasso G, Massone C. Palmoplantar pustulosis: Treatment. UpToDate. Last updated: Dec 4, 2019.
7. Chat VS, Ellebrecht CT, Kingston P, et al,. Vaccination recommendations for adults receiving biologics and oral therapies for psoriasis and psoriatic arthritis: Delphi consensus from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2024 Jun;90(6):1170-1181. doi: 10.1016/j.jaad.2023.12.070. Epub 2024 Feb 7.
8. Egeberg A, Jullien D, Gaarn Du Jardin K, Thaçi D. Five-year safety of tildrakizumab in patients with moderate-to-severe psoriasis from two phase 3 trials (reSURFACE 1 and reSURFACE 2): number needed to harm for occurrence of adverse events of special interest. J Dermatolog Treat. 2023 Dec;34(1):2220447. doi: 10.1080/09546634.2023.2220447.
9. Elmets CA, Korman NJ, Prater EF, et al,. Joint AAD-National Psoriasis Foundation (NPF) Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol. 2021 Feb;84(2):432-470. doi: 10.1016/j.jaad.2020.07.087. Epub 2020 Jul 30.

10. Elmets, CA, Leonardi CL, David DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. Journal of the American Academy of Dermatology.2019;80(4):1073-1113. DOI:https://doi.org/10.1016/j.jaad.2018.11.058.
11. Feldman, SR. Treatment of psoriasis in adults. UpToDate. Last updated: Feb 11, 2019.
12. Food and Drug Administration. Tildrakizumab package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761067s000lbl.pdf.
13. Gladman D, Ritchlin C. Treatment of psoriatic arthritis. UpToDate. Last updated: Nov 20, 2020.
14. Ilumya (tildrakizumab-asmn) [prescribing information]. Cranbury, NJ: Sun Pharmaceutical Industries Inc; April 2024.
15. Heim J, Vasquez JG, Bhutani T, et al,. Tildrakizumab Real-World Effectiveness and Safety Over 64 Weeks in Patients With Moderate-to-Severe Plaque Psoriasis. J Drugs Dermatol. 2024 Aug 1;23(8):612-618. doi: 10.36849/JDD.8217.
16. Kalb RE. Pustular psoriasis: Management. UpToDate. Last Updated: April 14, 2020.
17. Khalilieh S, Hussain A, Montgomery D et al. Effect of tildrakizumab (MK-3222), a high affinity, selective anti-IL23p19 monoclonal antibody, on cytochrome P450 metabolism in subjects with moderate to severe psoriasis. Br J Clin Pharmacol. 2018; 84:2292-2302.
18. Kimball AB, Papp KA, Reich K, et al,. Efficacy and safety of tildrakizumab for plaque psoriasis with continuous dosing, treatment interruption, dose adjustments and switching from etanercept: results from phase III studies. Br J Dermatol. 2020 Jun;182(6):1359-1368. doi: 10.1111/bjd.18484. Epub 2019 Nov 19.
19. Mehta D, Lim HW. Ultraviolet B phototherapy for psoriasis: review of practical guidelines. American journal of clinical dermatology. 2016 Apr 1;17(2):125-33.
20. Menter A, Gelfand JM, Wu JJ, et al. Joint AAD-NPF guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Am Acad Dematol. 2020; 82(6):1445-1486. DOI:https://doi.org/10.1016/j.jaad.2020.02.044.
21. Menter A, Strober BE, Kaplan DH, et al. 2019. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. JAAD. 2019, 80 (4), p.P1029-1072. https://www.jaad.org/article/S0190-9622(18)33001-9/fulltext
22. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. J Am Acad Dermatol. 2019; 80 (4): 1029-1072.
23. Merck & Co., Inc.Ilumya (tildrakizumab-asmn) injection, for subcutaneous use.Prescribing Information. Whitehouse Station, NJ: Merck & Co., Inc.; revised March 2018.
24. Nast A, Smith C, Spuls PI, et al,. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498. doi: 10.1111/jdv.16915.
25. Papp K, Thaci D, Reich K, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol. 2015;173(4):930-939.
26. Racz E, Prens EP. Phototherapy and photochemotherapy for psoriasis. Dermatologic clinics. 2015 Jan 1;33(1):79-89.
27. Reich K, Papp KA, Blauvelt A, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet. 2017 Jul 15;390(10091):276-288.
28. Reich K, Warren RB, Iversen L et al. Long-term efficacy and safety of tildrakizumab for moderate-to-severe psoriasis: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2) through 148 weeks. Br J Dermatol. 2020; 182:605-617.

29. Sbidian E, Chaimani A, Garcia-Doval I, et al.Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. Cochrane Database Syst Rev. 2017;12:CD011535. doi: 10.1002/14651858.CD011535.pub2.
30. Smith CH, Jabbar-Lopez ZK, Yiu ZZ, et al.British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017.Br J Dermatol. 2017;177(3):628.
31. Smith CH, Yiu ZZN, Bale T, et al,. British Association of Dermatologists guidelines for biologic therapy for psoriasis 2020: a rapid update. Br J Dermatol. 2020 Oct;183(4):628-637. doi: 10.1111/bjd.19039. Epub 2020 Jul 21.
32. Sun Pharmaceutical Industries, Inc. Ilumya US Prescribing Information. Cranbury, NJ: Sun Pharma Global FZE; revised July 2020. Retrieved from www.ilumyapro.com.
33. Sun Pharmaceutical Industries. Ilumya® (tildrakizumab-asmn) injection, for subcutaneous use prescribing information. Cranbury, NJ; 2021 Mar.
34. Ter Haar ELM, Van den Reek JMPA, Gaarn Du Jardin K, et al,. Efficacy and Safety of Tildrakizumab in Older Patients: Pooled Analyses of Two Randomized Phase III Clinical Trials (reSURFACE 1 and reSURFACE 2) Through 244 Weeks. Acta Derm Venereol. 2023 Oct 25;103:adv17752. doi: 10.2340/actadv.v103.17752.
35. Thaci D, Piaserico S, Warren RB, et al,. Five-year efficacy and safety of tildrakizumab in patients with moderate-to-severe psoriasis who respond at week 28: pooled analyses of two randomized phase III clinical trials (reSURFACE 1 and reSURFACE 2). Br J Dermatol. 2021 Aug;185(2):323-334. doi: 10.1111/bjd.19866. Epub 2021 May 4.
36. West, J and colleagues. Safety and Efficacy of Methotrexate in Psoriasis: A Meta-Analysis of Published Trials. PLoS One. 2016 May 11;11(5):e0153740

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Oscar Clinical Guideline: Casgevy (exagamglogene autotemcel) (CG113, Ver. 2)

Casgevy (exagamglogene autotemcel)

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Summary

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes and causes red blood cells to become rigid and sickle-shaped. This leads to vaso-occlusion (blockage of blood flow through blood vessels), hemolysis (destruction of red blood cells), and endothelial dysfunction, causing acute complications like painful vaso-occlusive crises, acute chest syndrome, and stroke, as well as chronic organ damage. Standard treatment includes hydroxyurea to increase fetal hemoglobin levels, red blood cell transfusions, and more recently, novel targeted therapies like voxelotor (which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab). However, many patients continue to experience recurrent severe crises despite available therapies. Allogeneic hematopoietic stem cell transplant can be curative but is limited by donor availability and transplant-related risks.

Beta thalassemia is an inherited blood disorder caused by mutations in the beta-globin gene, leading to reduced or absent beta-globin production. In transfusion-dependent beta thalassemia, the severe

imbalance in alpha- and beta-globin chains results in ineffective erythropoiesis (creation of red blood cells), severe anemia, and complications from iron overload due to chronic transfusions. Standard treatment is regular red blood cell transfusions and iron chelation therapy. Allogeneic hematopoietic stem cell transplant can be curative but has limitations as in sickle cell disease.

Casgevy (exagamglogene autotemcel) is an autologous ex vivo CRISPR-Cas9 gene-edited hematopoietic stem cell therapy for patients 12 years and older with sickle cell disease with recurrent vaso-occlusive crises or transfusion-dependent beta thalassemia. Casgevy works by disrupting a key erythroid enhancer of the BCL11A gene in autologous hematopoietic stem cells, thereby increasing fetal hemoglobin (HbF) expression and correcting the underlying pathophysiology of these disorders. In sickle cell disease, HbF reduces hemoglobin S concentration, preventing red blood cell sickling, reducing the risk of vaso-occlusive crises. In transfusion-dependent Beta-thalassemia, the increased gamma-globin (a benefit of reducing BCL11A expression) improves the alpha-globin to non-alpha-globin chains, reducing the production of ineffective red blood cells, reducing risk of hemolysis, and increasing hemoglobin (improving anemias). Casgevy (exagamglogene autotemcel) is given as a one-time, single dosage intravenous product.

Definitions

"**Beta thalassemia**" refers to a group of inherited blood disorders caused by mutations in the beta-globin gene, leading to reduced or absent beta-globin production and an imbalance in alpha- and beta-globin chains, resulting in ineffective erythropoiesis and anemia of varying severity.

"**Fetal hemoglobin (HgF)**" is the main hemoglobin produced during fetal development and has a higher affinity for oxygen than adult hemoglobin. Increasing fetal hemoglobin expression is a key therapeutic strategy in sickle cell disease and beta thalassemia, as it can inhibit sickle hemoglobin polymerization and compensate for deficient adult beta-globin production.

"**Hematopoietic stem cell transplantation**" refers to the procedure of infusing hematopoietic stem cells from a donor (allogeneic) or the patient (autologous) to re-establish normal hematopoiesis and potentially cure genetic blood disorders by replacing the patient's defective stem cells with functional ones.

"**Karnofsky Performance Status (KPS)**" refers to a widely used tool for assessing the functional status of adult patients. It is a scale that ranges from 0 to 100, where 100 represents normal functioning with no complaints or evidence of disease, and 0 represents death.

"**Lansky Performance Status (LPS)**" refers to a scale designed specifically for assessing the functional status of pediatric patients (typically under 16 years of age). Like the KPS, the LPS ranges from 0 to 100, with 100 representing fully active, normal functioning and 0 representing death.

"**Mobilization and apheresis**" refers to the process of administering medications (typically G-CSF and plerixafor) to mobilize hematopoietic stem cells from the bone marrow into peripheral blood, followed by collecting the stem cells by apheresis for cell processing and manufacturing of the gene-modified cell therapy product.

"**Myeloablative conditioning**" refers to high-dose chemotherapy (typically busulfan) given to eliminate the patient's diseased bone marrow and immune system prior to hematopoietic stem cell infusion, creating space for engraftment of the gene-edited cells and minimizing the risk of graft rejection.

"**Sickle cell disease**" refers to a group of inherited blood disorders caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped and prone to hemolysis and vaso-occlusion, leading to a complex pathophysiology involving chronic inflammation, endothelial dysfunction, and end-organ damage.

"**Transfusion-dependent beta thalassemia**" refers to the most severe phenotype of beta thalassemia (typically beta-zero thalassemia or hemoglobin E/beta-zero thalassemia) in which regular red blood cell transfusions every 2-5 weeks are required to maintain a pre-transfusion hemoglobin level above 9-10 g/dL, prevent complications of anemia and ineffective erythropoiesis, and allow for normal growth and development.

"**Vaso-occlusive crisis**" refers to the hallmark acute complication of sickle cell disease caused by obstruction of blood flow in the microcirculation by sickled red blood cells, leading to tissue ischemia and severe pain, often requiring hospitalization for pain management, intravenous fluids, and other supportive care. Frequent recurrent vaso-occlusive crises (≥2-3 per year) are a marker of severe disease and an indication for disease-modifying therapies and curative options like stem cell transplantation or gene therapy.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Casgevy (exagamglogene autotemcel)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a hematologist or specialist with expertise in sickle cell disease or gene therapies; ***AND***
2. The member is 12 years of age or older; ***AND***
3. The member has one of the following qualifying diagnoses confirmed by molecular or genetic testing:
    a. Sickle cell disease with documented **β**S/**β**S, **β**S/**β**0, or **β**S/**β**+ genotype and severe disease characterized by a history of at least 2 severe vaso-occlusive crises per year in the past 2 years despite receiving appropriate supportive care (e.g., hydroxyurea, L-glutamine, voxelotor, crizanlizumab, chronic transfusions). Severe vaso-occlusive crises are defined as any one of the following:
        i. Acute pain event requiring a medical facility visit and administration of pain medications (e.g., opioids or IV NSAIDs) or RBC transfusion; ***or***
        ii. Acute chest syndrome, as indicated by a new pulmonary infiltrate with pneumonia-like symptoms, pain, or fever; ***or***
        iii. Priapism lasting > 2 hours requiring a medical facility visit; ***or***
        iv. Splenic sequestration, as defined by an enlarged spleen, left upper quadrant pain, and an acute decrease in hemoglobin concentration of ≥2 g/dL; ***or***
    b. Transfusion-dependent beta thalassemia requiring ≥ 100 mL/kg/year or ≥ 10 packed RBC units/year of transfusions within the past 2 years; ***AND***
4. The member is an appropriate candidate for hematopoietic stem cell transplantation (HSCT), but does not have an available and suitable, complete HLA-matched related donor; ***AND***
5. For members ≥ 16 years of age, Karnofsky performance status ≥ 80%, or for members < 16 years of age, Lansky performance status ≥ 80%; ***AND***
6. The member does NOT have ANY of the following:
    a. A history of hypersensitivity to dimethyl sulfoxide (DMSO) or dextran 40; ***or***
    a. Any contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients; ***or***
    b. Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV); ***or***
    c. Pregnant or breastfeeding; ***or***
    d. Prior allogeneic or autologous stem cell transplant or gene therapy (Casgevy or any other) for the requested diagnosis; ***or***
    e. Significant organ dysfunction:

i. Liver: direct bilirubin > 2.5 times the upper limit of normal (ULN), aspartase transaminase or alanine transaminase > 3 times ULN, or bridging fibrosis or cirrhosis on liver biopsy; ***or***
ii. Kidney: estimated glomerular filtration rate < 60 mL/min/1.73 m^2; ***or***
iii. Heart (TDT only): Cardiac T2* < 10 ms by MRI or LVEF < 45% by ECHO; ***or***

f. For sickle cell disease:
i. For age 12-16 years: Abnormal transcranial Doppler velocity ≧ 200 cm/sec; ***or***
ii. History of stroke; ***or***
iii. Untreated or high-risk Moyamoya syndrome; ***AND***

7. Prescriber attests that:
a. Disease-modifying therapies and iron chelation will be discontinued at the specified intervals before cell collection and conditioning:
i. all disease-modifying therapies (e.g. hydroxyurea, voxelotor, crizanlizumab) at least 8 weeks prior to mobilization.
ii. iron chelation at least 7 days prior to conditioning.
b. back-up collection of ≥ 2 x 10^6 unmodified CD34+ rescue cells/kg will be collected and cryopreserved prior to myeloablative conditioning; ***AND***
8. Dose is within the recommended range of:
a. Minimum of 3.0 × 10^6 CD34+ cells/kg***; and***
b. Maximum of 19.7 x 10^6 CD34+ cells/kg.

If the above prior authorization criteria are met, Casgevy (exagamglogene autotemcel) will be authorized as a one-time 9-months approval for a single infusion.

Medical Necessity Criteria for Reauthorization

There are no medical necessity criteria for reauthorization of Casgevy (exagamglogene autotemcel). The FDA label specifies Casgevy as a single-dose gene therapy. Casgevy is intended to be a one-time gene therapy. It is expected to provide durable, potentially life-long effects with a single infusion by addressing the underlying genetic cause of sickle cell disease or transfusion-dependent beta thalassemia.

In clinical trials, a single infusion of Casgevy demonstrated sustained efficacy in eliminating severe vaso-occlusive crises in sickle cell disease and transfusion requirements in beta thalassemia for the duration of follow-up (at least 2 years and up to 4 years). There is no evidence to support the safety or efficacy of repeat administration.

Experimental or Investigational / Not Medically Necessary

Casgevy (exagamglogene autotemcel) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Re-treatment [Casgevy (exagamglogene autotemcel) is indicated for one-time single-dose intravenous use only. There is no evidence to support the safety or efficacy of repeat administration.]
- Use in pediatric members aged less than 12 years [The safety and efficacy of Casgevy (exagamglogene autotemcel) in pediatric patients aged less than 12 years has not been established.]
- Use in members who do not meet the specified clinical criteria for sickle cell disease severity or transfusion-dependence in beta thalassemia [Casgevy has only been studied in patients with severe, frequently symptomatic disease that is inadequately managed with available therapies.]
- Use in members with significant comorbidities or organ dysfunction that would preclude safe administration of myeloablative conditioning and hematopoietic stem cell transplantation [Certain pre-existing conditions increase the risk of serious complications and were excluded from clinical trials.]
- Use as salvage therapy after failure of allogeneic stem cell transplantation or a different gene therapy [The efficacy and safety of Casgevy in these contexts have not been established, and re-treatment would carry additional risks.]
- Prophylactic use to prevent sickle cell disease complications in asymptomatic individuals or those with infrequent, mild symptoms [The risk-benefit balance may not be favorable in low-risk patients given the intensive nature of the treatment and potential for adverse effects.]

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); additional sequential infusion of a new drug/substance, up to 1 hour (List separately in addition to code for primary procedure)
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); concurrent infusion (List separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
96376	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); each additional sequential intravenous push of the same substance/drug provided in a facility (List separately in addition to code for primary procedure)
96409	Chemotherapy administration; intravenous, push technique, single or initial substance/drug
J3392	Injection, exagamglogene autotemcel, per treatment
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
D56.1	Beta Thalassemia
D56.5	Hemoglobin E-beta thalassemia
D57.00	Hb-Ss Disease With Crisis, Unspecified
D57.01	Hb-Ss Disease With Acute Chest Syndrome
D57.02	Hb-Ss Disease With Splenic Sequestration
D57.03	Hb-Ss Disease With Cerebral Vascular Involvement
D57.04	Hb-Ss Disease With Dactylitis
D57.09	Hb-Ss Disease With Crisis With Other Specified Complication
D57.1	Sickle-Cell Disease Without Crisis
D57.20	Sickle-Cell/Hb-C Disease Without Crisis
D57.211	Sickle-Cell/Hb-C Disease With Acute Chest Syndrome
D57.212	Sickle-Cell/Hb-C Disease With Splenic Sequestration

D57.213	Sickle-Cell/Hb-C Disease With Cerebral Vascular Involvement
D57.214	Sickle-Cell/Hb-C Disease With Dactylitis
D57.218	Sickle-Cell/Hb-C Disease With Crisis With Other Specified Complication
D57.219	Sickle-Cell/Hb-C Disease With Crisis, Unspecified
D57.40	Sickle-Cell Thalassemia Without Crisis
D57.411	Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome
D57.412	Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration
D57.413	Sickle-Cell Thalassemia, Unspecified, With Cerebral Vascular Involvement
D57.414	Sickle-Cell Thalassemia, Unspecified, With Dactylitis
D57.418	Sickle-Cell Thalassemia, Unspecified, With Crisis With Other Specified Complication
D57.419	Sickle-Cell Thalassemia, Unspecified, With Crisis
D57.42	Sickle-Cell Thalassemia Beta Zero Without Crisis
D57.431	Sickle-Cell Thalassemia Beta Zero With Acute Chest Syndrome
D57.432	Sickle-Cell Thalassemia Beta Zero With Splenic Sequestration
D57.433	Sickle-Cell Thalassemia Beta Zero With Cerebral Vascular Involvement
D57.434	Sickle-Cell Thalassemia Beta Zero With Dactylitis
D57.438	Sickle-Cell Thalassemia Beta Zero With Crisis With Other Specified Complication
D57.439	Sickle-Cell Thalassemia Beta Zero With Crisis, Unspecified
D57.44	Sickle-Cell Thalassemia Beta Plus Without Crisis
D57.451	Sickle-Cell Thalassemia Beta Plus With Acute Chest Syndrome
D57.452	Sickle-Cell Thalassemia Beta Plus With Splenic Sequestration
D57.453	Sickle-Cell Thalassemia Beta Plus With Cerebral Vascular Involvement
D57.454	Sickle-Cell Thalassemia Beta Plus With Dactylitis
D57.458	Sickle-Cell Thalassemia Beta Plus With Crisis With Other Specified Complication
D57.459	Sickle-Cell Thalassemia Beta Plus With Crisis, Unspecified
D57.80	Other Sickle-Cell Disorders Without Crisis
D57.811	Other Sickle-Cell Disorders With Acute Chest Syndrome
D57.812	Other Sickle-Cell Disorders With Splenic Sequestration

D57.813	Other Sickle-Cell Disorders With Cerebral Vascular Involvement
D57.814	Other Sickle-Cell Disorders With Dactylitis
D57.818	Other Sickle-Cell Disorders With Crisis With Other Specified Complication
D57.819	Other Sickle-Cell Disorders With Crisis, Unspecified
H36.811	Nonproliferative sickle-cell retinopathy, right eye
H36.812	Nonproliferative sickle-cell retinopathy, left eye
H36.813	Nonproliferative sickle-cell retinopathy, bilateral
H36.819	Nonproliferative sickle-cell retinopathy, unspecified eye
H36.821	Proliferative sickle-cell retinopathy, right eye
H36.822	Proliferative sickle-cell retinopathy, left eye
H36.823	Proliferative sickle-cell retinopathy, bilateral
H36.829	Proliferative sickle-cell retinopathy, unspecified eye
O35.2XX0	Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified
O99.019	Anemia complicating pregnancy, unspecified trimester
P09.3	Abnormal findings on neonatal screening for congenital hematologic disorders

References

1. Casgevy (exagamglogene autotemcel) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; January 2024.
2. Beaudoin F, Thokala P, Nikitin D, et al. Draft Evidence Report. Gene therapies for sickle cell disease: effectiveness and value. Institute for Clinical and Economic Review; April 12, 2023. Available at: https://icer.org/wp-content/uploads/2023/04/SCD_FOR-PUBLICATION.pdf
3. Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, et al. Guidelines for the Clinical Management of Thalassaemia, 2nd Revised Edition. 2008. Thalassaemia International Federation. Available at: https://www.ncbi.nlm.nih.gov/books/NBK173968/
4. Cappellini MD, Farmakis D, Porter J, Taher A, editors. 2021 Guidelines: For the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th ed. Nicosia (Cyprus): Thalassaemia International Federation; 2023.
5. Esrick EB et al: Post-transcriptional genetic silencing of BCL11A to treat sickle cell disease. N Engl J Med. 384(3):205-15, 2021
6. Exagamglogene autotemcel for treating transfusion-dependent beta-thalassaemia in people 12 years and over. London: National Institute for Health and Care Excellence (NICE); 2024 Sep 11. PMID: 39812567.

7. Farmakis D, Porter J, Taher A, Domenica Cappellini M, et al. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. HemaSphere. 2022;6(8):e732. doi:10.1097/hs9.0000000000000732
8. Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med. 2021;384(3):252-260. doi:10.1056/NEJMoa2031054
9. Frangoul H, Locatelli F, Sharma A, et al,. Exagamglogene Autotemcel for Severe Sickle Cell Disease. N Engl J Med. 2024 May 9;390(18):1649-1662. doi: 10.1056/NEJMoa2309676. Epub 2024 Apr 24.
10. Kanter J et al: American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 5(18):3668-89, 2021
11. Kanter J et al: Biologic and clinical efficacy of LentiGlobin for sickle cell disease. N Engl J Med. 386(7):617-28, 2022
12. Locatelli F, Lang P, Wall D, et al,. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia. N Engl J Med. 2024 May 9;390(18):1663-1676. doi: 10.1056/NEJMoa2309673. Epub 2024 Apr 24.
13. Mahesri M, Lee SB, Levin R, et al,. Infrequent Resolution of Vaso-Occlusive Crises in Routine Clinical Care Among Patients Mimicking the Exa-Cel Trial Population: A Cohort Study of Medicaid Enrollees. Clin Pharmacol Ther. 2024 Dec;116(6):1572-1579. doi: 10.1002/cpt.3449. Epub 2024 Sep 27.
14. National Heart, Lung, and Blood Institute: Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. NHLBI website. Published 2014. Available at: https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease.
15. Schlenz AM et al: Practice patterns for stroke prevention using transcranial Doppler in sickle cell anemia: DISPLACE Consortium. Pediatr Blood Cancer. 67(4):e28172, 2020
16. Wu Y, Zeng J, Roscoe BP, et al. Highly efficient therapeutic gene editing of human hematopoietic stem cells. Nat Med. 2019;25(5):776-783. doi:10.1038/s41591-019-0401-y

Clinical Guideline Revision / History Information

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Clinical Guideline

Oscar Clinical Guideline: sodium oxybate (Xyrem) (PG009, Ver. 8)

sodium oxybate (Xyrem)

Disclaimer

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Summary

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement (REM) sleep manifestations. It is classified into two types: narcolepsy type 1 (NT1), which includes cataplexy, and narcolepsy type 2 (NT2), without cataplexy. The disorder affects approximately 1 in 2,000 people and is caused by the loss of hypothalamic neurons that produce hypocretin (orexin), a neuropeptide that regulates wakefulness and REM sleep.

Treatment options for narcolepsy include central nervous system stimulants (e.g., modafinil, armodafinil, methylphenidate, amphetamines) for EDS, and antidepressants (e.g., SSRIs, SNRIs, TCAs) or sodium oxybate for cataplexy. Behavioral modifications, such as scheduled naps and sleep hygiene, are also important components of management.

Xyrem (sodium oxybate) is an oral solution of gamma-hydroxybutyrate (GHB), approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with

narcolepsy. It is classified as a central nervous system depressant and is believed to act through GABA-B receptors, although its exact mechanism of action in narcolepsy is not fully understood. Xyrem (sodium oxybate) is typically administered in two equally divided doses: the first dose at bedtime and the second dose 2.5 to 4 hours later.

Definitions

"**Cataplexy**" refers to a sudden, transient episode of muscle weakness accompanied by full conscious awareness, typically triggered by emotions such as laughing, crying, or terror.

"**Excessive daytime sleepiness (EDS)**" is the inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep.

"Hypocretin-1" is a natural chemical in the brain that helps regulate wakefulness.

"**Idiopathic hypersomnia (IH)**" is a neurological disorder characterized by excessive daytime sleepiness that is not caused by disturbed sleep at night, other medical conditions, or medications.

"**Multiple Sleep Latency Test (MSLT)**" is a sleep study that measures how quickly a person falls asleep during the day and whether they enter rapid eye movement (REM) sleep.

"**Narcolepsy**" is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles.

"Polysomnography (PSG)" is a sleep study used to diagnose sleep disorders by measuring certain components such as brain activity, oxygen levels, heart rate, breathing, eye movements, and leg movements.

"Sleep latency" is the amount of time it takes to fall asleep.

"**Sleep-onset REM periods (SOREMPs)**" are periods of rapid eye movement sleep that occur within 15 minutes of falling asleep, which are characteristic of narcolepsy.

Medical Necessity Criteria for Initial Authorization

The Plan considers **sodium oxybate (Xyrem)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a sleep medicine specialist, neurologist, psychiatrist, or pulmonologist with expertise in treating sleep disorders***; AND***
2. The member is 7 years of age or older; ***AND***
3. The member has a diagnosis of narcolepsy that has been confirmed by sleep lab testing or documented clinical symptoms including excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** at least **ONE** of the following:
    a. Cataplexy episodes (for narcolepsy type 1)***; or***
    b. Hypocretin-1 (orexin A) deficiency (≤110 pg/mL or <1/3 of mean values of healthy individuals tested using the same standardized assay)***; or***
    c. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency ≤ 15 minutes, or a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency ≤ 8 minutes and ≥ 2 sleep-onset REM periods (SOREMPs). A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT***; AND***
4. The member has tried and failed prior treatments as follows:
    a. For members 18 years of age and older with narcolepsy, the member has tried and failed, or has a contraindication to, **ALL** of the following:
        i. Sunosi (solriamfetol); ***and***
        ii. Lumryz (sodium oxybate)***; and***
        iii. Wakix (pitolisant)***; or***
    b. For members 7 to 17 years of age with narcolepsy and excessive daytime sleepiness (EDS), the member has tried and failed, or has a contraindication to, **ALL** of the following:
        i. Wakix (pitolisant)***; and***
        ii. Lumryz (sodium oxybate); ***or***
    c. For members 7 to 17 years of age with narcolepsy and cataplexy, the member has tried and failed, or has a contraindication to, Lumryz (sodium oxybate)***; AND***
5. The member does **NOT** have **ANY** of the following:
    a. Succinic semialdehyde dehydrogenase (SSADH) deficiency***; or***
    b. Documentation indicating concomitant use with, or inability to abstain from, any of the following while taking Xyrem:
        i. Alcohol (e.g., beer, wine, whisky)***; or***
        ii. Sedative hypnotics (e.g., alprazolam, diazepam, lorazepam, zolpidem)***; or***

iii. Lumryz, Xywav, or other sodium oxybate products***; or***

c. A condition that better explains the hypersomnolence and/or MSLT findings, such as:

i. Insufficient sleep***; or***

ii. Obstructive sleep apnea***; or***

iii. Delayed sleep phase disorder***; or***

iv. The effect of medication or substances or their withdrawal***; AND***

6. Xyrem is being prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, sodium oxybate (Xyrem) will be approved for 12-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12-months will be granted if the member has recent (within the last 3-months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The member has experienced a positive clinical response to sodium oxybate (Xyrem) therapy as demonstrated by a reduction in symptoms of cataplexy and/or EDS; ***AND***
2. The member continues to abstain from alcohol and sedative hypnotics; ***AND***
3. sodium oxybate (Xyrem) will not be used in combination with Lumryz, Xywav, Wakix, or other sodium oxybate products; ***AND***
4. sodium oxybate (Xyrem) continues to be prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

Experimental or Investigational / Not Medically Necessary

Sodium oxybate (Xyrem) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Sodium oxybate (Xyrem) has been studied for various indications beyond its approved uses. However, the current evidence is limited and inconclusive for these non-supported indications:

- Alcohol Dependence/Alcohol Use Disorders (AUD).
- Alcohol Withdrawal Syndrome.
- Alternating Hemiplegia of Childhood.
- Anxiety, Post Traumatic/Post Traumatic Stress Disorder (PTSD).

- Binge Eating Disorder (BED).
- Chronic Fatigue Syndrome/Myalgic Encephalitis (CFS/ME).
- Cluster Headache.
- Essential Tremor.
- Fibromyalgia.
- Hypersomnia.
- Idiopathic Hypersomnia.
- Insomnia Related to Schizophrenia/Schizophrenia.
- Laryngeal Tremor/Spasmodic Dysphonia.
- Obstructive Sleep Apnea (OSA).
- Parkinson's Disease (PD)/Rapid Eye Movement Sleep Behavior Disorder.
- Sedative Abuse Prevention.
- Sleep Initiation and Maintenance Disorders.
- Traumatic Brain Injury (TBI).
- When used in combination with alcohol, sedative hypnotics, or other medications containing sodium oxybate, gamma-hydroxybutyrate (GHB), or GHB precursors.
- When used in members with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
- For members under 7 years of age, safety and efficacy have not been established in this pediatric population.

References

1. American Academy of Sleep Medicine. International Classification of Sleep Disorders: Diagnostic and Coding Manual. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Aran A, Einen M, Lin L, Plazzi G, Nishino S, Mignot E. Clinical and therapeutic aspects of childhood narcolepsy-cataplexy: a retrospective study of 51 children. Sleep. 2010;33(11):1457-1464
3. Donjacour, CE, Aziz, NA, Roelfsema, F, Frolich, M, Overeem, S, Lammers, GJ, Pijl, H. Effect of sodium oxybate on growth hormone secretion in narcolepsy patients and healthy controls. Am J Physiol Endocrinol Metab. 2011 Jun;300(6):E1069-75. doi: 10.1152/ajpendo.00623.2010. Epub 2011 Mar 29.
4. Hartley S, Quera-Salva MA, Machou M. Sodium oxybate and sleep apnea: a clinical case. J Clin Sleep Med. 2011;7(6):667-668. doi:10.5664/jcsm.1480
5. Huang, YS, Guilleminault, C. Narcolepsy: action of two gamma-aminobutyric acid type B agonists, baclofen and sodium oxybate. Pediatr Neurol. 2009 Jul;41(1):9-16. doi: 10.1016/j.pediatrneurol.2009.02.008.
6. Lumryz (sodium oxybate) [prescribing information]. Chesterfield, MO: Avadel CNS Pharmaceuticals, LLC; May 2023.

7. Mannucci, C, Pichini, S, Spagnolo, EV, Calapai, F, Gangemi, S, Navarra, M, Calapai, G. Sodium Oxybate Therapy for Alcohol Withdrawal Syndrome and Keeping of Alcohol Abstinence. Curr Drug Metab. 2018;19(13):1056-1064. doi: 10.2174/1389200219666171207122227.
8. Moresco M, Pizza F, Antelmi E, Plazzi G. Sodium oxybate treatment in pediatric type 1 narcolepsy. Curr Drug Metab. 2018;19(13):1073-1079.
9. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-17711
10. Robinson, DM, Keating, GM. Sodium oxybate: a review of its use in the management of narcolepsy. CNS Drugs. 2007;21(4):337-54. doi: 10.2165/00023210-200721040-00007.
11. van den Brink W, Addolorato G, Aubin HJ, et al. Efficacy and safety of sodium oxybate in alcohol-dependent patients with a very high drinking risk level. Addict Biol. 2018 Jul;23(4):969-986. doi: 10.1111/adb.12645.
12. Wallace DM, Maze T, Shafazand S. Sodium oxybate-induced sleep driving and sleep-related eating disorder. J Clin Sleep Med. 2011;7(3):310-311. doi:10.5664/JCSM.1082
13. Wise MS, Arand DL, Auger RR, et al. Treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1712-27.
14. Xyrem (sodium oxybate) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; October 2022.
15. Xyrem (sodium oxybate) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; April 2023.

Clinical Guideline Revision / History Information

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Oscar Clinical Guideline: sildenafil (PAH, Viagra) (PG051, Ver. 7)

sildenafil (PAH, Viagra)

- Sildenafil Citrate Powder for oral suspension [Pulmonary Hypertension]
- Sildenafil Citrate Oral tablet [Pulmonary Hypertension]
- Sildenafil Citrate Oral tablet (Viagra)

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Summary

Sildenafil is a selective phosphodiesterase type 5 (PDE5) inhibitor. It is administered orally for the treatment of pulmonary arterial hypertension (PAH) and male erectile dysfunction (ED). It can be administered intravenously for the treatment of PAH when the member is temporarily unable to tolerate the oral medication. There is also evidence to support the use of sildenafil in certain patients with a condition called Raynaud phenomenon (also referred to as idiopathic Raynaud phenomenon, primary Raynaud syndrome, or Raynaud disease) and for the prevention and treatment of high-altitude pulmonary edema.

Sildenafil comes in the following drug strengths and formulations: 20 mg tablets, 25 mg tablets, 50 mg tablets, 100 mg tablets, 10 mg/ml powder for suspension, and 10 mg/12.5 ml solution for injection.

- Sildenafil 25 mg tablets, 50 mg tablets, and 100 mg tablets are FDA indicated in the treatment of ED.
- Sildenafil 20 mg tablets, 10 mg/ml powder for suspension, and 10mg/12.5 ml solutions for injection are FDA indicated in the treatment of PAH.
- Sildenafil 20 mg tablets are also used off-label for Raynaud phenomenon.

NOTE: Erectile dysfunction is an excluded benefit for certain Plans. Coverage for medications to treat sexual dysfunction, including erectile dysfunction, varies depending on a member's benefits policy. Please review the member's coverage benefits to determine if erectile dysfunction is a covered benefit.

Definitions

"Erectile Dysfunction" refers to the consistent or recurrent inability to achieve or sustain an erection of sufficient rigidity and duration for sexual intercourse.

"**High-altitude pulmonary edema (HAPE)**" is a life-threatening condition that can occur in some people who rapidly ascend to high altitudes, usually higher than 2500 m [8202 ft] above sea level.

"Pulmonary arterial hypertension (PAH)" is a subset of pulmonary hypertension (PH), categorized into five groups based on etiology. Patients in the first group are considered to have PAH, whereas patients in the remaining four groups are considered to have PH.

"**Raynaud phenomenon (RP)**" is a condition characterized by temporary narrowing of the blood vessels that supply blood to the extremities, including the fingers and toes (and sometimes the ears, lips, nipples, or tip of the nose). This leads to skin discoloration, numbness, tingling, and potentially other complications.

Clinical Indications

The Plan considers **sildenafil (Viagra), sildenafil 20 mg tablets, sildenafil solution, and sildenafil oral suspension** medically necessary when **ALL** the following criteria are met for the applicable indication listed below:

For the treatment of Erectile Dysfunction (*if a covered benefit for the member*):

Medical Necessity Criteria for Initial Authorization

The Plan considers **sildenafil 25 mg, 50 mg, and 100 mg tablets (Viagra)** medically necessary when **ALL** of the following criteria are met:

1. the member is 18 years of age and older; ***AND***
2. the member is a male with erectile dysfunction (ED, impotence); ***AND***
3. clinical chart documentation is provided showing **ALL** of the following:
    a. a thorough medical history and physical examination has been undertaken to:
        i. support the diagnosis of erectile dysfunction**; *and***
        ii. determine potential underlying causes**; *and***
        iii. exclude potentially reversible or treatable causes (e.g., hypogonadism with inadequate testosterone replacement, hyperprolactinemia, drug-induced dysfunction, dyslipidemias, alcoholism, other substance abuse, hypertension, thyroid disease, cardiovascular or cerebrovascular disease, neurologic disease, adrenal dysfunction, psychologic dysfunction, marital discord, smoking)**; *and***
    b. a review of the member's current drug regimens has been conducted to detect possible drug-induced ED (e.g., antidepressant, antipsychotic, certain blood pressure medications); ***AND***
4. The member will not be taking sildenafil concomitantly with **ANY** of the following:
    a. Guanylate Cyclase Stimulators (such as Adempas (riociguat))**; *or***
    b. Nitrates and nitrites (e.g., nitroglycerin, isosorbide dinitrate).

If the above prior authorization criteria are met, sildenafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. the member still meets the applicable initial criteria; ***AND***
2. chart documentation shows the member has experienced a clinical improvement in symptoms since starting the requested medication.

For the treatment of Pulmonary Arterial Hypertension (PAH):

Medical Necessity Criteria for Initial Authorization

The Plan considers **sildenafil 20 mg tablets, sildenafil solution, and sildenafil oral suspension** medically necessary when **ALL** of the following criteria are met:

1. The member has a diagnosis of PAH defined as WHO Group 1 class pulmonary hypertension; ***AND***
2. The diagnosis of PAH has been confirmed by **ONE** of the following methods:
    a. Pre-treatment right heart catheterization with ALL of the following:
        i. mean pulmonary artery pressure (mPAP) ≥20 mmHg**; *and***
        ii. pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg**; *and***
        iii. pulmonary vascular resistance (PVR) ≥ 2 Wood units ***or*** pulmonary vascular resistance index (PVRI) > 3 Wood units x m^2 also acceptable for pediatric members**; *or***
    b. Doppler echocardiogram if right heart catheterization cannot be performed (e.g., for infants less than one year of age with post cardiac surgery, chronic heart disease, chronic lung disease associated with prematurity, or congenital diaphragmatic hernia); ***AND***
3. For sildenafil solution/suspension , the member must be unable to use, or has tried and failed sildenafil 20mg tablets; ***AND***
4. Chart documentation and supporting lab work are provided for review to validate the above-listed requirements.

If the above prior authorization criteria are met, sildenafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. the member still meets the applicable initial criteria**; *AND***
2. recent chart documentation shows the member experiencing therapeutic response to the requested medication as evidenced by **ONE** of the following:
    a. clinical improvement in symptoms since starting the requested medication**; *or***
    b. disease stability since starting the requested medication.

For the treatment of Raynaud phenomenon:

Medical Necessity Criteria for Initial Authorization

The Plan considers **sildenafil 20 mg tablets** medically necessary when **ALL** of the following criteria are met:

1. The medication is being requested for the treatment of Raynaud phenomenon (also called idiopathic Raynaud phenomenon, primary Raynaud syndrome, or Raynaud disease); ***AND***
2. The member has documented history of **ONE** of the following:
    a. signs of critical ischemia at the affected areas (e.g., fingers, toes, ears, lips, nipples, or the tip of the nose)**; *or***
    b. the quality of life of the member is affected to the degree that activities of normal living are no longer possible; ***AND***
3. The member is unable to use, or has tried and failed **BOTH** of the following:
    a. non-pharmacologic therapies (e.g., relaxation techniques, avoiding stressful situations, avoiding cold exposure, avoiding drugs that may precipitate RP)**; *and***
    b. calcium channel blocker (e.g., amlodipine, nifedipine); ***AND***
4. Chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, sildenafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. the member still meets the applicable initial criteria; ***AND***
2. recent chart documentation shows the member has experienced a clinical improvement in symptoms, quality of life, or experienced disease stability since starting the requested medication.

For the prevention and treatment of high-altitude pulmonary edema

Medical Necessity Criteria for Authorization

The Plan considers **sildenafil 50 mg tablets (Viagra)** medically necessary when **ALL** of the following criteria are met:

1. Sildenafil is being requested for prevention or treatment of high-altitude pulmonary edema **AND** **BOTH** of the following:
    a. The member will be or has been exposed to high altitudes, defined as higher than 2500 m [8202 ft] above sea level**; *and***
    b. The member has a history of high-altitude pulmonary edema **OR** known risk factors that increase susceptibility (e.g. intracardiac shunts, pulmonary hypertension); ***AND***

2. The member has tried and failed or has contraindications to first-line therapies such as gradual descent, oxygen therapy/supplementation, and/or portable hyperbaric therapy; ***AND***
3. The member is unable to use, or has tried and failed nifedipine; ***AND***
4. The requested dose and duration follow standard dosing guidelines:
    a. For prevention: 50 mg every 8 hours starting 1 day before ascent and continuing for 5-7 days after reaching target altitude**; *or***
    b. For treatment: 50 mg every 8 hours until descent is complete, signs/symptoms resolve, and oxygen saturation normalizes for altitude; ***AND***
5. Chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, sildenafil 50 mg tablets (Viagra) will be approved for the member's duration of high altitude exposure or persistence of signs/symptoms.

Experimental or Investigational / Not Medically Necessary

sildenafil (Viagra), sildenafil 20 mg tablets, sildenafil solution, and sildenafil oral suspension for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

Appendix

Table 1: Clinical Classification of Pulmonary Hypertension

Group 1: PAH 1.1 Idiopathic 1.1.1 Long-term responders to calcium channel blockers 1.2 Heritable# 1.3 Associated with drugs and toxins# 1.4 Associated with: 1.4.1 connective tissue disease 1.4.2 HIV infection 1.4.3 portal hypertension 1.4.4 congenital heart disease 1.4.5 schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease 2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction

2.1.3 cardiomyopathies with specific aetiologies¶ 2.2 Valvular heart disease: 2.2.1 aortic valve disease 2.2.2 mitral valve disease 2.2.3 mixed valvular disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: PH associated with lung diseases and/or hypoxia 3.1 COPD and/or emphysema 3.2 Interstitial lung disease 3.3 Combined pulmonary fibrosis and emphysema 3.4 Other parenchymal lung diseases+ 3.5 Nonparenchymal restrictive diseases: 3.5.1 hypoventilation syndromes 3.5.2 pneumonectomy 3.6 Hypoxia without lung disease (e.g. high altitude) 3.7 Developmental lung diseases
Group 4: PH associated with pulmonary artery obstructions 4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions§
Group 5: PH with unclear and/or multifactorial mechanisms 5.1 Haematological disorders*ƒ* 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1 5.3 Metabolic disorders## 5.4 Chronic renal failure with or without haemodialysis 5.5 Pulmonary tumour thrombotic microangiopathy 5.6 Fibrosing mediastinitis 5.7 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. #: patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers; ¶: hypertrophic, amyloid, Fabry disease and Chagas disease; +: parenchymal lung diseases not included in group 5; §: other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (e.g. renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumours (e.g. uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis; ƒ: including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders; ##: including glycogen storage diseases and Gaucher disease.

References

1. Andrigueti FV, Ebbing PCC, Arismendi MI, Kayser C. Evaluation of the effect of sildenafil on the microvascular blood flow in patients with systemic sclerosis: a randomised, double-blind, placebo-controlled study. Clin Exp Rheumatol. 2017;35(suppl 106)(4):151-158.

2. Bhasin S et al: Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 103(5):1715-44, 2018
3. Burnett AL, Nehra A, Breau RH, et al. Erectile Dysfunction: AUA Guideline. J Urol. 2018; 200(3):633. 2018 May 7.
4. Chetan C, Suryawanshi P, Patnaik S, et al. Oral versus intravenous sildenafil for pulmonary hypertension in neonates: a randomized trial. BMC Pediatr. 2022;22(1):311. doi:10.1186/s12887-022-03366-3
5. Fries R, Shariat K, von Wilmowsky H, Böhm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation. 2005;112(19):2980-2985.
6. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353:2148.
7. Gallagher SA, Hackett P. High altitude pulmonary edema. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
8. Hatzimouratidis K et al: Pharmacotherapy for erectile dysfunction: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 13(4):465-88, 2016
9. Hopkins WM, Rubin, LJ. Treatment of pulmonary arterial hypertension (group 1) in adults: Pulmonary hypertension-specific therapy. UpToDate.com. Last updated: Apr 12, 2021.
10. Humbert M, Kovacs G, Hoeper MM, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022;43(38):3618-3731. doi:10.1093/eurheartj/ehac237
11. Kamata Y, Minota S. Effects of phosphodiesterase type 5 inhibitors on Raynaud's phenomenon. Rheumatol Int. 2014;34(11):1623-1626.
12. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024;64(4):2401324.
13. Kowal-Bielecka O, Fransen J, Avouac J, et al; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-1339. doi:10.1136/annrheumdis-2016-209909
14. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Acute Altitude Illness: 2019 Update. Wilderness & Environmental Medicine. 2019;30(4_suppl):S3-S18. doi:10.1016/j.wem.2019.04.006
15. Mandras SA, Mehta HS, Vaidya A. Pulmonary Hypertension: A Brief Guide for Clinicians. Mayo Clinic Proceedings - Concise Review for Clinicians. Sept 2020; 95(9): P1978-1988. https://doi.org/10.1016/j.mayocp.2020.04.039
16. Nehra A et al: The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc. 87(8):766-78, 2012
17. Pepke-Zaba J, Gilbert C, Collings L, Brown MC. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Chest 2008; 133:183.
18. Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension. N Engl J Med 2000; 343:1342.
19. Revatio (sildenafil citrate) [prescribing information]. Morgantown, WV: Viatris Specialty LLC; January 2023.
20. Rezaee ME, Gross MS. Are we overstating the risk of priapism with oral phosphodiesterase type 5 inhibitors? J Sex Med. 2020;17(8):1579-1582. doi:10.1016/j.jsxm.2020.05.019
21. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomized trials. Ann Rheum Dis. 2013;72(10):1696-1699.

22. Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. Chest 2011; 140:1274.
23. Ruopp NF, Farber HQ. The New World Symposium on Pulmonary Hypertension Guidelines: Should Twenty-One Be the New Twenty-Five? Circulation AHA Journal. Oct 2019;140(14): 1134–1136. https://doi.org/10.1161/CIRCULATIONAHA.119.040292
24. Salonia A et al: European Association of Urology guidelines on sexual and reproductive health-2021 update: male sexual dysfunction. Eur Urol. 80(3):333-57, 2021
25. Sauer WH, Kimmel SE. Sexual activity in patients with cardiovascular disease. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
26. Viagra (sildenafil citrate) [prescribing information]. New York, NY: Pfizer Labs; December 2017.
27. Wigley FM. Clinical practice. Raynaud's phenomenon. N Engl J Med. 2002;347(13):1001-1008.
28. Wigley FM. Treatment of Raynaud phenomenon: Initial management. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.

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tadalafil (Adcirca, Alyq, Chewtadzy, Cialis, Tadliq)

- Oral Suspension - Tadliq 20 mg/5 mL
- Oral Tablet:
    - Cialis: 2.5 mg, 5 mg, 10 mg, 20 mg
    - Generic: Tadalafil Oral 2.5 mg, 5 mg, 10 mg, 20 mg
- Oral Tablet [Pulmonary Hypertension]
    - Adcirca: 20 mg
    - Alyq: 20 mg
    - Generic: Tadalafil 20mg
- Chewable Tablets:
    - Chewtadzy: 5 mg, 10 mg, 20 mg

Summary

Tadalafil is a medication that belongs to a class of drugs called phosphodiesterase-5 (PDE5) inhibitors. It is primarily used to treat several conditions, including pulmonary arterial hypertension (PAH), erectile

dysfunction (ED), benign prostatic hyperplasia (BPH), and concurrent ED/BPH. There is also evidence supporting the off-label use of tadalafil for Raynaud phenomenon and for the prevention and treatment of high-altitude pulmonary edema.

Tadalafil is available in different forms and strengths.

- It comes in several oral formulations:
    - Standard tablets in strengths of 2.5 mg, 5 mg, 10 mg, and 20 mg are indicated for ED and/or BPH.
    - Standard tablets with a strength of 20 mg are indicated for PAH.
    - Chewable tablets (Chewtadzy) in strengths of 5 mg, 10 mg, and 20 mg are indicated for ED and/or BPH.
    - Oral suspension (Tadliq) with a strength of 20 mg/5mL is indicated for PAH.
- The 20 mg tablets and oral suspension labeled for pulmonary arterial hypertension (PAH) are specifically indicated for the treatment of PAH and are labeled accordingly.
- The 2.5 mg and 5 mg tablets are FDA-approved for the treatment of BPH.
- All tablet strengths and formulations can be used to treat ED, although coverage for ED treatment may vary based on the member's specific plan's benefits and coverage.
  NOTE: *Erectile dysfunction is an excluded benefit for certain Plans. Coverage for medications to treat sexual dysfunction, including erectile dysfunction, varies depending on a member's benefit policy. Please review the member's coverage benefits to determine if erectile dysfunction is a covered benefit.*
- Tadalafil formulations indicated for PAH should be used for PAH, while those indicated for ED or BPH should be used for ED or BPH unless otherwise noted in the medical necessity criteria.

Definitions

"Benign prostatic hyperplasia (BPH)" is a histologic diagnosis that refers to the proliferation of glandular epithelial tissue, smooth muscle, and connective tissue within the prostate transition zone.

"Erectile Dysfunction" is the consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse.

"**High-altitude pulmonary edema (HAPE)**" is a life-threatening condition that can occur in some people who rapidly ascend to high altitudes, usually higher than 2500 m [8202 ft] above sea level.

"Pulmonary arterial hypertension (PAH)" is a subset of pulmonary hypertension (PH). Pulmonary hypertension is classified into five groups based upon etiology. Patients in the first group are considered to have PAH, whereas patients in the remaining four groups are considered to have PH.

"**Raynaud phenomenon (RP)", (also referred to as idiopathic Raynaud phenomenon, primary Raynaud syndrome, or Raynaud disease)** is a condition which causes the blood vessels that carry blood to the fingers and toes (sometimes even the ears, lips, nipples, and tip of the nose) to narrow for a time, leading to color changes in the skin, numbness, tingling, and other potential complications.

Clinical Indications

For the treatment of Erectile Dysfunction (*if a covered benefit for the member*):

Medical Necessity Criteria for Initial Authorization

The Plan considers **tadalafil tablets (all strengths and formulations)** medically necessary when **ALL** the following criteria are met:

1. The member is 18 years of age and older; ***AND***
2. The member is a male with erectile dysfunction (ED, impotence); ***AND***
3. Clinical chart document is provided showing **ALL** of the following:
    a. a thorough medical history and physical examination has been undertaken to:
        i. support the diagnosis of erectile dysfunction**; *and***
        ii. determine potential underlying causes**; *and***
        iii. exclude potentially reversible or treatable causes (e.g., hypogonadism with inadequate testosterone replacement, hyperprolactinemia, drug-induced dysfunction, dyslipidemias, alcoholism, other substance abuse, hypertension, thyroid disease, cardiovascular or cerebrovascular disease, neurologic disease, adrenal dysfunction, psychologic dysfunction, marital discord, smoking)**; *and***
    b. a review of the member's current drug regimens has been conducted to detect possible drug-induced ED (e.g., antidepressant, antipsychotic, certain blood pressure medications); ***AND***
4. The member will not be taking tadalafil concomitantly with **ANY** of the following:
    a. Guanylate Cyclase Stimulators (such as Adempas (riociguat))**; *or***
    b. Nitrates and nitrites (e.g., nitroglycerin, isosorbide dinitrate); ***AND***
5. For chewable tablet formulation (Chewtadzy) requests, **ONE** of the following:
    a. Documentation of difficulty swallowing solid oral dosage forms**; *or***
    b. Clinical rationale for requiring a chewable formulation**; *or***

c. Treatment failure with or intolerance to standard tablet formulation.

If the above prior authorization criteria are met, tadalafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. The member still meets the applicable initial criteria; ***AND***
2. Chart documentation shows the member has experienced a clinical improvement in symptoms since starting the requested medication.

For the treatment of Benign Prostatic Hyperplasia (BPH):

Medical Necessity Criteria for Initial Authorization

The Plan considers **tadalafil 2.5 mg and 5 mg tablets and chewable tablets** medically necessary when ALL the following criteria are met:

1. The member is 18 years of age and older; ***AND***
2. The member has a confirmed diagnosis of BPH; ***AND***
3. The member has tried and failed, or is unable to use an alpha blocker (i.e. alfuzosin, doxazosin, tamsulosin, terazosin); ***AND***
4. The member is unable to use, or has tried and failed a 5-alpha reductase inhibitor (i.e. dutasteride, finasteride); ***AND***
5. For chewable tablet formulation (Chewtadzy) requests, **ONE** of the following:
    a. Documentation of difficulty swallowing solid oral dosage forms**; *or***
    b. Clinical rationale for requiring a chewable formulation**; *or***
    c. Treatment failure with or intolerance to standard tablet formulation; ***AND***
6. Chart documentation and supporting lab work are provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, tadalafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. The member still meets the applicable initial criteria; ***AND***
2. Chart documentation shows the member has experienced a clinical improvement in symptoms since starting the requested medication.

For the treatment of Pulmonary Arterial Hypertension (PAH):

Medical Necessity Criteria for Initial Authorization

The Plan considers **tadalafil 20 mg tablets (PAH), chewable tablets, and tadalafil 20 mg/5 mL oral suspension** medically necessary when ALL of the following criteria are met:

1. The member has a diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH); ***AND***
2. The diagnosis of PAH has been confirmed by **ONE** of the following methods:
    a. Pre-treatment right heart catheterization with **ALL** of the following:
        i. mean pulmonary artery pressure (mPAP) $\geq$ 20 mmHg**; *and***
        ii. pulmonary capillary wedge pressure (PCWP) $\leq$ 15 mmHg**; *and***
        iii. pulmonary vascular resistance (PVR) $\geq$ 2 Wood units ***or*** pulmonary vascular resistance index (PVRI) > 3 Wood units x m^2 also acceptable for pediatric members**; *or***
    b. Doppler echocardiogram if right heart catheterization cannot be performed (e.g., for infants less than one year of age with post cardiac surgery, chronic heart disease, chronic lung disease associated with prematurity, or congenital diaphragmatic hernia); ***AND***
3. For chewable tablet formulation (Chewtadzy) requests, **ONE** of the following:
    a. Documentation of difficulty swallowing solid oral dosage forms**; *or***
    b. Clinical rationale for requiring a chewable formulation**; *or***
    c. Treatment failure with or intolerance to standard tablet formulation; ***AND***
4. Chart documentation and supporting lab work are provided for review to substantiate the above-listed requirements.

If the above prior authorization criteria are met, tadalafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. The member still meets the applicable initial criteria***; AND***
2. Recent chart documentation shows the member experiencing therapeutic response to the requested medication as evidenced by **ONE** of the following:
    a. clinical improvement in symptoms since starting the requested medication**; *or***
    b. disease stability since starting the requested medication.

For the treatment of Raynaud phenomenon:

Medical Necessity Criteria for Initial Authorization

The Plan considers **tadalafil 20 mg tablets and chewable tablets** medically necessary when **ALL** of the following criteria are met:

1. The medication is being requested for the treatment of Raynaud phenomenon (also called idiopathic Raynaud phenomenon, primary Raynaud syndrome, or Raynaud disease); ***AND***
2. The member has documented history of **ONE** of the following:
    a. signs of critical ischemia at the affected areas (e.g., fingers, toes, ears, lips, nipples, or the tip the nose)**; *or***
    b. the quality of life of the member is affected to the degree that activities of normal living are no longer possible; ***AND***
3. The member is unable to use, or has tried and failed **BOTH** of the following:
    a. non-pharmacologic therapies (e.g., relaxation techniques, avoiding stressful situations, avoiding cold exposure, avoiding drugs that may precipitate RP)**; *and***
    b. calcium channel blocker (e.g., amlodipine, nifedipine); ***AND***
4. For chewable tablet formulation (Chewtadzy) requests, **ONE** of the following:
    a. Documentation of difficulty swallowing solid oral dosage forms**; *or***
    b. Clinical rationale for requiring a chewable formulation**; *or***
    c. Treatment failure with or intolerance to standard tablet formulation; ***AND***
5. Chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, tadalafil will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **BOTH** of the following are met:

1. The member still meets the applicable initial criteria; ***AND***
2. Chart documentation shows the member has experienced a clinical improvement in symptoms, quality of life, or experienced disease stability since starting the requested medication.

For the prevention and treatment of high-altitude pulmonary edema

Medical Necessity Criteria for Authorization

The Plan considers **tadalafil 10 mg tablets and chewable tablets** medically necessary when **ALL** of the following criteria are met:

1. Tadalafil is being requested for prevention or treatment of high-altitude pulmonary edema **AND BOTH** of the following:

   a. The member will be or has been exposed to high altitudes, defined as higher than 2500 m [8202 ft] above sea level**; *and***
   b. The member has a history of high-altitude pulmonary edema **OR** known risk factors that increase susceptibility (e.g. intracardiac shunts, pulmonary hypertension); ***AND***
2. The member has tried and failed or has contraindications to first-line therapies such as gradual descent, oxygen therapy/supplementation, and/or portable hyperbaric therapy; ***AND***
3. The member is unable to use, or has tried and failed nifedipine; ***AND***
4. For chewable tablet formulation (Chewtadzy) requests, **ONE** of the following:
   a. Documentation of difficulty swallowing solid oral dosage forms**; *or***
   b. Clinical rationale for requiring a chewable formulation**; *or***
   c. Treatment failure with or intolerance to standard tablet formulation; ***AND***
5. The requested dose and duration follow standard dosing guidelines:
   a. For prevention: 10 mg every 12 hours starting 1 day before ascent and continuing for 5-7 days after reaching target altitude**; *or***
   b. For treatment: 10 mg every 12 hours until descent is complete, signs/symptoms resolve, and oxygen saturation normalizes for altitude; ***AND***
6. Chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, tadalafil will be approved for the member's duration of high altitude exposure or persistence of signs/symptoms.

Experimental or Investigational / Not Medically Necessary

Tadalafil for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

Appendix

Table 1: Clinical Classification of Pulmonary Hypertension

Group 1: PAH 1.1 Idiopathic 1.1.1 Long-term responders to calcium channel blockers 1.2 Heritable# 1.3 Associated with drugs and toxins# 1.4 Associated with: 1.4.1 connective tissue disease 1.4.2 HIV infection

1.4.3 portal hypertension 1.4.4 congenital heart disease 1.4.5 schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease 2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction 2.1.3 cardiomyopathies with specific aetiologies¶ 2.2 Valvular heart disease: 2.2.1 aortic valve disease 2.2.2 mitral valve disease 2.2.3 mixed valvular disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: PH associated with lung diseases and/or hypoxia 3.1 COPD and/or emphysema 3.2 Interstitial lung disease 3.3 Combined pulmonary fibrosis and emphysema 3.4 Other parenchymal lung diseases+ 3.5 Nonparenchymal restrictive diseases: 3.5.1 hypoventilation syndromes 3.5.2 pneumonectomy 3.6 Hypoxia without lung disease (e.g. high altitude) 3.7 Developmental lung diseases
Group 4: PH associated with pulmonary artery obstructions 4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions§
Group 5: PH with unclear and/or multifactorial mechanisms 5.1 Haematological disorders*ƒ* 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1 5.3 Metabolic disorders## 5.4 Chronic renal failure with or without haemodialysis 5.5 Pulmonary tumour thrombotic microangiopathy 5.6 Fibrosing mediastinitis 5.7 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. #: patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers; ¶: hypertrophic, amyloid, Fabry disease and Chagas disease; +: parenchymal lung diseases not included in group 5; §: other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (e.g. renal carcinoma, uterine

carcinoma, germ-cell tumours of the testis), nonmalignant tumours (e.g. uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis; ƒ: including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders; ##: including glycogen storage diseases and Gaucher disease.

References

1. Adcirca (tadalafil) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; December 2019.
2. Alyq (tadalafil) [prescribing information]. Parsippany, NJ: Teva Pharmaceuticals; April 2024.
3. Black L, Naslund MJ, Gilbert TD Jr, et al. An examination of treatment patterns and costs of care among patients with benign prostatic hyperplasia. Am J Manag Care 2006; 12:S99.
4. Burnett AL, Nehra A, Breau RH, et al. Erectile Dysfunction: AUA Guideline. J Urol. 2018; 200(3):633. 2018 May 7.
5. Chewtadzy (tadalafil) [prescribing information]. Baudette, MN: ANI Pharmaceuticals, Inc.; June 2024.
6. Cialis (tadalafil) [prescribing information]. Indianapolis, IN: Lilly USA LLC; April 2023.
7. Cialis (tadalafil) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; February 2018.
8. Hopkins WM, Rubin, LJ. Treatment of pulmonary arterial hypertension (group 1) in adults: Pulmonary hypertension-specific therapy. UpToDate.com. Last updated: Apr 12, 2021.
9. Kamata Y, Minota S. Effects of phosphodiesterase type 5 inhibitors on Raynaud's phenomenon. Rheumatol Int. 2014;34(11):1623-1626.
10. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024;64(4):2401324.
11. Kowal-Bielecka O, Fransen J, Avouac J, et al; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327-1339. doi:10.1136/annrheumdis-2016-209909
12. Luks AM, Auerbach PS, Freer L, et al. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of acute altitude illness: 2019 update. Wilderness Environ Med. 2019;30(4S):S3-S18. doi:10.1016/j.wem.2019.04.006[PubMed 31248818]
13. Maggiorini, Marco, et al. "Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial." Annals of internal medicine 145.7 (2006): 497-506.
14. Mandras SA, Mehta HS, Vaidya A. Pulmonary Hypertension: A Brief Guide for Clinicians. Mayo Clinic Proceedings - Concise Review for Clinicians. Sept 2020; 95(9): P1978-1988. https://doi.org/10.1016/j.mayocp.2020.04.039
15. Nickel JC, Gilling P, Tammela TL, et al. Comparison of dutasteride and finasteride for treating benign prostatic hyperplasia: the Enlarged Prostate International Comparator Study (EPICS). BJU Int 2011; 108:388.
16. Porst H, Giuliano F, Glina S, et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5mg and 10mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial.Eur Urol. 2006;50(2):351.
17. Roehrborn CG, Nuckolls JG, Wei JT, et al. The benign prostatic hyperplasia registry and patient survey: study design, methods and patient baseline characteristics. BJU Int 2007; 100:813.
18. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomized trials. Ann Rheum Dis. 2013;72(10):1696-1699.

19. Ruopp NF, Farber HQ. The New World Symposium on Pulmonary Hypertension Guidelines: Should Twenty-One Be the New Twenty-Five? Circulation AHA Journal. Oct 2019;140(14): 1134–1136. https://doi.org/10.1161/CIRCULATIONAHA.119.040292
20. Schiopu E, Hsu VM, Impens AJ, et al. Randomized placebo-controlled crossover trial of tadalafil in Raynaud's phenomenon secondary to systemic sclerosis. J Rheumatol. 2009;36(10):2264-2268.
21. Shenoy PD, Kumar S, Jha LK, et al. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. Rheumatology (Oxford). 2010;49(12):2420-2428.
22. Tadliq (tadalafil) [prescribing information]. Farmville, NC: CMP Pharma Inc; October 2023.
23. Tadliq (tadalafil) [prescribing information]. Farmville, NC: CMP Pharma Inc; June 2022.
24. Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. J Urol 2005; 173:1256.
25. Wigley FM. Clinical practice. Raynaud's phenomenon. N Engl J Med. 2002;347(13):1001-1008.

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Oscar Clinical Guideline: Adbry (tralokinumab) (PG110, Ver. 7)

Adbry (tralokinumab)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affects approximately 10% of adults and 20% of children worldwide. It is characterized by intense itching, redness, and eczematous lesions, which can be accompanied by skin dryness, scaling, and thickening. The clinical course of AD is characterized by chronic, relapsing episodes over months to years. In mild cases, one may experience intermittent flares that may or may not clear without the use of pharmacological intervention. In more moderate and severe cases, flares rarely clear without pharmacological intervention/therapy. The severity of AD can be classified as mild, moderate, or severe, depending on the extent and intensity of skin inflammation, as well as the impact on the patient's quality of life. Moderate-to-severe AD is defined by the presence of extensive or widespread lesions, intense pruritus, and a significant impairment of daily activities, sleep, and mood.

Treatment options for moderate-to-severe AD involve a combination of topical and systemic therapies, tailored to the individual patient's needs and preferences. The goal of treatment is to control inflammation, relieve itching, restore the skin barrier, prevent flares, and improve quality of life.

- Topical treatments for moderate-to-severe AD include corticosteroids, calcineurin inhibitors, Janus kinase inhibitors (JAK), antimicrobials/antiseptics, antihistamines, and phosphodiesterase-4 (PDE4) inhibitors. These drugs act by reducing inflammation and pruritus and promoting skin healing. However, their long-term use may be limited by adverse effects, such as skin atrophy, telangiectasias, or the potential risk of skin infections or malignancies.
- Systemic treatments for moderate-to-severe AD are reserved for patients with inadequate response or contraindications to topical therapies, or those with severe or rapidly worsening disease. The most commonly used systemic agents include oral immunosuppressants, such as cyclosporine, methotrexate, or mycophenolate mofetil, oral janus kinase inhibitors and biologic agents, such as dupilumab, which targets the interleukin-4 (IL-4)/interleukin-13 (IL-13) pathway.

Adbry (tralokinumab) is FDA-approved for the treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adbry (tralokinumab) can be used with or without topical corticosteroids. Adbry (tralokinumab) works by directly inhibiting interleukin (IL)-13 cytokine, which is a major driver of atopic dermatitis signs and symptoms.

Adbry (tralokinumab) is administered subcutaneously (SC):

- For adults 18 years and older - 300 mg (two 150 mg injections) every 2 weeks after an initial loading dose of 600 mg at the start of treatment. After 16 weeks of treatment, patients with a body weight <100 kg who achieve clear or almost clear skin may be eligible for dosing every 4 weeks.
- For pediatrics 12 to 17 years old - 150 mg (one 150 mg injection) every other week after an initial loading dose of 300 mg (two 150 mg injections) at the start of treatment. In pediatric patients, Adbry (tralokinumab) is to be administered by or under supervision of an adult.
- Adbry (tralokinumab) is available as both a prefilled syringe and an autoinjector. The autoinjector is only indicated for adults, available for both the initial loading dose and the subsequent dosages.
- It is recommended that all age appropriate vaccinations are completed prior to initiation of Adbry (tralokinumab).

Definitions

"Atopic Dermatitis" also known as **eczema** is a chronic skin condition that makes a person's skin red, itchy and scaly. Atopic dermatitis (AD) often begins during childhood and persists into adulthood. Some

people experience occasional flares followed by periods of improvement or a "waxing and waning" course of the disease.

"Biologics"or "Biologicals" or "Biological therapeutics" as defined by the World Health Organization (WHO) are a class of medicines which are grown and then purified from large-scale cell cultures such as bacteria, yeast, animal or plant cells. Biologics can include but are not limited to vaccines, growth factors, immune modulators, and monoclonal antibodies. Unlike other medicines, biologics are generally proteins purified from living culture systems and/or blood, and are often referred to as "large modules."

"**Interleukin (IL)-13 cytokine**" is a protein secreted by certain cells of the immune system that affects many aspects of chronic airway inflammation.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Adbry (tralokinumab)** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with a specialist in dermatology, allergy or immunology***; AND***
2. The member is 12 years of age or older***; AND***
3. The member has a documented diagnosis of moderate to severe atopic dermatitis **AND ONE** of the following:
    a. Involvement of (≥) 10% or more of body surface area***; or***
    b. Involvement of sensitive body areas (e.g., hands, feet, face, neck, scalp, genitals/groin, intertriginous areas)***; AND***
4. The member is unable to use, or has adequately tried and failed **ONE** of the following topical therapies for at least 8 weeks each in the past 365 days:
    a. A topical corticosteroid (TCS) from medium potency (group III to IV) classes to higher potencies (groups I to II) classes (see Table 1)***; and/or***
    b. Tacrolimus ointment***; and/or***
    c. Eucrisa (crisaborole) [PA may be required, please check the member's Plan-specific Formulary]***; AND***
5. Adbry (tralokinumab) will not be used concomitantly with other biologics (e.g., Dupixent, Cibinqo, or Rinvoq) in the treatment of atopic dermatitis***; AND***
6. Dosage does **NOT** exceed the following:
    a. Adult 18 years and older - an initial (one-time) dose of 600 mg (four 150 mg injections), followed by 300 mg (two 150 mg injections) administered every other week***; or***

b. Pediatric 12 to 17 years old - an initial (one-time) dose of 300 mg (two 150 mg injections), followed by 150 mg (one 150 mg injection) every other week***; AND***

7. Clinical chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Adbry (tralokinumab) will be approved for up to 4 months.

Medical Necessity Criteria for Reauthorization

Authorization of up to 12 months may be provided for members 12 years of age or older when recent chart documentation (within the past 4 months) is provided showing **ALL** of the following criteria are met:

1. The member is responding positively to Adbry (tralokinumab) treatment based upon the prescriber's assessment as demonstrated by **ONE** of the following:
    a. decreased disease activity (e.g., a reduction in BSA%)***; or***
    b. symptomatic improvement (e.g., redness, itching, oozing/crusting)***; AND***
2. Adbry (tralokinumab) will not be used concomitantly with other biologics (e.g., Dupixent, Cibinqo, or Rinvoq) in the treatment of atopic dermatitis***; AND***
3. The requested dosage does **NOT** exceed the following:
    a. Adult 18 years and older:
        i. 300 mg every 4 weeks for a member with body weight below 100 kg who achieve clear or almost clear skin after 16 weeks of treatment***; or***
        ii. 300 mg every 2 weeks for a member weighing at least 100 kg **OR** documentation supports member has not achieved clear or almost clear skin after 16 weeks of treatment***; or***
    b. Pediatric 12 to 17 years old - 150 mg (one 150 mg injection) every other week.

Table 1: Topical Corticosteroid Potency

NOTE: The following chart is only for approximate comparative purposes. Please check product-specific information to best assess product potency, which can also be affected by a multitude of factors (e.g., formulation, site of application, member and disease-specific factors)

Group	Potency	Steroid	Strength	Dosage Form
I	Very High	Betamethasone dipropionate (augmented)	0.05%	Gel, Lotion, and Ointment
		Clobetasol propionate	0.05%	Cream, Emollient Cream, Foam, Gel, Lotion, Ointment, Spray, and Solution
		Diflorasone diacetate	0.05%	Ointment
		Fluocinonide	0.1%	Cream
		Flurandrenolide	0.05%	Tape
		Halobetasol propionate	0.05%	Cream, Foam, Lotion and Ointment
II	High	Amcinonide	0.1%	Ointment
		Betamethasone dipropionate (augmented)	0.05%	Cream
		Betamethasone dipropionate	0.05%	Ointment
		Clobetasol propionate	0.025%	Cream
		Desoximetasone	0.25%	Cream, Ointment and Spray
		Desoximetasone	0.05%	Gel
		Diflorasone diacetate	0.05%	Cream, and Emollient Cream
		Fluocinonide	0.05%	Cream, Gel, Ointment, and Solution
		Halcinonide	0.1%	Cream, Ointment, and Solution
		Halobetasol propionate	0.01%	Lotion
III	Upper Medium	Amcinonide	0.1%	Cream and Lotion
		Betamethasone dipropionate	0.05%	Cream
		Betamethasone valerate	0.12%	Foam

		Betamethasone valerate	0.1%	Ointment
		Fluocinonide	0.05%	Emollient Cream
		Fluticasone propionate	0.005%	Ointment
		Mometasone furoate	0.1%	Ointment
		Triamcinolone acetonide	0.5%	Cream and Ointment
IV	Medium	Betamethasone dipropionate	0.05%	Spray
		Clocortolone pivalate	0.1%	Cream
		Desoximetasone	0.05%	Cream and Ointment
		Fluocinolone acetonide	0.025%	Ointment
		Flurandrenolide	0.05%	Ointment
		Fluticasone propionate	0.05%	Cream
		Hydrocortisone valerate	0.2%	Ointment
		Mometasone furoate	0.1%	Cream, Lotion, and Solution
		Triamcinolone acetonide	0.1%	Cream, Dental Paste, Ointment, and Spray
V	Lower Medium	Betamethasone dipropionate	0.05%	Lotion
		Betamethasone valerate	0.1%	Cream
		Desonide	0.05%	Gel and Ointment
		Fluocinolone acetonide	0.025%	Cream
		Fluocinolone acetonide	0.01%	Shampoo
		Flurandrenolide	0.05%	Cream and Lotion
		Fluticasone propionate	0.05%	Lotion
		Hydrocortisone butyrate	0.1%	Cream, Lotion, Ointment, and Solution
		Hydrocortisone probutate	0.1%	Cream
		Hydrocortisone valerate	0.2%	Cream

		Prenicarbate	0.1%	Emollient Cream and Ointment
		Triamcinolone acetonide	0.1%	Lotion
		Triamcinolone acetonide	0.025%	Ointment
VI	Low	Alclometasone dipropionate	0.05%	Cream and Ointment
		Betamethasone valerate	0.1%	Lotion
		Desonide	0.05%	Cream, Lotion, and Foam
		Fluocinolone acetonide	0.01%	Cream, Oil, Shampoo and Solution
		Triamcinolone acetonide	0.025%	Cream and Lotion
VII	Lowest	Hydrocortisone acetate	1% to 2%	Cream and Ointment
		Hydrocortisone base	0.5% to 2.5%	Cream, Gel, Lotion, Ointment, Solution, and Spray

Experimental or Investigational / Not Medically Necessary

Adbry (tralokinumab) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

References

1. AAAAI/ACAAI JTF Atopic Dermatitis Guideline Panel; Chu DK, Schneider L, Asiniwasis RN, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on practice parameters GRADE - and Institute of Medicine - based recommended. Ann Allergy Asthma Immunol. 2024 Mar; 132(3):274-312. Doi: 10.1016/j.anai.2023.11.009. Epub 2023 Dec 18.
2. Adbry (tralokinumab) [prescribing information]. Madison, NJ: LEO Pharma Inc; June 2024.
3. Blauvelt A, Gooderham M, Bhatia N, Langley RG, Schneider S, Zoidis J, Kurbasic A, Armstrong A, Silverberg JI. Tralokinumab Efficacy and Safety, with or without Topical Corticosteroids, in North American Adults with Moderate-to-Severe Atopic Dermatitis: A Subanalysis of Phase 3 Trials ECZTRA 1, 2, and 3. Dermatol Ther (Heidelb). 2022 Nov;12(11):2499-2516. doi: 10.1007/s13555-022-00805-y.
4. Blauvelt A, Langley RG, Lacour JP, et al. Long-term 2-year safety and efficacy of tralokinumab in adults with moderate-to-severe atopic dermatitis: interim analysis of teh ECZTEND open-label extension trial. J AM Acad Dermatol. 2022 Oct; 87(4):815-824. doi:10.1016/j.jaad.2022.07.019. Epub 2022 Jul 19.
5. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: Practical recommendations for an evolving therapeutic landscape. Ann Allergy Asthma Immunol. 2018 Jan;120(1):10-22.e2. doi: 10.1016/j.anai.2017.10.039. PMID: 29273118.

6. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J. Atopic dermatitis yardstick update. Ann Allergy Asthma Immunol. 2023 Jun; 130(6):811-820. doi:10.1016/j.anai.2023.03.010. Epub 2023 mar 16.
7. Davis DMW, Drucker AM, Alikhan A, et al. Executive summary: guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. J Am Acad Dermatol. 2024 Feb; 90(2):342-345. doi:10.1016/j.jaad.2023.08.103. Epub 2023 Nov 7.
8. Draelos, Z. D., Feldman, S. R., Berman, B., Olivadoti, M., Sierka, D., Tallman, A. M., ... & Baldwin, S. (2019). Tolerability of topical treatments for atopic dermatitis. Dermatology and Therapy, 9(1), 71-102.
9. Drucker AM, Ellis AG, Bohdanowicz M, et al. Systemic Immunomodulatory Treatments for Patients with Atopic Dermatitis: A Systematic Review and Network Meta-analysis. JAMA Dermatol. 2020;156(6):659-667.
10. Drucker AM, Lam M, Prieto-merino D. Systemic Immunomodulatory treatment for atopic dermatitis: living systemic review and network meta-analysis update. JAMA Dermatol. 2024;160(9):936-944. doi:10.1001/jamadermatol.2024.2192.
11. Eichenfield LF et al: Current guidelines for the evaluation and management of atopic dermatitis: a comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. J Allergy Clin Immunol. 139(4S):S49-S57, 2017
12. Eichenfield LF et al: Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol. 70(2):338-51, 2014
13. Eichenfield LF et al: Translating atopic dermatitis management guidelines into practice for primary care providers. Pediatrics. 136(3):554-65, 2015
14. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014;71:116-32. (Including potencies of topical corticosteroids).
15. Gutermuth J, Pink AE, Worm M, et al. Tralokinumab plus topical corticosteroids in adults with severe atopic dermatitis and inadequate response to or intolerance of ciclosporin A: a placebo-controlled, randomized, phase III clinical trial (ECZTRA 7). Br J Dermatol. 2022 Mar;186(3):440-452. doi:10.1111/bjd.20832. Epub 2021 Dec 22.
16. Mayo Clinic.org - Atopic Dermatitis (dermatitis). Available at: https://www.mayoclinic.org/diseases-conditions/atopic-dermatitis-eczema/symptoms-causes/syc-20353273. Last Update May 2024. Accessed Feb 6, 2025.
17. Paller AS, Flohr C, Cork M, et al. Efficacy and safety of tralokinumab in adolescents with moderate to severe atopic dermatitis: the phase 3 ECZTRA 6 randomized clinical trial. JAMA Dermatol. 2023 Jun 1;159(6):596-605. doi:10.1001/jamadermatol.2023.0627.
18. Sidbury R, Alikhan A, Bercovitch L, et al. Guidelines for care for the management of atopic dermatitis in adults with topical therapies. J Am Acad Dermatol. 2023 Jul;89(1): e1-e20. doi:10.1016/j.jaad/2022.12.029. Epub 2023 Jan 12.
19. Silverberg JI, Adam DN, Zirwas M, et al. Tralokinumab plus topical corticosteroids as needed provides progressive and sustained efficacy in adults with moderate-to-severe atopic dermatitis over 32-week period: an ECZTRA 3 post hoc analysis. Am J Clin Dermatol. 2022 Jul;23(4):547-559. doi:10.1007/s40257-022-00702-2. Epub 2022 Jul 20.
20. Silverberg JI, Guttman-Yassky E, Gooderham M, et al. Health-related quality of life with tralokinumab in moderate-to-severe atopic dermatitis: a phase 2b randomized study. Ann Allergy Asthma Immunol. 2021 May;126(5):576-583.e4. doi:10.1016/j.anai.2020.12.004. Epub 2020 Dec 15.

21. Silverberg JI, Toth D, Bieber T, et al; ECZTRA 3 study investigators. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol. 2021;184(3):450-463. doi:10.1111/bjd.19573.
22. Simpson EL, Merola JF, Silverberg JI, Reich K, Warren RB, Staumont-Sallé D, Girolomoni G, Papp K, de Bruin-Weller M, Thyssen JP, Zachariae R, Olsen CK, Wollenberg A. Safety of tralokinumab in adult patients with moderate-to-severe atopic dermatitis: pooled analysis of five randomized, double-blind, placebo-controlled phase II and phase III trials. Br J Dermatol. 2022 Sep 9. doi: 10.1111/bjd.21867.
23. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, Spelman L, Katoh N, Saeki H, Poulin Y, Lesiak A, Kircik L, Cho SH, Herranz P, Cork MJ, Peris K, Steffensen LA, Bang B, Kuznetsova A, Jensen TN, Østerdal ML, Simpson EL; ECZTRA 1 and ECZTRA 2 study investigators. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2021 Mar;184(3):437-449. doi: 10.1111/bjd.19574.
24. Wollenberg A, Christen-Zäch S, Taieb A, et al. ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children. J Eur Acad Dermatol Venereol. 2020 Dec;34(12):2717-2744.
25. Wollenberg A, Kinberger M, Arents B, et al. European guideline (EuroGuiDerm) on Atopic eczema: part I - systemic therapy. J Eur Acad Deermatol Venereol. 2022 Sep;36(9):1409-1431. doi:10.1111/jdv.18345.
26. Wollenberg A, Oranje A, Deleuran M, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. J Eur Acad Dermatol Venereol 2016; 30:729.
27. Wong, I. T., Tsuyuki, R. T., Cresswell-Melville, A., Doiron, P., & Drucker, A. M. (2017). Guidelines for the management of atopic dermatitis (eczema) for pharmacists. Canadian Pharmacists Journal/Revue des Pharmaciens du Canada, 150(5), 285-297.
28. World Health Organization - Biologicals. Available at: https://www.who.int/health-topics/biologicals#tab=tab_1. Accessed 5 Feb 2025.
29. Yew, Y. W., Thyssen, J. P., & Silverberg, J. I. (2019). A systematic review and meta-analysis of the regional and age-related differences in atopic dermatitis clinical characteristics. Journal of the American Academy of Dermatology, 80(2), 390-401.
30. Zheng Y, Ding RL, Bu J. Effectiveness and safety of systemic therapy for moderate-to-severe atopic dermatitis in children and adolescent patients: a systematic review. Front Immunol. 2024 May 15;15:1367099. doi:10.3389/fimmu/2024.1367099.

Clinical Guideline Revision / History Information

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Oscar Clinical Guideline: Livtencity (maribavir) (PG113, Ver. 4)

Livtencity (maribavir)

Disclaimer

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Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Post-transplant cytomegalovirus (CMV) infection/disease is a common complication following solid organ transplantation. CMV is a double-stranded DNA virus that belongs to the herpesvirus family, and it can cause severe morbidity and mortality in transplant recipients. While antiviral therapy is available for CMV infection/disease, some cases may be refractory to treatment.

Antiviral therapy is the mainstay of treatment for CMV infection/disease. The most commonly used drugs are ganciclovir, valganciclovir, and foscarnet. However, some cases of CMV infection/disease may be refractory to treatment. Refractory CMV infection/disease is defined as persistent or progressive CMV infection/disease despite appropriate antiviral therapy for at least 2 weeks.

Livtencity (maribavir) is indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant cytomegalovirus (CMV) infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet

Definitions

"Antiviral" is an agent that kills a virus or that suppresses its ability to replicate, multiply and reproduce.

"**Cytomegalovirus (CMV)"** is a common type of herpes virus.

"**Hematopoietic stem-cell transplantation (HSCT**)" is a medical procedure that consists of infusing stem cells after a short course of chemotherapy or radiotherapy to treat various types of cancers.

"**Refractory**" refers to a condition or disease that does not respond to treatment or becomes resistant to it. In the context of medical treatment, refractory can mean that a patient's symptoms or disease are persisting, progressing, or recurring despite receiving standard therapies.

"**Solid organ transplant (SOT)"** is a medical procedure where an organ is removed from one body and placed in the body of a recipient, to replace a damaged or missing organ.

Medical Necessity Criteria for Authorization

The Plan considers **Livtencity (maribavir)** medically necessary when **ALL** of the following criteria are met:

1. The member is 12 years of age or older; ***AND***
2. The member weighs at least 35 kg; ***AND***
3. The member has a history of hematopoietic stem cell transplant (HCST) or solid organ transplant (SOT); ***AND***
4. The member has a diagnosis of post-transplant cytomegalovirus (CMV) infection/disease that is refractory following at least 14 days of **ONE** of the following treatments:
    - **a.** cidofovir***; or***
    - **b.** foscarnet***; or***
    - **c.** ganciclovir***; or***
    - **d.** valganciclovir***; AND***
5. Is being prescribed for use meeting **ALL** of the following:
    - a. will not be used concomitantly with other CMV antivirals; ***and***
    - b. will not be used for prevention of CMV infection; ***and***
    - c. will be dosed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature; ***and***
    - d. treatment duration with Livtencity (maribavir) will not exceed 8 weeks; ***AND***
6. Supporting chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Livtencity (maribavir) will be approved for a single 8-weeks treatment course.

Experimental or Investigational / Not Medically Necessary

Livtencity (maribavir) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- as an initial treatment for CMV disease
- HIV-related CMV disease
- in combination with other CMV antiviral agents
- in other non-transplant populations
- prophylaxis of CMV infection

References

1. A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients With Cytomegalovirus (CMV) Infections That Are Refractory or Resistant to Treatment With Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir. ClinicalTrials.gov Identifier: NCT02931539. Updated November 3, 2021. Accessed February 28, 2022. https://clinicaltrials.gov/ct2/show/NCT02931539
2. Avery RK, Alain S, Alexander BD et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial. Clin Infect Dis 2022;75:690-701.
3. Chou S., Song K. Wu J, Bo T, Crumpacker C. Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection. J Infect Dis. 2022 Sep 4. 226 (4): 576-584. Doi: 10.1093/infdis/jiaa462.
4. Kotton CN, Kumar D, Caliendo AM et al. The Transplantation Society International CMV Consensus Group. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018 Jun;102(6):900-931.
5. Lalezari JP., Aberg JA., Wang LH., Wire MB., Miner R., Snowden W., ... & Drew WL. (2002). Phase I dose escalation trial evaluating the pharmacokinetics, anti-human cytomegalovirus (HCMV) activity, and safety of 1263W94 in human immunodeficiency virus-infected men with asymptomatic HCMV shedding. Antimicrobial agents and chemotherapy, 46(9), 2969-2976.
6. Livtencity (maribavir) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals America Inc; March 2024.
7. Maertens J, Cordonnier C, Jaksch P et al. Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation. N Engl J Med. 2019; 381:1136-47.
8. Marty FM, Ljungman P, Papanicolaou GA, et al. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. Lancet Infect Dis. 2011 Apr; 11(4): 284-92. doi:10.1016/S1473-3099(11):70024-X.Epub 2011 Mar 21.

9. Papanicolaou, G. A., Avery, R. K., Cordonnier, C., et al. Hematopoietic cell transplant in the AURORA trial: a multicenter, double-blind, randomized, phase-3 trial comparing maribavir with valganciclovir. Clin Infect Dis. 2024 Mar 20; 78(3): 562-572. Doi: 10.1093/cid/ciad709.
10. Papanicolaou GA, Silveira FP, Langston AA, et al Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, double-blind, phase 2 study. Clin Infect Dis. 2019 Apr 8;68(8):1255-1264. doi:10.1093/cid/ciy706..
11. Winston DJ, Young JAH, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. Blood. 2008 Jun 1;111(11):5403-10. doi:10.1182/blood-2007-11-121558. Epub 2008 Feb 19.

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Recorlev (levoketoconazole)

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Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Cushing's syndrome is a rare hormonal disorder that occurs when the body is exposed to high levels of the hormone cortisol for an extended period of time. Cortisol is produced by the adrenal glands, which are located on top of the kidneys, and is essential for many body functions, including regulating blood sugar levels, reducing inflammation, and aiding in the metabolism of fats, carbohydrates, and proteins.

There are two main types of Cushing's syndrome: exogenous and endogenous. Exogenous Cushing's syndrome is caused by the long-term use of high-dose corticosteroid medications, such as prednisone, to treat conditions such as asthma, rheumatoid arthritis, and lupus. Endogenous Cushing's syndrome is caused by the overproduction of cortisol by the adrenal glands themselves or by a tumor in the pituitary gland or elsewhere in the body.

Symptoms of Cushing's syndrome can be wide-ranging and may include:

- Weight gain, especially in the upper body and around the face (moon face)
- Thin skin that bruises easily and heals poorly
- Muscle weakness and wasting
- High blood pressure
- Insulin resistance or diabetes
- Irregular menstrual periods and decreased libido in women
- Decreased fertility and impotence in

men
- Mood changes, including depression and anxiety
- Fatigue and weakness

Diagnosis of Cushing's syndrome can be challenging because the symptoms can be caused by a variety of other conditions. Initial screening tests may include a 24-hour urine free cortisol test, late-night salivary cortisol test, or midnight plasma cortisol test. If screening tests are abnormal, confirmatory tests such as the dexamethasone suppression test or the corticotropin-releasing hormone (CRH) stimulation test may be performed. An ACTH level can help determine if the Cushing's syndrome is ACTH-dependent or ACTH-independent. Imaging studies, such as a CT scan or MRI, may also be used to identify the location of a tumor.

Treatment for Cushing's syndrome depends on the underlying cause. If the syndrome is caused by the long-term use of corticosteroids, gradually reducing the dosage of the medication can help to alleviate symptoms. If the syndrome is caused by a tumor, surgery may be necessary to remove the tumor or the affected gland. Radiation therapy or medication may also be used to shrink or control the tumor. In cases where surgery is not an option or has been unsuccessful, medications such as ketoconazole, metyrapone, and mitotane can be used to reduce cortisol production.

Recorlev (levoketoconazole) is indicated for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative.

- Recorlev (levoketoconazole) is not approved for the treatment of fungal infections.
- The safety and effectiveness of Recorlev (levoketoconazole) for the treatment of fungal infections have not been established.

Definitions

"Adrenal glands" are small organs on top of both kidneys that produce hormones regulating a person's metabolism, immune system, blood pressure, and response to stress.

"Adrenocorticotropic hormone (ACTH)" is a hormone made in the pituitary gland. Adrenocorticotropic hormone acts on the outer part of the adrenal gland to control the release of corticosteroid hormones. ACTH is elevated during times of stress.

"Arrhythmia" is a condition in which the heart beats with an irregular or abnormal rhythm.

"Carcinoma" is a cancer arising in the skin tissue or of the lining of internal organs.

"Endogenous" means having an internal cause or origin.

"Exogenous" means having an external cause or origin.

"QT prolongation" occurs when the heart muscle takes a longer time to contract and relax than usual, often causing fast or erratic heartbeats. QT prolongation may increase the risk of developing abnormal heart rhythms and may lead to sudden cardiac arrest.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Recorlev (levoketoconazole)** medically necessary when **ALL** of the following criteria are met:

1. The requested medication is prescribed by or in consultation with an endocrinologist***; AND***
2. The member is 18 years of age or older***; AND***
3. The member has a confirmed diagnosis of endogenous Cushing's syndrome **AND** recent (within the last 3 months) documentation of **BOTH** of the following:
    a. baseline 24-hour urinary free cortisol (UFC) is provided as evidence of hypercortisolism (normal cortisol range: 11-138 nmol/day or 4-50 mcg/day)***; and***
    b. baseline liver enzyme function test (LFTs)***; AND***
4. The member is not a candidate for pituitary surgery or has undergone pituitary surgery that was not curative***; AND***
5. The member is unable to use, or has tried and failed treatment with Signifor (pasireotide)***; AND***
6. The member does **NOT** have documentation of **ANY** of the following:
    a. pituitary or adrenal carcinoma***; or***
    b. baseline QTcF interval >470 msec, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history)***; or***
    c. cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT >3 times the ULN, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease***; or***
    d. known hypersensitivity to levoketoconazole, ketoconazole, or any component of the formulation***; or***
    e. Recorlev (levoketoconazole) will be used concomitantly with any medication(s) or product(s) that:
        i. cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes (e.g., bosutinib, cisapride, clarithromycin, cobimetinib,

crizotinib, disopyramide, dofetilide, dronedarone, eliglustat (in patients that are poor or intermediate metabolizers of CYP2D6 and in patients taking strong or moderate CYP2D6 inhibitors), ivabradine, methadone, midostaurin, nicardipine, pimozide, quinidine, and ranolazine)***; or***

ii. are sensitive substrates of CYP3A4 or CYP3A4 and P-gP (e.g., alfentanil, avanafil, buspirone, conivaptan, dabigatran etexilate, darifenacin, darunavir, digoxin, ebastine, everolimus, fexofenadine, ibrutinib, lomitapide, lovastatin, lurasidone, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, and vardenafil)***; AND***

7. Recorlev (levoketoconazole) will be dosed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature***; AND***
8. Chart documentation and supporting laboratory test results are provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Recorlev (levoketoconazole) will be approved for 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if **ALL** of the following are met:

1. the member still meets the applicable Initial Authorization criteria***; AND***
2. recent chart documentation (within the last 6 months) shows the member has experienced therapeutic response to Recorlev (levoketoconazole) as evidenced by **EITHER**:
    a. Reduction in 24-hour urinary free cortisol (UFC) levels compared to baseline***; or***
    b. Improvement in clinical signs and symptoms of Cushing's syndrome based on the prescriber's assessment (e.g., systolic and diastolic blood pressure, weight, body mass index [BMI], waist circumference)***; AND***
3. The member will continue to be monitored for adverse effects including liver function and QT prolongation while on therapy.

Table 1: Recorlev (levoketoconazole) Recommended Dosage

Indication	Initial dose	Maximum dose	Additional Considerations
endogenous hypercortisolemia in adult patients with	150 mg orally twice daily	1,200 mg per day, given as 600 mg orally twice daily	Titrate the dosage by 150 mg daily, no more frequently than every 2-

Cushing's syndrome			3 weeks based on 24-hour urine free cortisol levels and patient tolerability. The dosage may be reduced to 150 mg once daily if needed for reasons of tolerability

Experimental or Investigational / Not Medically Necessary

Recorlev (levoketoconazole) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Cushing's syndrome secondary to:
  - malignancy (including pituitary or adrenal carcinoma)***; or***
  - non-endogenous source of hypercortisolism, including pharmacological corticosteroids or ACTH***; or***
- the treatment of advanced prostatic carcinoma***; or***
- for treatment of dysfunctional hirsutism***; or***
- for the treatment of fungal infections***; or***
- for treatment of hypercalcemia***; or***
- for treatment of precocious puberty.

References

1. Braun LT, Riester A, Oßwald-Kopp A, et al. Toward a diagnostic score in Cushing's syndrome. Front Endocrinol (Lausanne). 2019;10:766. doi:10.3389/fendo.2019.00766
2. Burns EB. "Drugs Causing QT Prolongation." Life in the Fastlane. Available at: https://litfl.com/drugs-causing-qt-prolongation/. Updated Feb 2021. Accessed Feb 28, 2022.
3. Carvalho TF. "Recorlev." Cushing's Disease News. Available at: https://cushingsdiseasenews.com/recorlev-levoketoconazole-cor-003/. Updated Jan 2022. Accessed Feb 28, 2022.
4. Castinetti F, et al. Ketoconazole in Cushing's disease: is it worth a try? J Clin Endocrinol Metab. 2014;99(5):1623-1630. doi:10.1210/jc.2013-3628
5. Fleseriu M, Auchus RJ, Greenman Y, et al. Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical, and radiological outcomes. Eur J Endocrinol. 2022 Nov 24;187(6):859-871. doi:10/1530/EJE-22-0506.
6. Fleseriu M, Pivonello R, Elenkova A, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label,

single-arm trial [published correction appears in Lancet Diabetes Endocrinol. 2019;7(11):e22]. Lancet Diabetes Endocrinol. 2019;7(11):855-865. doi:10.1016/S2213-8587(19)30313-4
7. Geer EB, Salvatori R, Elenkova A, et al. Levoketoconazole improves clinical signs and symptoms and patient-reported outcomes in patients with Cushing's syndrome. Pituitary. 2021 Feb;24(1):104-115. doi:10.1007/s11102-020-01103-6.Epub 2020 Nov 20.
8. Gilis-Januszewska A, Bogusławska A, Rzepka E, Ziaja W, Hubalewska-Dydejczyk A. Individualized medical treatment options in Cushing disease. Front Endocrinol (Lausanne). 2022 Dec 2;13:1060884. doi: 10.3389/fendo.2022.1060884. PMID: 36531477; PMCID: PMC9755355.
9. Loriaux D.L.: Diagnosis and differential diagnosis of Cushing's syndrome. N Engl J Med 2017; 376: pp. 1451-1459.
10. Mayo Clinic.org - Cushing's Syndrome. Available at: https://www.mayoclinic.org/diseases-conditions/cushing-syndrome/. Updated Apr 2021. Accessed Feb 28, 2022.
11. Nieman LK, et al; Endocrine Society. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-2831. doi:10.1210/jc.2015-1818
12. Patra S, Dutta D, Nagendra L, Raizada N. Efficacy and safety of levoketoconazole in managing Cushing's syndrome: a systematic review. Indian J Endocrinol Metab. 2024 Jul-Aug;28(4):343-349. doi:10.4103/ijem.ijem_477_23. Epub 2024 Aug 28.
13. Pivonello R, Elenkova A, Fleseriu M, et al. Levoketoconazole in the treatment of patients with Cushing's syndrome and diabetes mellitus: results from the SONICS phase 3 study. Front Endocrinol (Lausanne). 2021 Apr 7:12:595894. doi:10..3389/fendo.2021.595894. eCollection 2021.
14. Pivonello R, Zacharieva S, Elenkova A, et al. Levoketoconazole in the treatment of patients iwth endogenous Cushing's syndrome: a double-blind, placebo-controlled, randomized withdrawal study (LOGICS). Pituitary. 2022 Dec;25(6):911-926. doi:10.1007/s/11102-022-01263-7. Epub 2022 Sep 9.
15. Recorlev (levoketoconazole) [prescribing information]. Chicago, IL: Xeris Pharmaceuticals Inc; June 2023.
16. Recorlev Fact Sheet. Available at: https://www.xerispharma.com/pdf/recorlev-fact-sheet.pdf. Accessed Feb 28, 2022.
17. Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. Clin Epidemiol. 2015;7:281-93. doi:10.2147/CLEP.S44336
18. The National Institute of Diabetes and Digestive and Kidney Diseases Health Information Center. Cushing's Syndrome. Available at: https://www.niddk.nih.gov/health-information/endocrine-diseases/cushings-syndrome.
19. Tisdale JE, Chung MK, Campbell KB, et al. Drug-induced arrhythmias: a scientific statement from the American Heart Association. Circulation. 2020;142(15):e214-e233. doi:10.1161/CIR.0000000000000905

Clinical Guideline Revision / History Information

Original Date: 03/17/2022
Reviewed/Revised: 3/23/2023, 3/21/2024, 7/1/2025

Tarpeyo (budesonide delayed release capsules)

Summary

IgA nephropathy, also known as Berger's disease, is a type of kidney disease that is caused by the accumulation of immunoglobulin A (IgA) in the kidneys. It is a chronic, progressive disease that can lead to kidney failure if left untreated.

The exact cause of IgA nephropathy is not fully understood, but it is believed to be related to an abnormal immune response that causes the body to produce aberrant galactose-deficient IgA1, which then accumulates in the kidneys. This accumulation can lead to inflammation and damage to the small blood vessels in the kidneys, leading to a decrease in kidney function over time.

The most common symptom of IgA nephropathy is blood in the urine, which may be visible or only detected through laboratory tests. Other symptoms may include proteinuria (excess protein in the urine), high blood pressure, swelling of the hands and feet, decreased kidney function and fatigue. However, some people with IgA nephropathy may have no symptoms at all.

Diagnosis of IgA nephropathy typically involves a combination of urine tests and blood tests and is confirmed via kidney biopsy. Treatment options depend on the severity of the disease and may include medications to control blood pressure and reduce inflammation (i.e., "supportive care"), as well as

dietary and lifestyle changes to help protect the kidneys. In high-risk patients (i.e, proteinuria >/= 1 g/day despite at least 3-6 months of optimized supportive care), immunosuppressive therapy is recommended (e.g., systemic glucocorticoids, targeted-release budesonide, mycophenolate mofetil, calcineurin inhibitors [cyclosporine, tacrolimus], rituximab, cyclophosphamide, azothiaprine, leflunomide, hydroxychloroquine).

In some cases, IgA nephropathy may progress to end-stage renal disease, which requires dialysis or kidney transplant. However, early diagnosis and treatment can help slow the progression of the disease and preserve kidney function. Tarpeyo (budesonide delayed release capsules) is indicated to reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression. Tarpeyo (budesonide delayed release capsules) approval was based on the findings of the NefIgArd study, which found that in participants on a stable dose of maximally tolerated renin-angiotensin-System (RAS) inhibitor therapy in the Tarpeyo arm had a significant reduction in **urine-protein-to-creatinine ratio (UPCR)** and significantly lower decline in renal function (measured by estimate glomerular filtration rate[eGFR]). The recommended dose of Tarpeyo (budesonide delayed release capsules) is 16 mg administered orally once daily for a duration of 9 months; this is followed by a reduced dose of 8 mg once daily for the last 2 weeks of (whether discontinued before 9 months or after the 9-month course).

Definitions

"**Angiotensin-converting enzyme (ACE) inhibitor"** is a class of medications that lowers blood pressure by relaxing blood vessels.

"**Angiotensin II receptor blocker (ARB)"** is a class of medications similar to ACE inhibitors, that lowers blood pressure.

"**C3 glomerular nephropathy"** is a set of rare kidney diseases caused by a disorder of the complement system, part of the body's immune system.

"Diabetic nephropathy" is a long-term complication of diabetes, resulting in damage to the kidneys, reduction in kidney function and can lead to chronic kidney disease or end-stage renal disease.

"**Dialysis**" is a procedure that removes waste and fluid from the blood when the kidneys stop working properly.

"**Estimated Glomerular Filtration Rate (eGFR)**" is a measure of how well the kidneys are working.

"**Glomerulopathies**" are a group of kidney diseases that affect the tiny blood vessels that filter blood in the kidney.

"Immunoglobulin A nephropathy (IgAN)" is a disease of the kidney that occurs when an antibody called immunoglobulin A (IgA) builds up in the kidney.

"Immunosuppressives" are any agent aimed at reducing the body's immune response, which may be used to treat conditions characterized by overactive immune systems, or to avoid rejection of bone marrow or organ transplant.

"**Nephrotic syndrome"** is a kidney disorder that causes the body to pass too much protein in the urine.

"**Proteinuria**" is when elevated levels of protein are found in the urine.

"Renin-angiotensin system (RAS)" refers to the system of hormones, proteins, enzymes adn reactions that help regulate blood pressure. RAS inhibitors include ACE inhibitors and ARBs, as well as direct renin inhibitors.

"Supportive care" is care administered in an attempt to improve quality of life in a person with an illness/disease by preventing or treating the symptoms of the disease and/or the side effects associated with the treatment of the illness/disease.

"Urine-protein-to-creatinine ratio (UPCR)" is a test that measures the amount of protein found in urine.

Medical Necessity Criteria for Authorization

The Plan considers **Tarpeyo (budesonide delayed release capsules)** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with a nephrologist**; *AND***
2. The member has a diagnosis of Immunoglobulin A nephropathy (IgAN) confirmed by kidney biopsy **AND** documentation of **ALL** of the following:
    a. is at risk of rapid disease progression; ***and***
    b. glomerular filtration rate (eGFR) is greater than 35 mL/min/1.73 m^2; ***and***
    c. proteinuria ≥1 g/day or UPCR ≥0.8 g/g despite at least three months of optimized supportive care consisting of **BOTH** of the following:

i. lifestyle modification (such as dietary sodium and protein restriction, smoking cessation, weight control, and exercise as appropriate); ***and***

ii. maximally tolerated renin-angiotensin system blockade (either an angiotensin-converting enzyme [ACE] inhibitor (e.g., benazepril, enalapril, lisinopril) or angiotensin receptor blocker [ARB] (e.g, candesartan, losartan, valsartan))**; *or*** the member is unable to use **ALL,** or has tried and/or failed **a maximally tolerated ACE inhibitor or ARB.**

3. The member does **NOT** have documentation of ANY of the following:
    a. currently receiving dialysis or has undergone kidney transplant; ***or***
    b. presence of other glomerulopathies, such as C3 glomerulopathy or diabetic nephropathy; ***or***
    c. nephrotic syndrome, characterized by proteinuria greater than 3.5 g/day, serum albumin levels below 3.0 g/dL, and with or without edema. The only exception to this exclusion criteria is for patients diagnosed with IgA nephropathy accompanied by nephrotic syndrome. In such cases, coverage for the drug may be considered; ***or***
    d. prior treatment with systemic immunosuppressive medications within the last 12 months; ***or***
    e. previously received a treatment course of Tarpeyo (budesonide delayed release capsules); ***AND***
4. Tarpeyo (budesonide delayed release capsules) will be used as an add-on treatment to optimized standard care including a maximally-tolerated, stable dose of an ACE inhibitor or ARB**; *AND***
5. Tarpeyo (budesonide delayed release capsules) will be dosed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature**; *AND***
6. Recent (within the last 3 months) chart documentation and supporting laboratory test results are provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Tarpeyo (budesonide delayed release capsules) will be approved for a single 9-month treatment course.

Experimental or Investigational / Not Medically Necessary

Tarpeyo (budesonide delayed release capsules) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Autoimmune hepatitis; ***or***
- Crohn disease; ***or***
- Eosinophilic esophagitis; ***or***
- Graft-versus-host disease; ***or***
- Microscopic (lymphocytic and collagenous) colitis; ***or***
- Pouchitis; ***or***
- Refractory celiac disease types 1 and 2; ***or***
- Ulcerative colitis.

References

1. Barratt J, Lafayette R, Kristensen J, Stone A, Cattran D, Floege J, Tesar V, Trimarchi H, Zhang H, Eren N, Paliege A, Rovin BH; NefIgArd Trial Investigators. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. Kidney Int. 2023 Feb;103(2):391-402. doi: 10.1016/j.kint.2022.09.017. Epub 2022 Oct 19. PMID: 36270561.
2. Barratt J, Floege J. SGLT-2 inhibition in IgA nephropathy: the new standard of care? Kidney Int 2021;100:24-26.
3. Campbell KN. Oral Glucocorticoids for IgA Nephropathy. JAMA 2022; 327:1872.
4. Canney M, Barbour SJ, Zheng Y, et al. Quantifying Duration of Proteinuria Remission and Association with Clinical Outcome in IgA Nephropathy. J Am Soc Nephrol 2021; 32:436.
5. Cattran DC, Appel GB, Coppo R. IgA nephropathy: treatment and prognosis. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
6. Cleveland Clinic - Renin-angiotenin-aldosterone system (RAAS). Available at: https://my.clevelandclinic.org/health/articles/24175-renin-angiotensin-aldosterone-system-raas. Last updated 13 Sep 2022. Accessed 6 Feb 2025.
7. Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. Lancet 2017.
8. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int 2021; 100:S1.
9. Lv J, Wong MG, Hladunewich MA, et al. Effect of oral methylprednisolone on decline in kidney function or kidney failure in patients with IgA nephropathy: the TESTING randomized clinical trial. JAMA 2022;327:1888-1898.
10. National Cancer Institute - Supportive Care. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/supportive-care. Accessed 6 Feb 2025.
11. National Cancer Institute - Immunosuppressive agent. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/immunosuppressive-agent. Access 7 Feb 2025.

12. National Organization for Rare Disorders (NORD) Rare Disease Database. IgA Nephropathy. Available at: https://rarediseases.org/rare-diseases/iga-nephropathy/. Updated July 19, 2018. Accessed February 24, 2022.
13. Smith RJH, Appel GB, Blom AM. C3 glomerulopathy - understanding a rare complement-driven renal disease. Nat Rev Nephrol. 2019 Mar; 15(3): 129-143. doi:10.1038/s41581-018-0107-2.
14. Tarpeyo (budesonide) [prescribing information]. Stockholm Sweden: Colliditas Therapeutics AB; June 2024.
15. Vaz de Castro PAS, Bitencourt L, Pereira BWS, et al. Efficacy and safety of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for IgA nephropathy in children. Pediatr Nephrol 2022; 37:499.
16. Wheeler D.C., et al.: A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy . Kidney Int 2021; 100 (1): pp. 215-224.

Clinical Guideline Revision / History Information

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Oscar Clinical Guideline: Tezspire (tezepelumab) (PG118, Ver. 5)

Tezspire (tezepelumab)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Asthma is a chronic respiratory disease that affects the airways, leading to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The condition is caused by a combination of genetic and environmental factors, such as allergens, pollutants, and respiratory infections. Asthma is characterized by inflammation of the airways, which makes them hypersensitive and prone to constricting in response to various triggers. The inflammation is driven by immune cells, including eosinophils, mast cells, and T lymphocytes, which release pro-inflammatory mediators, such as histamine, leukotrienes, and cytokines.

Severe asthma is a type of asthma that is difficult to control and is characterized by persistent and frequent symptoms, exacerbations, and airflow limitation, despite adherence to maximal optimized therapy. According to the Global Initiative for Asthma (GINA), severe asthma is a subset of a "difficult-to-treat" asthma, which is defined as asthma that is uncontrolled despite medium-or high-dose inhaled corticosteroid (ICS) with a second controlled (including long-acting beta-agonists (LABA) or with maintenance oral corticosteroid, or that requires high-dose treatment to maintain good symptom control and reduce risk of exacerbation. Severe asthma is specifically defined as asthma that is uncontrolled despite maximally optimized high-dose ICS/LABA treatment and management of contributory factors (e.g., inhaler technique, adherence, comorbidities), or that worsens when high-dose treatment is decreased. In addition, severe asthma may be associated with comorbidities such as obesity, sinusitis,

Commented [1]: Clinical Perspective
Several clinical practice guidelines are available for asthma management including the Global Initiative for Asthma (GINA) guidelines, which are published annually. The GINA guideline provides evidence-based recommendations for the management of asthma in adults, adolescents, and children ≥6 years of age. The guideline states that all patients with asthma should be evaluated for symptom control, risk of future exacerbations, treatment issues (e.g., inhaler technique and adherence), and comorbidities. A stepwise approach to treatment is recommended where specific drugs are added or adjusted up or down through a series of steps (1 through 5) to achieve symptom control while keeping the patient on the lowest effective treatment. Drugs used in the management of asthma include inhaled corticosteroids (ICS)-formoterol, long-acting beta agonists (LABA), short-acting beta agonists (SABA), long-acting muscarinic agonists (LAMA), leukotriene receptor antagonists, theophylline, oral corticosteroids, and biologic agents. Biologic agents such as tezepelumab are generally recommended as add-on therapy for severe asthma. Higher blood eosinophils and higher FeNO levels are associated with a greater risk of severe exacerbations and are predictive markers for Type 2 inflammation, which is found in the majority of individuals with severe asthma. The GINA guideline states that tezepelumab can be considered as add-on therapy in patients ≥12 years of age with severe asthma. High blood eosinophils and high FeNO levels are strongly predictive of a good response with the drug. The use of tezepelumab can also be considered in patients without elevation in type 2 inflammatory markers.

and gastroesophageal reflux disease (GERD), and may require additional diagnostic tests, such as lung function tests, bronchial challenge tests, and imaging studies, to confirm the diagnosis and guide treatment.

The treatment of severe asthma requires a multi-faceted approach, including medication management, environmental control, and lifestyle modifications. The goal of treatment is to improve asthma control and reduce the risk of exacerbations. The following are some of the treatment options available for severe asthma:

- High-dose inhaled corticosteroids: These medications are the mainstay of treatment for asthma and are often used in combination with long-acting beta-agonists. However, in severe asthma, higher doses may be required. As asthma progresses, patients may require the addition of a long-acting muscarinic antagonist (LAMA) to the ICS-LABA therapy.
- Biologic medications: These medications are specifically designed to target specific immune pathways that contribute to asthma. Biologics are effective in reducing exacerbations and improving asthma control in severe asthma. Examples include omalizumab, mepolizumab, benralizumab, and dupilumab.
- Oral corticosteroids: In severe asthma, oral corticosteroids may be necessary for short-term management of exacerbations. However, long-term use of oral corticosteroids can lead to serious side effects and should be avoided.
- Lifestyle modifications: Lifestyle modifications such as weight loss, exercise, and smoking cessation can help improve asthma control in people with severe asthma.

Commented [2]: update to include brand names if appropriate

Tezspire (tezepelumab), a thymic stromal lymphopoietin (TSLP) blocker which may reduce the effect of the asthma inflammatory cascade, is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma. It is not indicated for the relief of acute bronchospasm or status asthmaticus. The recommended dosage of Tezspire (tezepelumab) is 210 mg administered subcutaneously once every 4 weeks. The pivotal trials, NAVIGATOR (12-80 years) and PATHWAY (18-75 years) were randomized placebo-controlled trials assessing the role of Tezpire (tezepelumab) in those with severe asthma receiving a medium-to-high dose ICS and at least one additional controlled medication, with or without oral glucocorticoids. Tezspire (tezepelumab) is unique in the lack of requirement of oral corticosteroid dependence, thus allowing those with severe asthma to receive additional therapy and avoid the potential risks of long-term corticosteroid use. In a pooled analysis of the NAVIGATOR and PATHWAY study, they found a significant reduction in the number of annual asthma exacerbations, and exacerbation-related hospitalization and emergency department visits.

Commented [3]: add moa

Definitions

"Adjunctive therapy" refers to additional therapy, in addition to a primary treatment modality with a goal of enhancing the effectiveness of the primary treatment.

"**Biomarker**" is a substance found in the body that works as an indicator of exposure, effect, susceptibility, or clinical disease.

"IgG2 lambda monoclonal antibody" is a laboratory-produced molecule that acts as a substitute antibody that can restore, enhance or mimic the immune system's attack on cells.

"Inhaled corticosteroids (ICS)" refer to inhaled steroid medications, aimed at reducing inflammation associated with respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD).

"Leukotriene receptor antagonists (LTRA)" are oral medications which reduce inflammation associated with leukotrienes. Leukotrienes are released by the body and can cause coughing, excessive mucus production, inflammation of airways, tightness in the chest and wheezing or difficulty breathing.

"Long-Acting Beta-Agonist (LABA)" are long-acting inhalers which relax the smooth muscle of the airways, improving airflow in patients with asthma and/or COPD.

"Long-Acting Muscarinic Antagonists (LAMA)" are inhaled medications which block the muscarinic receptor, responsible for constriction of the airways, thus reducing inflammation in the airways associated with asthma and/or COPD.

"**Phenotype**" is a set of clinical characteristics, lung function and inflammation that is specific to a type of asthma as there are many different types of asthma.

"Thymic stromal lymphopoietin (epithelial cytokine)" is a regulator of a type of immunity, which drives a broad range of allergic responses.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Tezspire (tezepelumab)** medically necessary when **ALL** the following criteria are met:

1. Prescribed by or in consultation with an allergist, immunologist, or pulmonologist***; AND***
2. The member is 12 years of age or older***; AND***
3. The member has a documented diagnosis of severe asthma***; AND***
4. The member has a history of one or more of the following within the last 12 months:
    a. Two or more (≥2) exacerbations requiring oral/systemic corticosteroids treatment***; or***
    b. One or more (≥1) exacerbation resulting in hospitalization or intensive care unit (ICU) admission***; and***
5. The member has tried and failed, or is unable to use, **ALL** of the following at optimized# doses:
    a. High-dose inhaled corticosteroids (ICS)***; and***

Commented [4]: note changes may affect Dupixent changes d/t similar wording

however indication for dupixent in asthma is more strict re: steroids: Asthma as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma"

Commented [5]: NAVIGATOR and PATHWAY studies required patients be on med or high dose ICS,

to review the other required therapies

b. Adjunctive therapy (in combination with inhaled corticosteroid), such as **ONE** of the following:
    i. Long-Acting Beta-2 Agonists (LABA), such as formoterol or salmeterol***; or***
    ii. Leukotriene Receptor Antagonist (LTRA), such as montelukast (Singulair) or zafirlukast (Accolate)***; or***
    iii. Long-Acting Muscarinic Antagonists (LAMA), such as tiotropium; ***or***
    iv. Extended-release theophylline***. AND***

[#]*member should be receiving treatment with inhaled corticosteroid and additional controller (adjunctive therapy) for at least the previous 3 months.*

6. Clinical chart documentation is provided showing **BOTH** of the following:
    a. Tezspire (tezepelumab) will not be used as monotherapy***; and***
    b. Tezspire (tezepelumab) will not be used concomitantly with other biologics (e.g., Cinqair, Fasenra, Nucala or Xolair) in the treatment of asthma***; AND***
7. Tezspire (tezepelumab) is being prescribed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature***; AND***
8. Clinical chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, Tezspire (tezepelumab) will be approved for up to 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 12 months will be granted for members 12 years of age or older when recent chart documentation (within the past 6 months) is provided showing **ALL** of the following criteria are met:

1. The member's asthma has improved on Tezspire (tezepelumab) treatment based upon the prescriber's assessment as demonstrated by at least **ONE** of the following:
    a. A reduction in the frequency and/or severity of symptoms and exacerbations***; or***
    b. A reduction in the daily maintenance oral corticosteroid dose***; AND***
2. Clinical chart documentation is provided showing **BOTH** of the following:
    a. Tezspire (tezepelumab) will not be used as monotherapy***; and***
    b. Tezspire (tezepelumab) will not be used concomitantly with other biologics (e.g., Cinqair, Fasenra, Nucala or Xolair) in the treatment of asthma***; AND***
3. Tezspire (tezepelumab) is being prescribed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature.

Commented [6]: ? add LAMA - review guidelines - to review study as well here

Commented [7]: in GINA 2024 guidelines, theophylline is not recommended therapy, and would not come between an ICS/LABA w/o or or without an addition al inhaler and a biologic

theophylline is on formulary (tier 1)

add-on therapies recommended by GINA after ICS include: LABA, LAMA, LTRA.

my recommendation: given GINA guidelines i would add LAMAs to options i-iii, such that it becomes option "iv" - can continue to include theophylline but would rec add LAMA to the list. There are LABAs and LAMAs on our formulary that are on tier 2

Commented [8]: would recommend removing all OCS requirements from this- "c." and after "3 months..." d/t the inclusion criteria/requirements of the original studies. Different Indication than dupixent.

Commented [9]: I think this may be too strict re: corticosteroid use. from the original NAVIGATOR trial "Patients were 12 to 80 years of age with physician-diagnosed asthma, who had received medium- or high-dose inhaled glucocorticoids (daily dose of ≥500 μg of fluticasone propionate or equivalent) for at least 12 months before screening and at least one additional controller medication, with or without oral glucocorticoids, for at least 3 months before the date of informed consent."

I read this as they did not necessarily need to have failed corticosteroids. Even if we are strict and they should have trialed corticosteroids regardless, I do not think a majority of days is evidence based as the goal is to minimize oral corticosteroids as much as possible.

per the study PI "Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or 1 asthma exacerbation resulting in hospitalization in the past 12 months." - indicating 1 use of corticosteroids over the last 12 months. there was another study where they looked at n=150 who were on daily steroids, but this was a subgroup analysis, not a requirement.

Experimental or Investigational / Not Medically Necessary

Tezspire (tezepelumab) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Atopic dermatitis (AD)
- Chronic rhinosinusitis with nasal polyps
- Chronic obstructive pulmonary disease (COPD)
- Chronic spontaneous urticaria
- Eosinophilic esophagitis (EoE)

References

1. AstraZeneca plc. (2020, December 22). Update on SOURCE Phase III trial for Tezepelumab in patients with severe, oral corticosteroid-dependent asthma. Available at: https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-source-phase-iii-trial-for-tezepelumab-in-patients-with-severe-oral-corticosteroid-dependent-asthma.html. Last accessed December 27, 2021.
2. Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. JAMA. 2020;324(22): 2301-2317.
3. Corren J, AMbrose CS, Griffiths JM, et al. Efficacy of tezepelumab in severe allergic asthma: results from the phase 3 NAVIGATOR study. Clin Exp Allergy. 2023 Apr;53(4):417-428. doi:10.1111/cea.14256. Epub 2022 Dec 12.
4. Corren J, Menzies-Gow A, Chupp G, et al. Efficacy of tezepelumab in severe, uncontrolled asthma: a pooled analysis of the PATHWAY and NAVIGATOR clinical trials. Am J Respi Crit Care Med. 2023 Jul 1;208(1):13-24. doi:10.1164/rccm.202210-2005OC.
5. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. N Engl J Med. 2017;377(10):936-946.
6. Expert Panel Working Group of the National Heart, Lung, and Blood Institute. Guidelines 2020 focused updates for asthma management-summary reported. J Allergy Clin Immunol 2020;146(6):1217-1270.
7. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Updated 2021.
8. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Updated 2024. https://ginasthma.org/wp-content/uploads/2024/05/GINA-2024-Strategy-Report-24_05_22_WMS.pdf
9. Menzies-Gow A, Ambrose CS, Colice G, et al. Effect of tezepelumab on lung function in patients with severe uncontrolled asthma in the phase 3 NAVIGATOR study. Adv Ther. 2023 Nov;40(11):4957-4971. doi:10.1007/s12325-023-02659-y. Epub 2023 Sep 19.

10. Menzies-Gow A, Bourdin A, Chugg G, et al. Effect of tezepelumab on healthcare utilization in patients with severe, uncontrolled asthma: the NAVIGATOR study. Ann Allergy Asthma Immunol. 2023 Sep; 131(3):343-348. E2. doi:10.1016/j.anai.2023.05.028. Epub 2023 May 30.
11. Menzies-Gow A, Colice G, Griffiths JM, et al. NAVIGATOR: a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res. 2020;21(1):266. doi:10.1186/s12931-020-01526-6
12. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. N Engl J Med. 2021;384(19):1800-1809. doi:10.1056/NEJMoa2034975.
13. Menzies-Gow A, Ponnarambil S, Downie J, et al. DESTINATION: a phase 3, multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the long-term safety and tolerability of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respir Res. 2020 Oct 21;21(1):279. doi:10.1186/s12931-020-01541-7.
14. Menzies-Gow A, Wechsler ME, Brightling CE, et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. Lancet Respir Med. 2023 May;11(5):425-438. doi:10.1016/S2213-2600(22)00492-1. Epub 2023 Jan 23.
15. Pavord ID, Hoyte FCL, Lindsley AW, et al. Tezepelumab reduces exacerbations across all seasons in patients with severe, uncontrolled asthma (NAVIGATOR). Ann Allergy Asthma Immunol. 2023 Nov;131(5):587-597.e3. doi:10.1016/j.anai.2023.08.015. Epub 2023 Aug 23.
16. Tezspire (tezepelumab) [prescribing information]. Thousand Oaks, CA: Amgen, Inc; May 2023.
17. Wechsler ME, Brusselle G, Virchow JC, et al. Clinical response and on-treatment clinical remission with tezepelumab in a broad population of patients with severe uncontrolled asthma: results over 2 years from the NAVIGATOR and DESTINATION studies. Eur Respir J. 2024 Dec 5;64(6):2400316. doi:10.1183/13993003.00316-2024. Print 2024 Dec.
18. Wechsler ME, Menzies-Gow A, Christopher E Brightling CE, et al, SOURCE study group. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. Lancet Respir Med. 2022 Mar 29;S2213-2600(21)00537-3. Online ahead of print.

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Continuous Glucose Monitors (CGMs) Prescription Products

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Diabetes mellitus (DM) (commonly referred to as diabetes) is a chronic (long-term) medical condition characterized by high blood glucose (sugar). This may be because the pancreas (an organ in the belly) does not make enough insulin (a hormone), or because the body is not responding to insulin the way it should. Insulin helps glucose get into cells in the body, giving it energy. With diabetes, sugar builds up in the blood because the body stops responding to insulin, or because there is not enough of it. Diabetes is broadly grouped into two types:

- Type 1 diabetes mellitus - the pancreas makes no insulin or a very small amount
- Type 2 diabetes mellitus - cells in the body do not respond to insulin the way they should; sometimes, the pancreas also does not make enough insulin

Diabetes is usually managed by eating healthy foods, getting plenty of exercise, and sometimes with medicines. Medicines are used to either control blood sugar or to lower the chance of problems that can happen in the future because of diabetes. These medications can be insulin itself, or medications that

help the body make more insulin or help insulin do its job. In addition, Plan members who have been diagnosed with Type 1 or 2 DM, and meet certain medical necessity criteria and standards of care developed by the American Diabetes Association (ADA), may be eligible for specific supplies and equipment subject to plan benefits, such as those used to monitor blood sugar and inject insulin. Members with more advanced disease or those requiring more frequent insulin may qualify for continuous glucose monitoring and specialized insulin delivery systems.

Continuous glucose monitoring (CGM) is a new way to monitor blood sugar for members who need it. CGMs check blood sugar about every one to five minutes, show the reading, and alerts members when blood sugar is not within the defined range. CGMs allow members to use the measurement, pattern or trends, to make better decisions about lifestyle or medication changes. There are different types of CGMs, such as:

- Professional CGM[#] - for use at prescriber's offices, usually a specialist in managing diabetes. They may also be given to members for a short time (e.g. a few days) in order to measure and evaluate trends. These are products such as Freestyle Libre Pro, Dexcom G6 Pro, and iPro2 Professional.
- Combination CGMs and external insulin pumps[#] - integrated with an external insulin pump, making available technology and functionality from both devices available to the member. These are products such as Tandem T:slim X2 systems (using Dexcom G6/7 or Freestyle Libre 2 Plus CGM sensors), Medtronic MiniMed 630G (using Guardian Sensor 3), or MiniMed 780G (using Guardian Sensor 4).

  [#]not covered by Pharmacy Benefit. May be covered via Medical Benefit; please refer to Medical Clinical Guideline (CG029) - Insulin Delivery Systems and Continuous Glucose Monitoring.
- Stand-alone CGM - a personal system for long-term use, providing ongoing measurements of blood sugar levels, and readily available data.
- Over-the-Counter Continuous Glucose Monitoring Systems (OTC CGMs) - devices that have been cleared by the FDA for sale without a prescription. They are designed to help certain individuals monitor their glucose levels. OTC CGMs are not in-scope for this Oscar Clinical Guideline. Coverage of OTC CGMs, if any, depends on a member's specific benefit policy. Members should refer to their applicable benefit plan document to determine benefit availability and the terms and conditions of coverage for OTC CGMs.

NOTE: This Pharmacy Clinical Guideline is specific to only stand-alone prescription CGMs; examples of available, commonly prescribed products (not all-inclusive) are listed below in **Table 1: Stand-alone Prescription CGM Systems**.

- For information on medical necessity criteria of medical nutrition counseling, please refer to the Plan's Medical Clinical Guideline: Medical Nutrition Therapy (CG010).
- For information on medical necessity criteria of diabetes equipment and supplies, please refer to the Plan's Medical Clinical Guideline: Diabetes Equipment and Supplies (CG028).
- For the Plan's Medical Clinical Guideline of professional diagnostic or short-term continuous glucose monitoring and insulin pump delivery systems, please refer to the Plan's Medical Clinical Guideline: Insulin Delivery Systems and Continuous Glucose Monitoring (CG029).
- The Plan also covers home glucose monitors and products for self-monitoring of blood sugar as an alternative to CGMs. Please contact CVS/Caremark, the Plan's Prescription Benefit Manager, to obtain a standard blood glucose meter from the preferred brand.
- Coverage for OTC CGMs, if any, is determined by a member's specific benefit plan.

Table 1: Stand-alone Prescription CGM Systems

CGM System	FDA-approved or cleared for	Components	Use Life
Formulary Agents*			
Dexcom G6	at least two years old	Receiver	1 year
		Sensor	10 days per sensor
		Transmitter	90 days
Dexcom G7	at least two years old	Receiver	about 3 years
		Sensor	10 days per sensor
Non-Formulary Agents*‡			
Freestyle Libre 2	at least four years old	Sensor	14 days per sensor
		Reader	about 3 years
FreeStyle Libre 2 Plus	at least two years old		
		Sensor	15-days per sensor
Freestyle Libre 3	at least four years old	Sensor	14 days per sensor

		Reader	about 3 years
FreeStyle Libre 3 Plus	at least two years old		
		Sensor	15-days per sensor
Freestyle Libre 14-day	≥18 years old	Sensor	14 days per sensor
		Reader	about 3 years
Medtronic Guardian Connect	between the ages of 14 and 75 years old	Guardian Sensor 3	7 days per sensor
		Guardian Connect Transmitter	can be cleaned up to 122 times or one year, whichever comes first
Senseonics Eversense 365	≥18 years old	Eversense 365 Sensor[#]	365 days
		Transmitter	1 year

[*]*The Plan may review all requests made under the Medical or Pharmacy benefit against specific prior authorization criteria, as applicable and at its discretion. Products considered Formulary or Preferred for the Plan may still require a clinical prior authorization review. The Formulary status of these medications may change over time. Always refer to the member's Plan current Formulary for the most up-to-date information.*

[ɳ]*Subject to Plan's Non-Formulary Products Criteria (PG069).*

[#]*The sensor insertion and removal procedures must be performed by a healthcare provider.*

NOTE: This table provides a general overview of stand-alone prescription CGM systems for informational purposes only.

- It is not exhaustive and does not reflect all potential variations among devices. Features may vary by specific device and manufacturer. Always refer to the most up-to-date FDA-approved/cleared labeling.
- The Plan requires that members meet specific medical necessity criteria for coverage of Continuous Glucose Monitoring Systems (CGMS). This includes demonstrating inability to use, or documented trial and failure of, the Formulary and preferred system(s) before considering non-preferred or non-formulary options.
    - The order of CGM systems in this table does not indicate preference or tier status.
    - For specific coverage information, please refer to the applicable formulary and the member's benefit plan documents.

Definitions

"Insulin" is a hormone made by the beta cells of the pancreas. Insulin allows glucose to enter the cells in the body for use in energy production, and when it is inadequate, the sugar remains in the blood leading to diabetes. There are a variety of oral and parenteral medications that can increase insulin production, increase the body's sensitivity to existing insulin and reduce blood sugar. Insulin can also be injected or infused when lifestyle changes and non-insulin medications are inadequate.

"Type 1 Diabetes" is an autoimmune condition that occurs when the beta cells of the pancreas are unable to produce enough insulin and therefore blood glucose cannot enter cells to be used for energy. Type 1 diabetes is often referred to as "insulin-dependent" because these patients require insulin daily to maintain their blood glucose at acceptable levels.

"Type 2 Diabetes" is a condition that occurs when either the pancreas doesn't produce enough insulin or the body cells become resistant to insulin. Type 2 diabetes is much more common than Type 1, and is often treated with combinations of lifestyle changes and non-insulin medications, although insulin can be required later in the disease course. Many individuals with Type 2 Diabetes are "insulin-requiring".

"Blood Glucose" is the main sugar found in the blood and the body's main source of energy. It is also called glucose or blood sugar. The blood level of glucose is noted in milligrams per deciliter (mg/dL). When blood sugar is too high for long periods of time, complications can occur as a result of blood vessel damage.

"Blood Glucose Monitors" are small, portable machines used to check blood glucose levels in the ambulatory setting. A member will prick his/her fingertip and place a small sample of blood into the device for a glucose reading. There are a number of different types of blood glucose monitors for specialized situations, such as those for members with visual impairments.

"Continuous Glucose Monitoring (CGM)" serves as an alternative to self-monitoring of blood glucose (SMBG) with a home glucose monitor for patients who have diabetes and require multiple daily measurements.

"External Continuous Subcutaneous Insulin Infusion (CSII) Pumps" or **"Insulin Infusion Pumps"** are non-implantable insulin-delivery devices that can be worn on a belt, kept in a pocket, or attached directly to the skin. An insulin pump connects to narrow, flexible plastic tubing that ends with a needle

inserted just under the skin. Users set the pump to give a basal amount of insulin continuously throughout the day. Pumps release bolus doses of insulin (several units at a time) at meals and at times when blood glucose is too high, based on programming done by the user. Insulin infusion pumps serve as an alternative to multiple daily injections of insulin. The infusion cannula should be changed every 2-3 days to avoid lipid hypertrophy at the infusion site. Insulin infusion pumps can be differentiated by programmable/non-programmable, disposable/reusable, and subcutaneous/transdermal/implantable.

"Gestational Diabetes Mellitus (GDM)" is a type of diabetes mellitus that develops only during pregnancy and usually disappears upon delivery, but increases the risk that the mother will develop diabetes later. GDM is managed with meal planning, activity, oral agents, and, in some cases, insulin.

"Hemoglobin A1c (HbA1c)" is a test that measures a person's average blood glucose level over the past 2 to 3 months. It is also known as "A1c" or "glycosylated hemoglobin". A1c should be measured at least twice annually for stable glycemic control and at least quarterly for unstable glycemic control. A1c test results may be affected by age, certain conditions, ethnicity, genetic traits, and pregnancy; the ADA recommends that treating providers review for discrepancies between A1c results and blood glucose results.

"Hyperglycemia" is excessive blood glucose. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours. Postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

"Hypoglycemia" is a condition that occurs when one's blood glucose is lower than normal, usually less than 70 mg/dL. Signs include hunger, nervousness, shakiness, perspiration, dizziness or lightheadedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. Hypoglycemia is treated by consuming a carbohydrate-rich food such as a glucose tablet or juice. It may also be treated with an injection of glucagon if the person is unconscious or unable to swallow.

"Hypoglycemia Unawareness" is a state in which a person does not feel or recognize the symptoms of hypoglycemia. People who have frequent episodes of hypoglycemia may no longer experience the warning signs of it.

Medical Necessity Criteria for Authorization

The Plan considers **Continuous Glucose Monitoring Systems (CGMS) and its components** medically necessary when **ALL** the following criteria are met as applicable below:

Medical Necessity Criteria for Initial Authorization

The Plan considers **Continuous Glucose Monitoring Systems and its components** medically necessary when **ALL** of the following criteria are met:

1. The requested device is age-appropriate for the member based on the U.S. Food and Drug Administration (FDA) approval/clearance; ***AND***
2. The member has a documented diagnosis of diabetes mellitus; ***AND***
3. Long-term continuous glucose monitoring is needed for the member's diabetes management, as evidenced by clinical documentation in the past 6 months showing **ALL** of the following:
    a. The member has documented adherence to diabetic treatment plan and can be trained to use a CGM; ***and***
        i. The member requires blood glucose checks daily; ***and***
    b. The member meets at least **ONE** of the following:
        i. Type 1 diabetes; ***or***
        ii. Type 2 diabetes treated with insulin who have hemoglobin A1c above goal, despite appropriate changes in insulin therapy and compliance with the treatment plan; ***or***
        iii. Pregnant; ***or***
        iv. Problematic hypoglycemia, defined as having a history of:
            1. Frequent/severe hypoglycemia; ***or***
            2. Nocturnal hypoglycemia; ***or***
            3. Hypoglycemia unawareness; ***or***
            4. Severe hypoglycemia (≥2 episodes with blood glucose <54 mg/dL in the past 30 days); ***AND***
4. The requested product is for **ONE** of the following:
    a. The Plan's preferred CGMS; ***or***
    b. The Plan's non-preferred CGMS **AND** the member is unable to use, or has tried and failed the Plan's preferred CGMS; ***or***
    c. A non-formulary CGMS, **AND** the member meets **BOTH** of the following criteria:
        i. is unable to use or has tried and failed **ALL** of the Plan's Formulary CGMS; ***and***
        ii. IF the request is for, or a component of, the Senseonics Eversense 365 system, **ALL** of the following are met:
            1. The member has inadequate glycemic control despite compliance, with trial and failure of **ONE** of the following:
                a. Standard blood glucose monitors with frequent self-monitoring finger sticks; ***or***

b. Flash glucose monitoring; ***or***
c. Continuous glucose monitoring (non-implantable); ***or***
d. Allergy to adhesive or other materials in non-implantable CGM devices; ***and***

2. The insertion and removal of the glucose sensor in the upper arm will be conducted by a healthcare practitioner; ***and***
3. The member does not have **ANY** of the following contraindications:
    a. Critically ill or hospitalized***; or***
    b. Expecting to undergo an MRI (magnetic resonance imaging) procedure↕ within 365 days for Eversense 365***; or***
    ↕*NOTE: The Eversense Smart Transmitter is MR Unsafe and MUST BE REMOVED before undergoing an MRI procedure. The Eversense Sensor is MR Conditional under specific conditions. MRI staff should be informed about implanted sensors before any MRI procedure.*
    c. Has another active implantable device, e.g., an implantable defibrillator (passive implants are allowed, e.g., cardiac stents)***; or***
    d. History of dexamethasone or dexamethasone acetate contraindication, or allergies to systemic glucocorticoids***; or***
    e. Need mannitol or sorbitol intravenously, or as a component of an irrigation solution or peritoneal dialysis solution***; or***
    f. Pregnant or nursing, unless the potential benefits of CGM use outweigh the risks, as determined by the prescribing physician***; or***
    g. Receiving immunosuppressant therapy, chemotherapy, or anticoagulant therapy, unless specifically approved by the prescribing physician in consultation with the healthcare practitioner performing the sensor insertion.

<u>If the above prior authorization criteria are met, the requested Continuous Glucose Monitoring System and its components will be approved as follows:</u>

- <u>For non-pregnant members, approve for 12 months</u>
- <u>For pregnant members, approve through the end of pregnancy plus 4 weeks postpartum in accordance with the expected delivery date</u>

Medical Necessity Criteria for Reauthorization

The Plan considers reauthorization requests (including members who have been on the CGMS prior to enrollment with the Plan) for **Continuous Glucose Monitoring Systems and its components** medically necessary when **ALL** of the following criteria are met:

1. The member continues to meet the above applicable **Initial Authorization** criteria; ***AND***
2. There is documented provider evaluation within the last 6 months that demonstrates the member's adherence to their diabetic treatment plan and devices. This evaluation should assess the member's compliance with the prescribed treatment regimen and use of the CGMS, defined as documentation indicating **ANY** of the following:
    a. confirmed improvement in glycemic management or time in range compared to previous fingerstick or CGM monitoring alone. This improvement should be documented and show that the CGMS has contributed to better glycemic control for the member, such as:
        i. Sustained reduction in HbA1c of ≥ 0.5%***; or***
        ii. Increased time with glucose levels between 70-180 mg/dL***; or***
        iii. Reduced glycemic variability***; or***
        iv. Decreased frequency or severity of hypoglycemic episodes***; or***
    b. the member is effectively utilizing the CGM, defined as sensor wear of more than 70% of the time***; or***
    c. the member is consistently using the CGMS as intended and benefiting from its continuous monitoring capabilities.

If the above prior authorization criteria are met, the requested Continuous Glucose Monitoring System and its components will be approved for 12 months.

Medical Necessity Criteria for Requests to Switch Continuous Glucose Monitoring Systems

The Plan considers requests to switch **Continuous Glucose Monitoring Systems** medically necessary if the member meets **ONE** of the following:

1. The member has an allergy or reaction to their current CGM system adhesive or components that is unable to be managed or resolved; ***OR***
2. The member requires a switch to a CGM system compatible with their insulin pump or automated insulin delivery system; ***OR***

3. For members enrolled in an Oscar-designated disease management program - the member requires a switch to a CGMS meeting designated program requirements (i.e., switch their non-Dexcom Glucose Monitor to a Dexcom branded CGM device).

If the above switch criteria are met, the requested replacement Continuous Glucose Monitoring System and its components will be approved for the remaining duration of the member's current authorization period.

Exception Criteria for Additional Receivers/Readers (*see Table 1: Stand-alone Prescription CGM Systems*)

The Plan recognizes that there may be situations where an additional receiver/reader for a covered stand-alone Continuous Glucose Monitoring (CGM) system is needed prior to the 3-year replacement period for select products. In such cases, the following criteria must be met:

1. The currently owned receiver/reader must be non-functional and unable to be repaired or replaced by the manufacturer. Documentation should clearly indicate that the receiver/reader is no longer operational and cannot be fixed or replaced.
2. The member or healthcare provider must have made reasonable attempts to troubleshoot and resolve the issue with the non-functional receiver/reader. Documentation should demonstrate the efforts made to troubleshoot the device and the inability to repair or replace it.
   NOTE: Replacement is limited to one receiver/reader per 3-year. Exceptions may be considered for special populations, such as children who may accidentally damage the device within the 3-year period.

Experimental or Investigational / Not Medically Necessary

Continuous Glucose Monitoring Systems and its components for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Additionally, the Plan does not consider medically necessary the replacement or repair of units or associated equipment when lost or damaged due to neglect or improper care.

Appendix

A. Over-the-Counter Continuous Glucose Monitoring Systems (OTC CGMs)

Recent FDA clearances have introduced over-the-counter (OTC) Continuous Glucose Monitoring Systems (CGMs) to the market. OTC CGMs are continuous glucose monitoring systems that can be

purchased without a prescription. They are generally designed for use by individuals aged 18 and older who do not use insulin to manage their diabetes.

- OTC CGMs are not covered under this clinical policy. Coverage of OTC CGMs, if any, depends on a member's specific benefit policy. Members should refer to their applicable benefit plan document to determine benefit availability and the terms and conditions of coverage for OTC CGMs.

Table 2: Key Differences from Prescription CGMs

Feature	OTC CGMs	Prescription CGMs
User Age	≥18 years	Varies (may include pediatric use)
Insulin Use	Not for insulin users	Often indicated for insulin users
Glucose Range	May be limited	Typically broader
Alerts	Generally no alerts	May include customizable alerts
Data Sharing	May have limited options	Often include robust sharing features
Integration	Not for use with insulin delivery systems	May integrate with insulin pumps/AID systems

NOTE: This table provides a general comparison between OTC and prescription CGMs for informational purposes only. It is not exhaustive and does not reflect all potential differences or variations among devices. Features may vary by specific device and manufacturer. This information does not constitute medical advice or endorsement of any particular product. Always consult with a healthcare professional for personalized advice on glucose monitoring options.

Table 3: FDA-Cleared OTC CGM Devices

Feature	Dexcom Stelo Glucose Biosensor System	Abbott Lingo Glucose System	Abbott Libre Rio Continuous Glucose Monitoring System
Intended Use	Adults 18 years and older not on insulin	Adults 18 years and older not on insulin	Non-insulin using persons age 18 and older
Sensor Life	Up to 15 days	Up to 14 days	Up to 14 days
Glucose Range	55-200 mg/dL	40-400 mg/dL	40-400 mg/dL
Special Features	- Readings updated every 15 minutes - Extended 12-hour grace period after 15 days	- Helps detect euglycemic and dysglycemic glucose levels - May help users understand lifestyle impacts on glucose	- Detects trends and tracks patterns - Aids in detection of euglycemia, hyperglycemia, and hypoglycemia
FDA Clearance	K234070	K233655	K233861

NOTE: This table provides a summary of FDA-cleared OTC CGM devices as of October 2024 for informational purposes only. It is not intended to be a comprehensive comparison or to recommend any particular device. Information is based on publicly available data and may not reflect the most current product specifications or features. These devices are not covered under this clinical policy, and their inclusion here does not imply coverage or endorsement. Members should consult the official product documentation, their healthcare provider, and their benefit plan for the most up-to-date and relevant information regarding these devices and their potential use.

References

1. Ahmet A, Dagenais S, Barrowman NJ, et al. Prevalence of nocturnal hypoglycemia in pediatric type 1 diabetes: a pilot study using continuous glucose monitoring. J Pediatr. 2011 Aug; 159(2):297-302.e1.

2. American Diabetes Association Professional Practice Committee et al: 15. Management of diabetes in pregnancy: standards of medical care in diabetes-2022. Diabetes Care. 45(Supplement_1):S232-43, 2022
3. American Diabetes Association (ADA). Standards of Medical Care in Diabetes—2020 Diabetes Care 2020 Jan; 43(Supplement 1): S1-S212.
4. American Diabetes Association. Addendum. 7. Diabetes Technology: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020 Aug;43(Suppl. 1):S77–S88. https://doi.org/10.2337/dc20-ad08c
5. American Diabetes Association. Diabetes Technology: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2020 Jan; 43(Supplement 1): S77-S88. https://doi.org/10.2337/dc20-S007
6. American Diabetes Association. Gestational diabetes mellitus. Diabetes Care. 2004b Jan; 27 Suppl 1:S88-90.
7. American Diabetes Association. Introduction: Standards of Medical Care in Diabetes—2021. Diabetes Care. 2021 Jan; 44(Supplement 1): S1-S2. https://doi.org/10.2337/dc21-Sint
8. American Diabetes Association. Position Statement. Continuous subcutaneous insulin infusion. Diabetes Care 2004a; 27 (suppl 1):S110.
9. American Diabetes Association. Standards of medical care in diabetes - 2017. Available at: http://professional.diabetes.org/ResourcesForProfessionals.aspx?cid=84160. Accessed March 15, 2017.
10. American Diabetes Association. Standards of medical care in diabetes - 2019. Available at: https://professional.diabetes.org/content-page/practice-guidelines-resources. Accessed July 23, 2019.
11. American Diabetes Association. Standards of Medical Care in Diabetes—2020 Abridged for Primary Care Providers. Clinical Diabetes. 2020; 38(1):10-38.
12. American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(Supplement_1):S239-S251.
13. Amin R, Ross K, Acerini CL, et al. Hypoglycemia prevalence in prepubertal children with type 1 diabetes on standard insulin regimen: Use of continuous glucose monitoring system. Diabetes Care. 2003;26(3):662-667.
14. Arguello, Vanessa, Continuous Glucose Monitoring in Patients with Type 2 Diabetes Receiving Insulin Injections: Does this Mean Continuous Monitoring for Everyone, Ann Int Med; 2017, 167:436-437.
15. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet 2014;383(9911):69-82.
16. Beck, R. W., Riddlesworth, T. D., Ruedy, K., Ahmann, A., Haller, S., Kruger, D., ... & DIAMOND Study Group*. (2017). Continuous glucose monitoring versus usual care in patients with type 2

diabetes receiving multiple daily insulin injections: a randomized trial. Annals of internal medicine, 167(6), 365-374.

17. Beck, R. W., Riddlesworth, T., Ruedy, K., Ahmann, A., Bergenstal, R., Haller, S., ... & DIAMOND Study Group. (2017). Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. Jama, 317(4), 371-378.
18. Boland E, Monsod T, Delucia M, et al. Limitations of conventional methods of self-monitoring of blood glucose: Lessons learned from 3 days of continuous glucose sensing in pediatric patients with type 1 diabetes. Diabetes Care. 2001;24(11):1858-1862.
19. Chase HP, Beck RW, Xing D, et al. Continuous glucose monitoring in youth with type 1 diabetes: 12-month follow-up of the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. Diabetes Technol Ther. 2010 Jul;12(7):507-15.
20. Cheyne EH, Cavan DA, Kerr D. Performance of a continuous glucose monitoring system during controlled hypoglycaemia in healthy volunteers. Diabetes Technol Ther. 2002;4(5):607-613.
21. Chico A, Vidal-Rios P, Subira M, et al. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care. 2003;26(4):1153-1157.
22. Christiansen MP, Klaff LJ, Bailey TS, Brazg R, Carlson G, Tweden KS. A Prospective Multicenter Evaluation of the Accuracy and Safety of an Implanted Continuous Glucose Sensor: The PRECISION Study. Diabetes Technol Ther. 2019 May;21(5):231-237. doi: 10.1089/dia.2019.0020. Epub 2019 Mar 29. PMID: 30925083; PMCID: PMC6532543.
23. Christiansen MP, Klaff LJ, Brazg R, Chang AR, Levy CJ, Lam D, Denham DS, Atiee G, Bode BW, Walters SJ, Kelley L, Bailey TS. A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor: PRECISE II. Diabetes Technol Ther. 2018 Mar;20(3):197-206. doi: 10.1089/dia.2017.0142. Epub 2018 Jan 30. PMID: 29381090; PMCID: PMC5867508.
24. Cooke D, Hurel SJ, Casbard A, et al. Randomized controlled trial to assess the impact of continuous glucose monitoring on HbA1c in insulin-treated diabetes (MITRE Study). Diabet Med. 2009 May;26(5):540-7.
25. Dehennis A, Mortellaro MA, Ioacara S. Multisite study of an implanted continuous glucose sensor over 90 days in patients with diabetes mellitus. J Diabetes Sci Technol. 2015;9(5):951-956.
26. Deiss D, Szadkowska A, Gordon D, Mallipedhi A, Schütz-Fuhrmann I, Aguilera E, Ringsell C, De Block C, Irace C. Clinical Practice Recommendations on the Routine Use of Eversense, the First Long-Term Implantable Continuous Glucose Monitoring System. Diabetes Technol Ther. 2019

May;21(5):254-264. doi: 10.1089/dia.2018.0397. Epub 2019 Apr 25. PMID: 31021180; PMCID: PMC6532544.

27. Desouza C, Salazar H, Cheong B, et al. Association of hypoglycemia and cardiac ischemia: A study based on continuous monitoring. Diabetes Care. 2003;26(5):1485-1489.
28. Diabetes Research in Children Network (DirecNet) Study Group, Buckingham B, Beck RW, Tamborlane WV, Xing D, Kollman C, Fiallo-Scharer R, Mauras N, Ruedy KJ, Tansey M, Weinzimer SA, Wysocki T. Continuous glucose monitoring in children with type 1 diabetes. J Pediatr. 2007 Oct;151(4):388-93, 393.e1-2.
29. Diabetes Research in Children Network (DirecNet) Study Group. Psychological aspects of continuous glucose monitoring in pediatric type 1 diabetes. Pediatr Diabetes. 2006;7(1):32-38.
30. Diabetes Research in Children Network (DirecNet) Study Group. Use of the DirecNet Applied Treatment Algorithm (DATA) for diabetes management with a real-time continuous glucose monitor (the FreeStyle Navigator). Pediatr Diabetes. 2008 Apr;9(2):142-7.
31. Ehrhardt, N. M., Chellappa, M., Walker, M. S., Fonda, S. J., & Vigersky, R. A. (2011). The effect of real-time continuous glucose monitoring on glycemic control in patients with type 2 diabetes mellitus. Journal of Diabetes Science and Technology, 5(3), 668-675.
32. Feig, D. S., Donovan, L. E., Corcoy, R., Murphy, K. E., Amiel, S. A., Hunt, K. F., ... & Pragnell, M. (2017). Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): a multicentre international randomised controlled trial. The Lancet, 390(10110), 2347-2359.
33. Floyd B, Chandra P, Hall S, et al. Comparative analysis of the efficacy of continuous glucose monitoring and selfmonitoring of blood glucose in type 1 diabetes mellitus. J Diabetes Sci Technol. 2012 Sep 1;6(5):1094-102.
34. Gandhi, G. Y., Kovalaske, M., Kudva, Y., Walsh, K., Elamin, M. B., Beers, M., ... & Murad, M. H. (2011). Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. Journal of diabetes science and technology, 5(4), 952-965.
35. Golden SH, Brown T, Yeh HC, et al. Methods for Insulin Delivery and Glucose Monitoring: Comparative Effectiveness. Comparative Effectiveness Review No. 57. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 12-EHC036-EF. Rockville, MD: Agency for Healthcare Research and Quality. July 2012.
36. Grunberger, G., Handelsman, Y., Bloomgarden, Z., Fonseca, V. A., Garber, A. J., Haas, R. A., ... & Umpierrez, G. E. (2018). American Association of Clinical Endocrinologists and American College of Endocrinology 2018 position statement on integration of insulin pumps and continuous glucose monitoring in patients with diabetes mellitus. Endocrine Practice, 24(3), 302-308.

37. Handelsman Y, Bloomgarden ZT, Grunberger G, et al.; American Association of Clinical Endocrinologists and American College of Endocrinology. Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocr Pract. 2015 Apr;21 Suppl 1:1-87.
38. Hay LC, Wilmshurst EG, Fulcher G. Unrecognized hypo- and hyperglycemia in well-controlled patients with type 2 diabetes mellitus: The results of continuous glucose monitoring. Diabetes Technol Ther. 2003;5(1):19-26.
39. Hayes, Inc. Health Technology Assessment. Eversense Continuous Glucose Monitor For Maintaining Glycemic Control In Adults With Diabetes Mellitus. Lansdale, PA: Hayes, Inc.; July 2020.
40. Hayes, Inc. Health Technology Brief. Eversense Continuous Glucose Monitor for Maintaining Glycemic Control in Adults with Diabetes Mellitus. http://www.hayesinc.com. Published September 14, 2018. Accessed July 23, 2019.
41. Institute for Clinical and Economic Review (ICER). Comparative Effectiveness Public Advisory Council (CEPAC). Controversies in the management of patients with type 2 diabetes. December 2014. Available at: http://www.icerreview.org/wp-content/uploads/2015/03/CEPAC-T2D-Final-Report-December-22.pdf. Accessed March 23, 2017.
42. International Consensus on Use of Continuous Glucose Monitoring, Diabetes Care, 2017, Dec; 40(12); 1631-1640. Available at http://care.diabetesjournals.org/content/40/12/1631.
43. Jafri RZ, Balliro CA, El-Khatib F, Maheno MM, Hillard MA, O'Donovan A, Selagamsetty R, Zheng H, Damiano ER, Russell SJ. A Three-Way Accuracy Comparison of the Dexcom G5, Abbott Freestyle Libre Pro, and Senseonics Eversense Continuous Glucose Monitoring Devices in a Home-Use Study of Subjects with Type 1 Diabetes. Diabetes Technol Ther. 2020 Nov;22(11):846-852. doi: 10.1089/dia.2019.0449. PMID: 32453604.
44. Jeitler K, Horvath K, Berghold A, et al. Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. Diabetologia. 2008 Jun;51(6):941-51.
45. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Beck RW, Buckingham B, et al. Factors predictive of use and of benefit from continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2009a Nov;32(11):1947-53.
46. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76.
47. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. The effect of continuous glucose monitoring in well-controlled type 1 diabetes. Diabetes Care. 2009b Aug;32(8):1378-83.

48. Juvenile Diabetes Research Foundation. Continuous Glucose Monitoring Study Group, Bode B, Beck RW, et al. Sustained benefit of continuous glucose monitoring on A1c, glucose profiles, and hypoglycemia in adults with type 1 diabetes. Diabetes Care. 2009c Nov;32(11):2047-9.
49. Kaufman FR, Austin J, Neinstein A, et al. Nocturnal hypoglycemia detected with the Continuous Glucose Monitoring System in pediatric patients with type 1 diabetes. J Pediatr. 2002;141(5):625-630.
50. Kaufman FR, Gibson LC, Halvorson M, et al. A pilot study of the continuous glucose monitoring system: Clinical decisions and glycemic control after its use in pediatric type 1 diabetic subjects. Diabetes Care. 2001;24(12):2030-2034.
51. Klonoff DC, et al. Continuous glucose monitoring: an Endocrine Society Clinical Practice Guideline. Journal of Clinical Endocrinology and Metabolism 2011;96(10):2968-79. (Reaffirmed November 2015)
52. Klonoff DC, Parkes JL, Kovatchev BP, et al. Investigation of the Accuracy of 18 Marketed Blood Glucose Monitors. Diabetes Care 2018 Aug; 41(8): 1681-1688.
53. Kropff J, Choudhary P, Neupane S, et al. Accuracy and longevity of an implantable continuous glucose sensor in the PRECISE Study: A 180-day, prospective, multicenter, pivotal trial. Diabetes Care. 2017;40(1):63-68.
54. Langendam M, Luijf YM, Hooft L, et al. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008101.
55. Langendam, M., Luijf, Y. M., Hooft, L., DeVries, J. H., Mudde, A. H., & Scholten, R. J. (2012). Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews, (1).
56. Lee MK, Lee KH, Yoo SH, Park CY. Impact of initial active engagement in self-monitoring with a telemonitoring device on glycemic control among patients with type 2 diabetes. Sci Rep. 2017;7(1):3866.
57. Lind, M., Polonsky, W., Hirsch, I. B., Heise, T., Bolinder, J., Dahlqvist, S., ... & Hellman, J. (2017). Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. Jama, 317(4), 379-387.
58. Maran A, Crepaldi C, Tiengo A, et al. Continuous subcutaneous glucose monitoring in diabetic patients: A multicenter analysis. Diabetes Care. 2002;25(2):347-352.
59. Mastrototaro JJ, Gross TM. Reproducibility of the continuous glucose monitoring system matches previous reports and the intended use of the product. Diabetes Care. 2003;26(1):256.
60. Mauras N, et al. A randomized clinical trial to assess the efficacy and safety of real-time continuous glucose monitoring in the management of type 1 diabetes in young children aged 4 to <10 years. Diabetes Care 2012;35(2):204-10.

61. McAdams BH, Rizvi AA. An Overview of Insulin Pumps and Glucose Sensors for the Generalist. J Clin Med. 2016;5(1):5. Published 2016 Jan 4. doi:10.3390/jcm5010005.
62. Meade LT. The use of continuous glucose monitoring in patients with type 2 diabetes. Diabetes Technology & Therapeutics 2012;14(2):190-5.
63. Oppel E, Kamann S, Heinemann L, Reichl FX, Högg C. The implanted glucose monitoring system Eversense: An alternative for diabetes patients with isobornyl acrylate allergy. Contact Dermatitis. 2020 Feb;82(2):101-104. doi: 10.1111/cod.13392. Epub 2019 Sep 17. PMID: 31463958.
64. Peters, A. L., Ahmann, A. J., Hirsch, I. B., & Raymond, J. K. (2018). Advances in glucose monitoring and automated insulin delivery: supplement to Endocrine Society Clinical Practice Guidelines. Journal of the Endocrine Society, 2(11), 1214-1225.
65. Petrovski G, Dimitrovski C, Bogoev M, Milenkovic T, Ahmeti I, Bitovska I. Is there a difference in pregnancy and glycemic outcome in patients with type 1 diabetes on insulin pump with constant or intermittent glucose monitoring? A pilot study. Diabetes Technology and Therapeutics 2011;13(11):1109-13.
66. Poomalar GK. Changing trends in management of gestational diabetes mellitus. World Journal of Diabetes 2015;6(2):284-95.
67. Professional Practice Committee: Standards of Medical Care in Diabetes—2021. Diabetes Care 1 January 2021; 44 (Supplement_1): S3. Retrieved from: https://doi.org/10.2337/dc21-Sppc
68. Robert JJ. Continuous monitoring of blood glucose. Horm Res. 2002;57 Suppl 1:81-84.
69. Rosenfeld CR, Bohannon NJ, Bode B, et al. TheV-Go insulin delivery device used in clinical practice: Patient perception and retrospective analysis of glycemic control. Endocr Pract. 2012;18(5):660-667.
70. Sanchez P, Ghosh-Dastidar S, Tweden KS, Kaufman FR. Real-World Data from the First U.S. Commercial Users of an Implantable Continuous Glucose Sensor. Diabetes Technol Ther. 2019 Dec;21(12):677-681. doi: 10.1089/dia.2019.0234. Epub 2019 Aug 28. PMID: 31385732.
71. Secher, A. L., Ringholm, L., Andersen, H. U., Damm, P., & Mathiesen, E. R. (2013). The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial. Diabetes care, 36(7), 1877-1883.
72. Sutton D, Higdon C, Carmon M, Abbott S. Regular Insulin Administered With the V-Go Disposable Insulin Delivery Device in a Clinical Diabetes Setting: A Retrospective Analysis of Efficacy and Cost. Clin Diabetes. 2016;34(4):201-205.
73. Szypowska A, Ramotowska A, Dzygalo K, Golicki D. Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Eur J Endocrinol. 2012 Apr;166(4):567-74.

74. Szypowska, A., Ramotowska, A., Dzygalo, K., & Golicki, D. (2012). Beneficial effect of real-time continuous glucose monitoring system on glycemic control in type 1 diabetic patients: systematic review and meta-analysis of randomized trials. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet].
75. Tamborlane, W. V., Beck, R. W., Bode, B. W., Buckingham, B., Chase, H. P., Clemons, R., ... & Xing, D. (2008). Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med, 359(14), 1464-1476.
76. Tanenberg R, Bode B, Lane W, et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: A randomized controlled trial. Mayo Clin Proc. 2004;79(12):1521-1526.
77. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329(14):977-986.
78. Tierney MJ, Tamada JA, Potts RO, et al. Clinical evaluation of the GlucoWatch biographer: A continual, non-invasive glucose monitor for patients with diabetes. Biosens Bioelectron. 2001;16(9-12):621-629.
79. Trajanoski Z, Wach P, Gfrerer R, et al. Portable device for continuous fractionated blood sampling and continuous ex vivo blood glucose monitoring. Biosens Bioelectron. 1996;11(5):479-487.
80. U.S. Food and Drug Administration (FDA). MiniMed 770G System. (Medtronic MiniMed, Inc. Northridge, CA). Summary of Safety and Effectiveness PMA Number: P160017/S076. Notice of Approval 8/31/2020. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017S076B.pdf
81. US Food and Drug Administration (FDA). Eversense continuous glucose monitoring system. (Senseonics, Incorporated, Germantown, MD) PMA Number: P160048. Jun 21, 2018. Accessed August 19, 2021. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P160048
82. Vigersky RA, Fonda SJ, Chellappa M, Walker MS, Ehrhardt NM. Short and long-term effects of real-time continuous glucose monitoring in patients with type 2 diabetes. Diabetes Care 2012;35(1):32-8.
83. Wei, Q., Sun, Z., Yang, Y., Yu, H., Ding, H., & Wang, S. (2016). Effect of a CGMS and SMBG on maternal and neonatal outcomes in gestational diabetes mellitus: a randomized controlled trial. [5], 6(1), 1-9.
84. Wolpert HA. Continuous glucose monitoring--coming of age. N Engl J Med. 2010;363(4):383-384.

85. Yoo, H. J., An, H. G., Park, S. Y., Ryu, O. H., Kim, H. Y., Seo, J. A., ... & Baik, S. H. (2008). Use of a real time continuous glucose monitoring system as a motivational device for poorly controlled type 2 diabetes. Diabetes research and clinical practice, 82(1), 73-79.
86. Zick R, Petersen B, Richter M, Haug C; SAFIR Study Group. Comparison of continuous blood glucose measurement with conventional documentation of hypoglycemia in patients with Type 2 diabetes on multiple daily insulin injection therapy. Diabetes Technol Ther. 2007;9(6):483-492.

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Disposable Insulin Pump Devices

- Omnipod DASH Insulin Management System
- Omnipod 5 Automated Insulin Delivery System
- Omnipod GO

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Diabetes mellitus (DM), commonly referred to as diabetes,is a chronic (long-term) medical condition characterized by high blood glucose (sugar). This may be because the pancreas (an organ in the belly) does not make enough insulin (a hormone), or because the body is not responding to insulin the way it should. Insulin helps glucose get into cells in the body, giving it energy. With diabetes, sugar builds up in the blood because the body stops responding to insulin, or because there is not enough of it. Diabetes is broadly grouped into two types:

- Type 1 diabetes mellitus - the pancreas make no insulin, or a very small amount
- Type 2 diabetes mellitus - cells in the body do not respond to insulin the way they should; sometimes, the pancreas also does not make enough insulin

Diabetes is usually managed by eating healthy foods, getting plenty of exercise, and sometimes with medicines. Medicines are used to either control blood sugar, or to lower the chance of problems that can happen in the future because of diabetes. These medications can be insulin itself, or medications that help the body make more insulin or help insulin do its job. In addition, Plan members who have been diagnosed with Type 1 or 2 DM, and meet certain medical necessity criteria and standards of care developed by the American Diabetes Association (ADA), may be eligible for specific supplies and equipment subject to plan benefits, such as those used to monitor blood sugar and inject insulin. Members with more advanced disease or those requiring more frequent insulin may qualify for continuous glucose monitoring and specialized insulin delivery systems.

This Pharmacy Clinical Guideline is specific to only Disposable Insulin Pump Devices listed in **Table 1** below.

- For the Plan's Medical Clinical Guideline on medical necessity criteria of:
    - diabetes equipment and supplies, see Oscar Clinical Guideline: Diabetes Equipment and Supplies (CG028).
    - continuous glucose monitoring, implantable continuous glucose monitoring, and insulin infusion pumps, see Oscar Clinical Guideline: Insulin Delivery Systems and Continuous Glucose Monitoring (CG029).
- For the Plan's Pharmacy Clinical Guideline for Stand-alone CGM Systems, please refer to Oscar Clinical Guideline: Continuous Glucose Monitors (CGMs) (PG121).
- The Plan also covers home glucose monitors and products for self-monitoring of blood sugar as an alternative to CGMs. Please contact CVS/Caremark, the Plan's Prescription Benefit Manager, to obtain a standard blood glucose meter from the preferred brand.

Table 1: Disposable Insulin Pump Devices

Systems	Components	Use Life
Omnipod DASH Insulin Management System	Personal Diabetes Manager (PDM)	every 5 years (warranty covers first 4 years of life)
	Pods	Up to 3 days (48-72 hours) or after delivering 200 units of insulin (whichever comes first)
	Contour Next One Blood Glucose Monitor (separate but compatible)	
Omnipod 5 System	Controller	every 2 years (based on 300-500 charge cycles) with typical use

		Starter kit shelf life of 18 months
	Pods	Up to 3 days (48-72 hours) or after delivering 200 units of insulin (whichever comes first)
	Dexcom G6 and Dexcom G7 Continuous Glucose Monitor (separate but compatible with the pod) Freestyle Libre 2 Plus Sensor (separate but compatible with Omnipod 5 App)	
Omnipod GO	Pods	3 days

NOTE: V-Go (20, 30, 40) Disposable Insulin Delivery Device is a Non-Formulary product and is subject to Oscar Clinical Guideline: Medical Necessity Criteria for Non-Formulary Products (PG069).

Definitions

"Insulin" is a hormone made by the beta cells of the pancreas. Insulin allows glucose to enter the cells in the body for use in energy production, and when it is inadequate, the sugar remains in the blood leading to diabetes. There are a variety of oral and parenteral medications that can increase insulin production, increase the body's sensitivity to existing insulin and reduce blood sugar. Insulin can also be injected or infused when lifestyle changes and non-insulin medications are inadequate.

"Type 1 Diabetes" is an autoimmune condition that occurs when the beta cells of the pancreas are unable to produce enough insulin and therefore blood glucose cannot enter cells to be used for energy. Type 1 diabetes is often referred to as "insulin-dependent" because these patients require insulin daily to maintain their blood glucose at acceptable levels.

"Type 2 Diabetes" is a condition that occurs when either the pancreas doesn't produce enough insulin or the body cells become resistant to insulin. Type 2 diabetes is much more common than Type 1, and is often treated with combinations of lifestyle changes and non-insulin medications, although insulin can be required later in the disease course. Many individuals with Type 2 Diabetes are "insulin-requiring".

"Blood Glucose" is the main sugar found in the blood and the body's main source of energy. It is also called glucose or blood sugar. The blood level of glucose is noted in milligrams per deciliter (mg/dL). When blood sugar is too high for long periods of time, complications can occur as a result of blood vessel damage.

"Blood Glucose Monitors" are small, portable machines used to check blood glucose levels in the ambulatory setting. A member will prick his/her fingertip and place a small sample of blood into the device for a glucose reading. There are a number of different types of blood glucose monitors for specialized situations, such as those for members with visual impairments.

"Continuous Glucose Monitoring (CGM)" serves as an alternative to self-monitoring of blood glucose (SMBG) with a home glucose monitor for patients who have diabetes and require multiple daily measurements.

"Hemoglobin A1c (HbA1c)" is a test that measures a person's average blood glucose level over the past 2 to 3 months. It is also known as "A1C" or "glycosylated hemoglobin". A1C should be measured at least twice annually for stable glycemic control and at least quarterly for unstable glycemic control. A1C test results may be affected by age, certain conditions, ethnicity, genetic traits, and pregnancy; the ADA recommends that treating providers review for discrepancies between A1c results and blood glucose results.

"Hyperglycemia" is excessive blood glucose. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours. Postprandial hyperglycemia is blood glucose above a desirable level 1 to 2 hours after a person has eaten.

"Hypoglycemia" is a condition that occurs when one's blood glucose is lower than normal, usually less than 70 mg/dL. Signs include hunger, nervousness, shakiness, perspiration, dizziness or lightheadedness, sleepiness, and confusion. If left untreated, hypoglycemia may lead to unconsciousness. Hypoglycemia is treated by consuming a carbohydrate-rich food such as a glucose tablet or juice. It may also be treated with an injection of glucagon if the person is unconscious or unable to swallow.

"Hypoglycemia Unawareness" is a state in which a person does not feel or recognize the symptoms of hypoglycemia. People who have frequent episodes of hypoglycemia may no longer experience the warning signs of it.

Medical Necessity Criteria for Initial Authorization

Omnipod DASH and Omnipod 5

The Plan considers **Omnipod DASH and Omnipod 5 and its components** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with an endocrinologist or diabetes specialist***; AND***

2. The member has a diagnosis of diabetes mellitus***; AND***
3. Recent chart documentation within the last six (6) months of the request is provided showing **BOTH** of the following:
    a. The member self-monitors blood glucose at least three (3) times per day, **OR** is using a continuous glucose monitor (CGM); ***and***
    b. The member meets **ONE** of the following:
        i. is currently using an insulin pump; ***or***
        ii. uses at least three (3) insulin injections per day **AND BOTH** of the following:
            1. The member or caregiver has completed a comprehensive diabetes education program***; and***
            2. The member meets **ONE** of the following:
                a. Diagnosis of type-1 diabetes***; or***
                b. A child, where multiple daily insulin injections would be impractical or inappropriate***; or***
                c. Complications of inadequate glycemic control (e.g., neuropathy, nephropathy, retinopathy) indicative of more intensive insulin regimens***; or***
                d. Dawn phenomenon unresponsive to management with long-acting insulin agents (e.g., insulin glargine or detemir)***; or***
                e. For initial requests, HbA1c greater than 7%, despite an adequate regimen of multiple daily injections***; or***
                f. Hypoglycemic episodes requiring third-party assistance (e.g., seizure, loss of consciousness, glucagon administration, transport to an emergency room, hospitalization)***; or***
                g. Recurrent hypoglycemia (<70 mg/dL on at least two occasions despite adherence to recommended diabetic treatment plan)***; or***
                h. Pregnancy or planning for pregnancy; ***or***
                i. Wide swings in blood glucose values before meal time (e.g., regular fluctuations of preprandial blood glucose to levels <70 mg/dL and/or >140 mg/dL); ***AND***
4. The product being requested meets **ONE** of the following:
    a. is being prescribed for use within the Plan's Quantity Limit of:
        i. Starter Kit - 1 Kit per 4-years; ***or***
        ii. Pods Refill Pack - 10 Pods per month (i.e. 2 boxes, 5 Pods per box); ***or***

b. if the requested dosing instructions exceeds the Plan's Quantity Limit AND a valid clinical rationale is provided demonstrating medical necessity (e.g., for 48-hour Pod change).

Omnipod GO

The Plan considers the **Omnipod GO Insulin Delivery Device** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with an endocrinologist or diabetes specialist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a confirmed diagnosis of type 2 diabetes mellitus; ***AND***
4. The member meets **ALL** of the following:
    a. Has completed a comprehensive diabetes education program; ***and***
    b. Self-monitors blood glucose at least three (3) times per day, **OR** is using a continuous glucose monitor (CGM); ***and***
    c. Does not require the ability to deliver bolus doses of insulin or utilize variable basal delivery rates; ***and***
    d. In conjunction with their treating provider, has determined that a pre-set continuous basal insulin delivery rate of 10, 15, 20, 25, 30, 35 or 40 units per day via the Omnipod GO system is appropriate to manage their diabetes; ***AND***
5. The member has suboptimal glycemic control despite adherence to their current insulin regimen, as evidenced by any **ONE** of the following:
    a. Frequent hypoglycemia; ***or***
    b. Hemoglobin A1c > 7.0%; ***or***
    c. Significant glucose variability (i.e., fluctuations) based on self-monitoring or continuous glucose monitoring (CGM) data; ***AND***
6. The requested quantity of Omnipod GO meets **ONE** of the following:
    a. Is within the Plan's Quantity Limit of 10 Pods per 30-days (or 30 Pods per 90-days); ***or***
    b. The requested quantity exceeds the Plan's Quantity Limit, and a valid clinical rationale is provided demonstrating medical necessity.

If the above prior authorization criteria are met, the requested Disposable Insulin Pump Device will be approved for up to 12 months.

Medical Necessity Criteria for Reauthorization

The Plan considers reauthorization requests for **Disposable Insulin Pump Devices** medically necessary when **ALL** of the following criteria are met:

1. The member continues to meet all **Initial Authorization** criteria; ***AND***
2. There is documented provider evaluation within the last 6 months demonstrating **BOTH** of the following:
    a. The member's adherence to their diabetic treatment plan and insulin pump therapy; ***AND***
    b. Improvement in glycemic control from baseline, as evidenced by any **ONE** of the following:
        i. Reduction in hemoglobin A1c; ***or***
        ii. Reduction in frequency or severity of hypoglycemia episodes; ***or***
        iii. Reduction in glycemic variability; ***or***
        iv. Achievement of individual glycemic targets.

If the above prior authorization criteria are met, the requested Disposable Insulin Pump Device will be approved for up to 12 months.

Experimental or Investigational / Not Medically Necessary

The Plan considers the use of Disposable Insulin Pump Devices (Omnipod DASH, Omnipod 5, and Omnipod GO) experimental, investigational, or unproven, and therefore not medically necessary, in the following circumstances:

- Use of the devices for any indication or purpose other than those specifically listed in the **Initial Authorization** criteria.
- Use of the devices in combination with medications other than insulins (e.g., Novolog, Fiasp, Humalog, Lyumjev, Admelog) that have been tested and found to be compatible with the devices.
- Use of Omnipod GO in individuals under 18 years of age or those with type 1 diabetes, as the safety and effectiveness of the device have not been established in these populations.

Additionally, the Plan does not consider medically necessary the replacement or repair of Disposable Insulin Pump Devices when lost or damaged due to neglect, misuse, or improper care. Replacement may be approved when the device meets **ALL** of the following:

1. Is malfunctioning; ***AND***
2. Is out of warranty; ***AND***
3. Cannot be furbished.

References

1. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: Standards of Medical Care in Diabetes—2022. Diabetes Care 2022;45(Suppl. 1):S97–S112.
2. American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S126–S144. https://doi.org/10.2337/dc24-S007.
3. American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: Standards of Care in Diabetes - 2025. Diabetes Care. 2025;48(suppl. 1):S146-S166. https://doi.org/10.2337/dc25-S007.
4. American Diabetes Association Professional Practice Committee et al: 15. Management of diabetes in pregnancy: standards of medical care in diabetes-2022. Diabetes Care. 45(Supplement_1):S232-43, 2022
5. American Diabetes Association Professional Practice Committee et al: 15. Management of diabetes in pregnancy: standards of medical care in diabetes-2025. Diabetes Care. 2025; 48(Suppl. 1):S306-320. https://doi.org/10.2337/dc25-25.
6. American Diabetes Association Professional Practice Committee; Summary of Revisions: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S5–S10. https://doi.org/10.2337/dc24-SREV.
7. American Diabetes Association Professional Practice Committee; Summary of Revisions: Standards of Care in Diabetes—2025. Diabetes Care 2025; 48 (Supplement_1): S6–S13. https://doi.org/10.2337/dc25-SREV.
8. Brown SA, Forlenza GP, Bode BW, et al. Multicenter trial of a tubeless, on-body automated insulin delivery system with customizable glycemic targets in pediatric and adult participants with type 1 diabetes. Diabetes Care. 2021 Jul;44(7):1630-1640. doi:10.2337/dc21-0172. Epub 2021 Jun 7.
9. Buckingham BA, Christiansen MP, Forlenza GP, et al. Performance of the Omnipod personalized model predictive control algorithm with meal bolus challenges in adults with type 1 diabetes. Diabetes Technol Ther 2018;20:585–595.
10. Carlson AL, Huyett LM, Jantz J, et al. Improved glycemic control in 3,592 adults with type 2 diabetes mellitus initiating a tubeless insulin management system. Diabetes Res Clin Pract. 2021 Apr;174:108735. doi:10.1016/j.diabres.2021.108735. Epub 2021 Mar 9.
11. Davis GM, Peters AL, Bode BW, et al. Glycaemic outcomes in adults with type 2 diabetes over 24 weeks with the Omnipod(r) 5 automated insulin delivery system. Diabetes Obes Metab. 2025 Jan;27(1):143-154. doi:10.1111/dom.15993. Epub 2024 Oct 9.

12. Grunberger G, Rosenfeld CR, Bode BW, et al. Effectiveness of V-Go® for patients with type 2 diabetes in a real-world setting: a prospective observational study. Drugs Real World Outcomes 2020;7:31–40
13. Omnipod 5 ACE Pump (Pod) 510(k) summary, No. K203768. Acton, MA: Insulet Corporation; January 2022. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K203768.pdf.
14. Omnipod 5 Automated Insulin Delivery System User Guide. Available at https://www.omnipod.com/sites/default/files/Omnipod-5_Quick-Start-Guide.pdf Accessed February 12, 2025.
15. Omnipod 5 Technical User Guide. Available at https://www.omnipod.com/sites/default/files/Omnipod-5_User-guide.pdf. Access February 12, 2025.
16. Omnipod DASH Insulin Management System. Podder's Handbook User Guide. Available at https://www.omnipod.com/sites/default/files/2021-04/Omnipod-DASH_User-Guide_English.pdf. Accessed February 12, 2024.
17. Omnipod GO User Guide. Available at: https://www.omnipod.com/sites/default/files/Omnipod-GO_User_Guide_US_English.pdf. Access February 12, 2025.
18. Omnipod GO. 510(k) Premarket Notification FDA Home Medical Devices Databases. Available at: https://www.accessdata.fda.gov/cdrh_docs/reviews/K223372.pdf. Accessed March 6, 2024.
19. Omnipod Insulin Management System and Omnipod DASH Insulin Management System 510(k) summary, No. K192659. Acton, MA: Insulet Corporation; October 2019. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192659.pdf. Accessed August 29, 2022.
20.
21. Raval AD, Nguyen MH, Zhou S, Grabner M, Barron J, Quimbo R. Effect of V-Go versus multiple daily injections on glycemic control, insulin use, and diabetes medication costs among individuals with type 2 diabetes mellitus. J Manag Care Spec Pharm 2019;25:1111–1123
22. Sherr JL, Buckingham BA, Forlenza GP, et al. Safety and performance of the Omnipod hybrid closed-loop system in adults, adolescents, and children with type 1 diabetes over 5 days under free-living conditions. Diabetes Technol Ther 2020;22:174–184
23. V-Go Insulin Delivery System 510(k) summary, No. K103825. Shrewsbury, MA: Valeritas, Inc.; February 2011. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/K103825.pdf. Accessed August 29, 2022.
24. Wilkinson T, meier R, Hewapathirana N, et al. EValuating glucose ContrOL Using a next-GeneraTION automated insulin delivery algorithm in patients with type 1 and type 2 diabetes: the EVOLUTION study. Diabetes Technol Ther. 2025 Jan 27. doi:10.1089/dia.2024.0463. Online ahead of print.

Clinical Guideline Revision/History Information

Original Date: 9/15/2022 Reviewed/Revised: 3/23/2023, 3/21/2024, 7/1/2025

Azstarys (serdexmethylphenidate and dexmethylphenidate)

Disclaimer

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Summary

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder that is often characterized by difficulty with paying attention, hyperactivity, impulsivity, and poor self-control. It is a neurological condition that affects an individual's development and functioning, often impacting their academic performance and social relationships. The cause of ADHD is still unknown, however it is believed to be genetically linked and has been associated with a range of environmental and lifestyle factors.

Symptoms of ADHD can vary from person to person, and can be further divided into three primary categories: inattention, hyperactivity, and impulsivity. Inattention symptoms may include a lack of focus, not listening when spoken to, difficulty following instructions, disorganization, and easily distracted. Hyperactivity symptoms may include fidgeting, talking excessively, and a need for constant activity or motion. Impulsivity symptoms can include difficulty waiting for their turn, blurting out answers, and interrupting others.

Treatment for ADHD is often a combination of counseling and medication, depending on the individual and the severity of their symptoms. Cognitive Behavioral Therapy (CBT) is often used to help those with

ADHD better manage their thoughts and behaviors, while medications such as stimulants, nonstimulants, and antidepressants can help regulate dopamine levels, which often play an important role in the disorder.

Azstarys is a combination medication consisting of two drugs, serdexmethylphenidate (a prodrug of dexmethylphenidate) and dexmethylphenidate, and is used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). This medication is indicated for children aged 6-17 years, as well as adults aged 18-65 years (Azstarys was not studied in those > 65 years of age). Azstarys is a stimulant, and works by increasing levels of neurotransmitters in the brain that are associated with concentration, focus, and impulse control. It works quickly, with effects typically felt within an hour after taking the medication.

Definitions

"Attention Deficit Hyperactivity Disorder (ADHD)" is a mental health disorder characterized by difficulty paying attention, impulsivity, and hyperactivity.

"Hyperactivity" refers to excessive activity or restlessness, often expressed as difficulty sitting still, fidgeting, or talking excessively.

"Impulsivity" refers to difficulty controlling impulses, often expressed as interrupting others, blurting out answers, or making decisions without thinking.

"Inattention" refers to difficulty with paying attention, difficulty sustaining attention, or difficulty concentrating on tasks.

"Stimulant" medications refer to the class of medications used primarily for ADHD that increase the neurotransmitters dopamine and norepinephrine (chemicals in the brain). Stimulants typically fall under the class of amphetamines or methylphenidates, and predominantly work by increasing alertness, focus, and attention.

Medical Necessity Criteria for Initial Authorization

The Plan considers Azstarys (serdexmethylphenidate and dexmethylphenidate) medically necessary when **ALL** of the following criteria are met:

1. The member is 6 years of age or older; ***AND***
2. The member has a diagnosis of attention-deficit/hyperactivity disorder (ADHD) per the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria; ***AND***

3. The member is unable to use or has adequately tried and failed **TWO** preferred (long-acting) once-daily stimulant preparation alternatives (e.g., generic Adderall XR, Concerta, Focalin XR, Metadate CD, Ritalin LA); ***AND***
4. Clinical chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, the requested medication will be approved for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if recent chart documentation (within the last 6 months) shows that the member has experienced clinical benefit(s) to the requested medication as evidenced by **ONE (1)** of the following:

1. Achievement of target functional goals established at the onset of therapy (e.g., improved academic performance, relationships (e.g., peer, sibling), safety in the community); ***OR***
2. Improvements in core symptoms of inattention and hyperactivity/impulsivity.

Experimental or Investigational / Not Medically Necessary

Azstarys (serdexmethylphenidate and dexmethylphenidate) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

References

1. Attention-deficit/hyperactivity disorder. In: diagnostic and statistical manual of mental disorders. 5th ed. DSM-5 Washington, DC: American Psychiatric Association. 2013:59-66.
2. Austerman J. ADHD and behavioral disorders: Assessment, management, and an update from DSM-5. Cleve Clin J Med. 2015; 82:S2-7.
3. Azstarys (serdexmethylphenidate and dexmethylphenidate) [prescribing information]. Grand Rapids, MI: Corium Inc; Oct 2023.
4. Barbaresi WJ, Campbell L, Diekroger EA, et al. Society for developmental and behavioral pediatrics clinical practice guideline for the assessment and treatment of children and adolescents with complex attention-deficit/hyperactivity disorder. J Dev Behav Pediatr. 2020 Feb/Mar:31 Suppl 2S:S35-S57. doi:10.1097/DBP.0000000000000770.
5. Barnhardt EA, Narayanan A, Coury DL. Evaluating serdexmethylphenidate and dexmethylphenidate capsules as a once-daily treatment option for ADHD. Expert Opin Pharmacother. 2023 May-Aug; 24(11): 1215-1219. doi:10.1080/14656566.2023.2218544. Epub 2023 May 26.

6. Childress AC, Cutler AJ, Patel M, Oh C. Analysis of growth velocity in children with attention-deficit/hyperactivity disorder treated for up to 12 months with serdexmethylphenidate/dexmethylphenidate.
7. Childress AC, Marraffino A, Cutler AJ, Oh C, Brams MN. Safety and tolerability of serdexmethylphenidate/dexmethylphenidate capsules in children with attention-deficit/hyperactivity disorder: a 12-month, open-label safety study. J Child Adolesc Psychopharmacol. 2023 Marl 33(2):51-58. doi:10.1089/cap.2022.0076. Epub 2023 Feb 20.
8. Cortese S. Pharmacologic Treatment of Attention Deficit-Hyperactivity Disorder. N Engl J Med. 2020; 383:1050-1056.
9. Cutler AJ, Kollins SH, Brams MN, et al. Serdexmethylphenidate/dexmethylphenidate for children with attention-deficit/hyperactivity disorder: dose optimization from a laboratory classroom study. Front Psychiatry. 2024 Mar 19;15:1310483. doi:10.3389/fpsyt.2024.1310483. eCollection 2024.
10. Faraone SV, Banaschewski T, Coghill D et al. The World Federation of ADHD International Consensus Statement: 208 Evidence-based conclusions about the disorder. Neurosci Biobehav Rev. 2021; 128:789-818.
11. Kollins SH, Braeckman R, Guenther S, et al. A randomized, controlled laboratory classroom study of serdexmethylphenidate and d-methylphenidate capsules in children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychpharmacol. 2021 Nov;31(9):597-609. Doi: 10.1089/cap.2021.0077. Epub 2021 Oct 29.
12. Kooij JJS, Bijlenga D, Salerno L et al. Updated European Consensus Statement on diagnosis and treatment of adult ADHD. Eur Psychiatry. 2019; 56:14-34.
13. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. Lancet. 2020; 395:450-462.
14. Shram MH, Setnik B, Webster L, et al. Oral, intranasal, and intravenous abuse potential of serdexmethylphenidate, a novel prodrug of d-methylphenidate. Curr Med Res Opin. 2022 Jul;38(7):1237-1250. doi:10.1080/03007995.2022.2076474. Epub 2022 Jun 3.
15. Steingard R, Taskiran S, Connor DF et al. New Formulations of Stimulants: An Update for Clinicians. J Child Adolesc Psychopharmacol. 2019; 29:324-339.
16. Volkow ND, Swanson JM. Clinical practice: Adult attention deficit-hyperactivity disorder. N Engl J Med. 2013; 369:1935-44.
17. Wigal S, Chappell P, Palumbo D et al. Diagnosis and Treatment Options for Preschoolers with Attention-Deficit/Hyperactivity Disorder. J Child Adolesc Psychopharmacol. 2020; 30:104-118.
18. Wolraich ML, Hagan JF Jr, Allan C et al. Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2019; 144

Clinical Guideline Revision / History Information

Original Date: 3/23/2023
Reviewed/Revised: 3/21/2024, 7/1/2025

Oscar Clinical Guideline: Furoscix (furosemide) 8mg/1mL Solution for injection [On-Body Infusor] (PG132, Ver. 4)

Furoscix (furosemide) 8mg/1mL Solution for injection [On-Body Infusor]

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Summary

Chronic heart failure (CHF) is a common yet complex clinical syndrome. It affects millions of people every year and can be a debilitating condition. CHF is a progressive disorder of the heart characterized by an inability of the heart to pump enough blood to meet the needs of the body. This results in symptoms such as shortness of breath, fatigue, and edema. Treatment of CHF is multifactorial and includes lifestyle modifications, pharmacologic interventions, and device therapy.

Fluid overload is a common problem in patients with New York Heart Association (NYHA) Class II-IV chronic heart failure and can lead to increased morbidity and mortality if not properly managed. Treatment of fluid overload in these patients involve a combination of non-pharmacological and pharmacological measures. Pharmacological measures include the use of Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor neprilysin inhibitor (ARNIs), beta-blockers, loop diuretics, and thiazide diuretics. These medications can help reduce blood pressure, reduce oxygen demand on the health, reduce fluid overload and improve symptoms. In addition, aldosterone antagonists may also be used if other measures are inadequate.

Furoscix (furosemide) is indicated for the treatment of congestion due to fluid overload in adult patients with chronic heart failure.

- Furoscix is not indicated for use in patients with acute pulmonary edema.
- Furoscix is intended for outpatient treatment.
- The product is supplied in a single-dose prefilled cartridge for subcutaneous infusion co-packaged with the On-body Infusor. Each single-use on-body infusor contains 80 mg of Furoscix (furosemide)per 10 mL single-dose prefilled cartridge. It is designed to deliver a pre-programmed dose of 30 mg of Furoscix (furosemide) over the first hour, then 12.5 mg per hour for the subsequent 4 hours.
- Furoscix (furosemide) is not for chronic use, and should be replaced with oral diuretics as soon as practical.

Definitions

"**Anuria**" is a medical term used to describe a condition in which a person's kidneys stop producing urine, or produce very little urine. Specifically, anuria is defined as the production of less than 50 milliliters of urine per day in adults.

"**Ascites**" is a medical condition in which fluid accumulates in the abdominal cavity, causing abdominal swelling and discomfort. Ascites can be a complication of a variety of underlying health problems, including liver disease, heart failure, and certain types of cancer.

"**Chronic heart failure (CHF)**" is a medical condition in which the heart is unable to pump enough blood to meet the body's needs. It occurs when the heart muscle is weakened or damaged, resulting in decreased blood flow to the organs and tissues. CHF can be caused by a variety of factors, including coronary artery disease, hypertension, heart valve disease, and cardiomyopathy.

"**Cirrhosis**" is a chronic liver disease that results from damage to liver cells and the formation of scar tissue in the liver. This can lead to a variety of symptoms and complications, including jaundice, fatigue, fluid retention, and an increased risk of liver cancer.

"**Diuretic**" is a medication that promotes the excretion of excess water and salt from the body through the kidneys, thereby increasing urine output. Diuretics are commonly used to treat conditions such as high blood pressure, heart failure, and edema. Diuretics can be classified into several categories based

on their mechanism of action, such as loop diuretics, thiazide diuretics, potassium-sparing diuretics, and osmotic diuretics.

"**Edema**" refers to the swelling of the body's tissues, typically due to the accumulation of excess fluid. In the context of heart failure, edema often occurs in the legs, ankles, and feet, but it can also affect the abdomen, lungs, and other parts of the body. Edema is caused by an imbalance in the body's fluid levels, which can result from the heart's inability to pump blood effectively.

"**Parenteral**" is a term used to describe medications or nutrients that are delivered into the body through non-oral routes, such as injection or infusion. This is in contrast to enteral administration, which involves delivering medications or nutrients through the digestive system, such as by mouth or through a feeding tube.

"**The New York Heart Association (NYHA) classification system**" is used to assess the severity of heart failure symptoms. It is based on a patient's ability to carry out physical activity without experiencing symptoms such as shortness of breath or fatigue. The NYHA classification system has four stages:

- NYHA class I: No limitation of physical activity. Ordinary physical activity does not cause symptoms of heart failure.
- NYHA class II: Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of heart failure.
- NYHA class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of heart failure.
- NYHA class IV: Unable to carry out any physical activity without symptoms of heart failure, or symptoms of heart failure at rest.

Medical Necessity Criteria for Authorization

The Plan considers **Furoscix (furosemide injection)** medically necessary when **ALL** of the following criteria are met:

1. The member is 18 years of age or older; ***AND***
2. The member has chronic heart failure; ***AND***
3. The medication is being used for the treatment of congestion due to fluid overload; ***AND***
4. The member has been taking an oral loop diuretic (i.e., furosemide, torsemide, bumetanide) at an optimized dose; ***AND***
5. The medication is being used for the short-term management of acute episodes of edema and **NOT** for long-term management; ***AND***

6. The member is an appropriate candidate for parenteral diuresis outside of the hospital, defined as all the following:
    a. Documentation of **ALL** of the following:
        i. Oxygen saturation ≥ 90% on exertion; ***and***
        ii. Respiratory Rate < 24 breaths per minute; ***and***
        iii. Resting Heart Rate < 100 beats per minute; ***and***
        iv. Systolic Blood Pressure > 100 mmHg; ***and***
    b. The member does **NOT** have documentation of **ANY** of the following:
        i. Anuria (urine output <50 mL/day); ***or***
        ii. History of hypersensitivity to furosemide or medical adhesives; ***or***
        iii. Hepatic cirrhosis or ascites; ***or***
        iv. Presence of a complicating condition that requires immediate hospitalization or anticipated hospitalization in the next 30 days; ***AND***
7. The medication is being prescribed for use within **ONE** of the following Plan's Quantity Limit:
    a. 5 kits per 3 months; ***or***
    b. 10 Furoscix kits per 3 months **AND** a valid clinical rationale is provided demonstrating medical necessity; ***AND***
8. Recent (within the last 3 months) clinical chart documentation is provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, the requested medication will be approved for 3 months.

Experimental or Investigational / Not Medically Necessary

Furoscix (furosemide injection) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. This includes but are not limited to:

- for chronic use. Furoscix is not for chronic use and should be replaced with oral diuretics as soon as practical.
- for the management of hypertension.
- in patients with hepatic cirrhosis.
- in the management of edema associated with nephrotic syndrome.
- in the treatment of acute pulmonary edema.
- in the treatment of hypertensive crises.
- to increase renal excretion of calcium in patients with hypercalcemia.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
J1941	Injection, furosemide (furoscix), 20 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
I50.1	Left ventricular failure
I50.20	Unspecified systolic (congestive) heart failure
I50.22	Chronic systolic (congestive) heart failure
I50.23	Acute on chronic systolic (congestive) heart failure
I50.30	Unspecified diastolic (congestive) heart failure
I50.32	Chronic diastolic (congestive) heart failure
I50.33	Acute on chronic diastolic (congestive) heart failure
I50.40	Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.42	Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.43	Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure
150.810	Right heart failure, unspecified
I50.9	Heart failure, unspecified
ICD-10 codes that are not covered for indications specified in the Clinical Guideline	
I50.21	Acute systolic (congestive) heart failure
I50.31	Acute diastolic (congestive) heart failure
I50.41	Acute combined systolic (congestive) and diastolic (congestive) heart failure

References

1. 2023 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023;71(7):2052-2081. doi:10.1111/jgs.18372[PubMed 37139824]
2. Andre AD, Mohr JF, Cornelius BW, et al. Human factors validation of a wearable, on-body infusor for subcutaneous administration of furosemide. Med Devices (Auckl). 2024 Jun 24:17:229-235. doi:10.2147/MDER.S462573. eCollection 2024.
3. Bensimhon D, Weintraub WS, Peakcock WF, et al. Reduced heart failure-related healthcare costs with Furoscix versus in-hospital intravenous diuresis in heart failure patients: the FREEDOM-HF study. Future Cardiol. 2023 Jun;19(8):385-396. doi:10.2217/fca-2023-0071. Epub 2023 Aug 23.
4. Bozkurt B et al: Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. ePub, 2021
5. Ezekowitz JA et al: 2017 comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol. 33(11):1342-433, 2017
6. FUROSCIX® (furosemide injection 80 mg/10 mL) for subcutaneous use [prescribing information]. Burlington, MA: scPharmaceuticals, Inc.; August 2024.
7. Furosemide injection [prescribing information]. Lake Forest, IL: Hospira Inc; August 2022.
8. Furosemide tablet, solution [prescribing information]. Eatontown, NJ: West-Ward Pharmaceuticals Corp.; January 2016.
9. Gilotra NA, Princewill O, Marino B, et al. Efficacy of intravenous furosemide versus a novel, pH-neutral furosemide formulation administered subcutaneously in outpatients with worsening heart failure. JACC Heart Fail. 2018 Jan;6(1):65-70. doi:10.1016/j.jchf.2017.10.001. Epub 2017 Dec 6.
10. Heidenreich PA et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263-421
11. Heidenreich PA et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2022;79(17):e263-421
12. Houston BA, Kalathiya RJ, Kim DA et al. Volume Overload in Heart Failure: An Evidence-Based Review of Strategies for Treatment and Prevention. Mayo Clin Proc. 2015; 90:1247-61.
13. Ioannidis JPA. Diagnosis and treatment of hypertension in the 2017 ACC/AHA guidelines and in the real world. JAMA. 2018; 319(2):115-6.
14. Malhamé I, Dong S, Syeda A, et al. The use of loop diuretics in the context of hypertensive disorders of pregnancy: a systematic review and meta-analysis. J Hypertens. 2023;41(1):17-26. doi:10.1097/HJH.0000000000003310[PubMed 36453652]
15. McDonagh TA et al: 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 42(36):3599-726, 2021
16. Ponikowski P et al: 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 18(8):891-975, 2016.
17. Wierda E, DIckhoff C, Handoko ML, et al. Outpatient treatment of worsening heart failure with intravenous and subcutaneous diuretics: a systematic review of the literature. ESC Heart Fail. 2020 Jun;7(3):892-902. doi:10.1002/ehf2.12677. Epub 2020 Mar 11.

18. Zafar MR et al: Pharmacological and non-pharmacological strategies for volume overload in acute decompensated congestive heart failure: a review article. Cureus. 12(2):e6952, 2020

Clinical Guideline Revision / History Information

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Pedmark (sodium thiosulfate)

Summary

Cisplatin is a potent chemotherapy drug that is commonly used to treat pediatric cancers such as neuroblastoma, osteosarcoma, and medulloblastoma. While cisplatin is highly effective in treating cancer, it can also cause ototoxicity, which is damage to the inner ear and the hearing system.

Ototoxicity is a common side effect of cisplatin treatment in pediatric patients, with a reported incidence ranging from 20% to 80%. The risk of ototoxicity is dependent on various factors, including the dose and duration of cisplatin treatment, patient age, and pre-existing hearing deficits.

Cisplatin-induced ototoxicity can present in different ways, including tinnitus (ringing in the ears), hearing loss, and balance disorders (such as vertigo). The severity of hearing loss can vary from mild to profound and can affect one or both ears. The hearing loss may be temporary or permanent, and the degree of recovery depends on the individual patient and the severity of the damage.

The mechanism of cisplatin-induced ototoxicity is not fully understood, but it is thought to involve damage to the hair cells in the inner ear, which are responsible for detecting sound and transmitting it to the brain. Cisplatin can also cause damage to the auditory nerve and other structures in the ear.

To minimize the risk of cisplatin-induced ototoxicity, various strategies have been investigated, including administering early detection monitoring techniques, reducing the dose and duration of cisplatin treatment, administering cisplatin as a continuous infusion, and using otoprotective agents such as sodium thiosulfate or amifostine. Pedmark (sodium thiosulfate) is thought to reduce the risk of ototoxicity by interacting directly with cisplatin to produce an inactive platinum species, reducing its toxicity.

Pedmark (sodium thiosulfate) in an intravenous product indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

- The safety and efficacy of Pedmark (sodium thiosulfate) have not been established when administered following cisplatin infusions longer than 6 hours.
- Pedmark (sodium thiosulfate) may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.
- The dosage of Pedmark (sodium thiosulfate) is based on surface area according to actual body weight.

Definitions

"**Cisplatin**" is a chemotherapy drug that is commonly used to treat various types of cancer, including ovarian, bladder, and lung cancer. However, cisplatin is also known to cause ototoxicity, and can result in hearing loss, tinnitus, and balance problems. Otoprotective agents are often used alongside cisplatin to reduce the risk of ototoxicity.

"**Chemotherapy**" is a type of cancer treatment that uses drugs to kill cancer cells. Chemotherapy drugs work by targeting rapidly dividing cells, which includes cancer cells. However, they can also affect normal, healthy cells in the body, leading to side effects such as hair loss, nausea, and fatigue.

"Metastatic" tumors (or metastasis) refer to the spread of cancer cells from the site of the primary cancer to another part of the body.

"**Otoprotective agents**" are drugs or compounds that are used to protect the ear from damage caused by ototoxic drugs or chemicals. Otoprotective agents may work by reducing the amount of ototoxic drug

that reaches the ear, by reducing oxidative stress and inflammation in the ear, or by promoting the repair of damaged cells in the ear.

"**Ototoxicity**" refers to the harmful effects of drugs or chemicals on the auditory system, including the cochlea, auditory nerve, and other parts of the ear. Ototoxicity can result in hearing loss, tinnitus, and balance problems.

Medical Necessity Criteria for Authorization

The Plan considers **Pedmark (sodium thiosulfate)** medically necessary when **ALL** of the following criteria are met:

1. The member is a pediatric patient between 1 month of age and 18 years of age; ***AND***
2. The member is being treated for a localized, non-metastatic solid tumor; ***AND***
3. The member is receiving a chemotherapy regimen that includes cisplatin; ***AND***
4. Individual cisplatin doses will be infused over 6 hours or less.

If the above prior authorization criteria are met, the requested medication will be approved for 12 months.

Experimental or Investigational / Not Medically Necessary

Pedmark (sodium thiosulfate) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- for the treatment of adults or in ovarian cancer
- for the treatment of acute cyanide toxicity
- in metastatic solid tumors or in patients receiving high-dose carboplatin
- when administered following cisplatin infusions longer than 6 hours. Pedmark (sodium thiosulfate) may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.

Applicable Billing Codes (HCPCS/CPT Codes)

CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
J0208	Injection, sodium thiosulfate (pedmark), 100 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter
H91.01	Ototoxic hearing loss, right ear
H91.02	Ototoxic hearing loss, left ear
H91.03	Ototoxic hearing loss, bilateral
H91.09	Ototoxic hearing loss, unspecified ear

References

1. Brock PR, Maibach R, Childs M, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. N Engl J Med. 2018;378(25):2376-2385. doi:10.1056/NEJMoa1801109
2. Freyer DR, Brock PR, Chang KW, et al. Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. Lancet Child Adolesc Health. 2020;4(2):141-150. doi:10.1016/S2352-4642(19)30336-0
3. Freye DR, Brock P, Knight K, et al. Interventions for cisplatin-induced hearing loss in children and adolescents with cancer. Lancet Child Adolesc Health. 2019 Aug;3(8):578-584. doi:10.1016/S2352-4642(19):30115-4. Epub 2019 May 31.
4. Freyer DR, Chen L, Krailo MD, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2017;18(1):63-74. doi:10.1016/S1470-2045(16)30625-8.
5. Jordan B, Margulies A, Cardoso F, et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO clinical practice guidelines for diagnosis, prevention,

treatment and follow-up. Ann Oncol. 2020 Oct;31(10):1306-1319. doi:10.1016/j.annonc.2020.07.003. Epub 2020 Jul 30.
6. National Cancer Institute - Metastasis. Available at https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis. Accessed 20 February 2025.
7. National Cancer Institute. Sodium thiosulfate prevents cisplatin-induced hearing loss in some children. July 13, 2018. Accessed January 28, 2022. https://www.cancer.gov/news-events/cancer-currents-blog/2018/cisplatin-hearing-loss- sodium-thiosulfate
8. Orgel E, Knight KR, Villaluna D, et al. Reevaluation of sodium thiosulfate otoprotection using teh consensus international society of paediatric oncology ototoxicity scale: a report from the children's oncology group study ACCL0431. Pediatr Blood Cancer. 2023 Jul 7:e30550. doi:10.1002/pbc.30550. Online ahead of press.
9. Pedmark (sodium thiosulfate) [prescribing information]. Hoboken, NJ: Fennec Pharmaceuticals Inc; September 2022.
10. Romano A, Capozza MA, Mastrangelo S, Maurizi P, Triarico S, Rolesi R, Attinà G, Fetoni AR, Ruggiero A. Assessment and Management of Platinum-Related Ototoxicity in Children Treated for Cancer. Cancers (Basel). 2020 May 17;12(5):1266. doi: 10.3390/cancers12051266.
11. Sodium thiosulfate [prescribing information]. Scottsdale, AZ: Hope Pharmaceuticals; June 2020.

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oscar

Clinical Guideline

Guideline Number: Hemangeol (propranolol hydrochloride oral solution) (PG135, Ver. 3)

Hemangeol (propranolol hydrochloride oral solution)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Infantile hemangioma is a common benign tumor of infancy that affects the blood vessels. It is the most common type of vascular tumor in children and is estimated to occur in 4-10% of infants. Infantile hemangioma typically appears as a raised, red or purple bump on the skin and can vary in size and location.

The exact cause of infantile hemangioma is unknown, but it is believed to be related to an abnormal proliferation of blood vessels during early infancy. It is more common in female infants and in premature infants. Diagnosis of infantile hemangioma is usually made based on the characteristic appearance of the lesion and the patient's age and medical history. In some cases, a biopsy may be performed to confirm the diagnosis.

Treatment for infantile hemangioma is generally not needed for small, asymptomatic lesions. However, if a larger lesion causes symptoms or interferes with daily activities and developmental milestones, drug therapy options such as beta blockers and corticosteroids (oral, intralesional, or topical) may be

considered. Active monitoring is typically required for most lesions, with treatment being necessary in cases of ulceration, vital structure interference, or potential disfigurement. Complications of cutaneous hemangiomas depend on factors like size, location, and shape, and can include ulceration, cosmetic disfigurement, and functional issues like eye complications, airway obstruction, feeding difficulties, limited mobility, and, rarely, heart failure. Hemangeol (propranolol hydrochloride oral solution) is a beta-adrenergic blocker indicated for treating proliferating infantile hemangioma that requires systemic therapy. Its safety and effectiveness have not been established for pediatric patients older than 1 year of age.

Definitions

"**Infantile hemangioma (IH)**" is a benign (noncancerous) tumor that affects the blood vessels and is the most common type of vascular tumor in children. It typically appears as a raised, red or purple bump on the skin and can vary in size and location.

"**Asthma**" is a chronic respiratory condition that is characterized by inflammation and narrowing of the airways, leading to difficulty breathing.

"**Bronchospasm**" is a sudden contraction or narrowing of the muscles in the walls of the bronchial tubes, making it difficult to breathe.

"**Bradycardia**" is a medical condition in which the heart beats at a slower rate than normal.

"**Decompensated Heart Failure**" is a medical condition in which the heart is unable to pump enough blood to meet the body's demands, leading to symptoms such as shortness of breath, fatigue, and swelling in the legs and ankles.

"**Premature infant**" is a baby born before 37 weeks of gestation.

"**Pheochromocytoma**" is a rare type of tumor that affects the adrenal glands and produces excess amounts of catecholamines, which can lead to high blood pressure and other symptoms.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Hemangeol (propranolol hydrochloride oral solution)** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with a specialist with experience treating hemangioma (e.g., pediatric dermatologist)***; AND***

2. The member is between the ages of 5 weeks (i.e., 35 days) to 1 year of age***; AND***
3. The member has a confirmed diagnosis of proliferating infantile hemangioma***; AND***
4. The member does not have documentation of **ANY** of the following:
    a. Asthma or history of bronchospasm***; or***
    b. Blood pressure <50/30 mmHg***; or***
    c. Bradycardia (<80 beats per minute)***; or***
    d. Decompensated heart failure***; or***
    e. Greater than first degree heart block***; or***
    f. Is a premature infant with corrected age <5 weeks***; or***
    g. Pheochromocytoma***; or***
    h. Weighing less than 2 kg***; AND***
5. Hemangeol (propranolol hydrochloride oral solution) will be dosed within the manufacturer's published dosing guidelines or falls within dosing guidelines found in a compendia of current literature **AND BOTH** of the following:
    a. Treatment will be initiated between ages 5 weeks to 5 months***; and***
    b. Treatment will not extend beyond 1 year of age***; AND***
6. Recent clinical chart documentations (within the last month) are provided for review to substantiate the above listed requirements.

If the above prior authorization criteria are met, the requested medication will be approved for 6 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 6 months or up to 1 year of age (whichever is less) will be granted if **BOTH** of the following are met:

1. the member still meets the applicable initial criteria; ***AND***
2. chart documentation shows **BOTH** of the following:
    a. recurrence of hemangiomas***; and***
    b. the member has shown a clinical improvement (e.g., resolution of the target hemangioma) in symptoms since starting the requested medication.

Experimental or Investigational / Not Medically Necessary

Hemangeol (propranolol hydrochloride oral solution) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Akathisia, antipsychotic-induced***; or***
- Angina, chronic stable***; or***
- Atrial fibrillation/flutter***; or***
- Essential tremor***; or***
- Hypertension***; or***
- Migraine, prevention***; or***
- Myocardial infarction, early treatment and secondary prevention***; or***
- Infantile hemangioma in pediatric patients greater than 1 year of age. Safety and effectiveness for infantile hemangioma have not been established in pediatric patients greater than 1 year of age***; or***
- Initiating treatment at ages less than 5 weeks or greater than 5 months***; or***
- Infants weighing less than 2 kg***; or***
- Performance anxiety disorder***; or***
- Pheochromocytoma***; or***
- Postural orthostatic tachycardia syndrome***; or***
- Premature infants with corrected age <5 weeks***; or***
- Supraventricular tachycardia***; or***
- Thyroid storm***; or***
- Thyrotoxicosis***; or***
- Treatment for cosmetic improvement rather than focusing on the patient's functionality, such as:
    - Situations where the lesions do not require medical or surgical intervention***; or***
    - Instances where small, localized, non facial lesions without ulceration can be safely managed through active observation***; or***
    - Cases where allowing lesions to follow their natural involution process is expected to result in the most favorable cosmetic outcome***; or***
- Tremor, lithium-induced, moderate to severe***; or***
- Variceal hemorrhage prophylaxis***; or***
- Ventricular arrhythmias.

References

1. Bessar H, Kandil AH, Nasr NM, Khattab F. Itraconazole versus propranolol: therapeutic and pharmacological effect on serum angiopoietin-2 in patients with infantile hemangioma. J Dermatolog Treat. 2022 Feb;33(1):105-110. doi:10.1080/09546634.2019.1687822. Epub 2021 Oct 28.
2. Chen T, Gudipudi R, Nguyen SA, Carroll W, Clemmens C. Should propranolol remain the gold standard for treatment of infantile hemangioma? A systematic review and meta-analysis of propranolol versus atenolol. Ann Otol Rhinol Laryngol. 2023 Mar;132(3):332-340. doi:10.1177/00034894221089758. Epub 2022 Apr 25.
3. Chinnadurai S, Sathe NA, Surawicz T. Laser treatment of infantile hemangioma: A systematic review. Lasers Surg Med. 2016 Mar;48(3):221-33. doi: 10.1002/lsm.22455. Epub 2015 Dec 29. PMID: 26711436.
4. Darrow DH, Greene AK, Mancini AJ, et al. Diagnosis and management of infantile hemangioma. Pediatrics. 2015;136(4):e1060-1104.
5. Diociaiuti A, Baselga E, Boon LM, et al. The VASCERN-VASCA working group diagnostic and management pathways for severe and/or rare infantile hemangiomas. Eur J Med Genet. 2022 Jun;65(6):104517. doi:10.1016/j.ejmg.2022.104517. Epub 2022 Apr 27.
6. Drolet BA, Frommelt PC, Chamlin SL, et al. Initiation and use of propranolol for infantile hemangioma: report of a consensus conference. Pediatrics. 2013;131(1):128-140.
7. Finstad A, Lytvyn Y, Pope E, Sibbald C. J Am Acad Dermatol. 2025 Jan 15:S0190-9622(25)00048-9.doi:10.1016/j.jaad.2024.11.077.Online ahead of print.
8. Frieden IJ, Püttgen KB, Drolet BA, et al. Management of infantile hemangiomas during the COVID pandemic. Pediatr Dermatol. 2020;37(3):412-418.
9. Hemangeol (propranolol) [prescribing information]. Parsippany, NJ: Pierre Fabre Pharmaceuticals Inc; August 2021.
10. Hoeger PH, Harper JI, Baselga E, et al. Treatment of infantile haemangiomas: recommendations of a European expert group. Eur J Pediatr. 2015 Jul;174(7):855-65. doi:10.1007/s00431-015-2570-0. Epub 2015 May 29.
11. Huang X, Si W, Zou Z, et al. Efficacy and safety of oral propranolol and topical timolol in the treatment of infantile hemangioma: a meta-analysis and systematic review. Front Pharmacol. 2024 Dec 2; 15:1515901. eCollection 2024.
12. Ji Y, Chen S, Yang K, et al. Efficacy and safety of propranolol vs atenolol in infants with problematic infantile hemangiomas: a randomized clinical trial. JAMA Otolaryngol Head Neck Surg. 2021 Jul 1;147(7): 599-607. doi:10.1001/jamaoto.2021.0454.
13. Krowchuk DP et al: Clinical practice guideline for the management of infantile hemangiomas. Pediatrics. 143(1):e20183475, 2019
14. Léauté-Labrèze C, Frieden I, Delarue A. Early initiation of treatment with oral propranolol for infantile hemangioma improves success rate. Pediatr Dermatol. 2023 Mar; 40(2):261-264. doi:10.1111/pde.15198. Epub 2022 Dec 13.
15. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. N Engl J Med. 2015;372(8):735-746.
16. Ma F, Liu X, Wang C, Duan H, Zhou K, Hu F. Comparison of efficacy and safety between oral propranolol combined with an without intralesional injection of lauromacrogol for infantile hemangioma. Front Pediatr. 2024 Jun 26;12:1361105. doi:10.3389/fped.2024.1361105. eCollection 2024.

17. Pattanshetti SA, Mahalmani VM, Sarma P, et al. Oral atenolol versus propranolol in the treatment of infantile hemangioma: a systematic review and meta-analysis. J Indian Assoc Pediatr Surg. 2022 May-Jun;27(3):279-286. doi:10.4103/jiaps.jiaps_3_21. Epub 2022 May 12.
18. Pope E, Lara-Corrales I, SIbbald C, et al. Noninferiority and safety of nadolol vs propranolol in infants with infantile hemangioma: a randomized clinical trial. JAMA Pediatr. 2022 Jan 1;176(1):34-41. doi:10.1001/jamapediatrics.2021.4565.
19. Rodríguez Bandera AI, Sebaratnam DF, Wargon O, Wong LF. Infantile hemangioma. Part 1: Epidemiology, pathogenesis, clinical presentation and assessment. J Am Acad Dermatol. 2021 Dec;85(6):1379-1392. doi: 10.1016/j.jaad.2021.08.019. Epub 2021 Aug 19. PMID: 34419524.
20. Rwebah H, Alkhodair R, Al-Khenaizan S. Propranolol-induced hyperkalemia in the management of infantile hemangioma. JAAD Case Rep. 2020;6(4):359-361. doi:10.1016/j.jdcr.2020.01.028
21. Sebaratnam DF, Rodríguez Bandera AL, Wong LF, Wargon O. Infantile hemangioma. Part 2: Management. J Am Acad Dermatol. 2021 Dec;85(6):1395-1404. doi: 10.1016/j.jaad.2021.08.020. Epub 2021 Aug 19. PMID: 34419523.
22. Soloman L, Glover M, Beattie PE, et al. Oral propranolol in the treatment of proliferating infantile haemangiomas. British society for paediatric dermatology consensus guidelines. Br J Dermatol. 2018 Sep;179(3):582-589. doi:10.1111/bjd.16779.
23. Thareja S, Lucero E, Ramasubramanian A. Choroidal hemangioma treatment with propranolol - a case study in Sturge-Weber syndrome and systematic literature review. Semin Opthalmol. 2025 Jan 7:1-9. doi:10.1080/08820538.2025.2450689.Online ahead of print.
24. Wang X, Feng W, Zhao X, Liu Z, Dong L. The efficacy and safety of topical B-blockers in treating infantile hemangiomas: a meta-analysis including 11 randomized controlled trials. Dermatology. 2021;237(3):433-443. Doi: 10.1159/000510029. Epub 2020 Oct 7.
25. Wedgeworth E, Glover M, Irvine AD, et al. Propranolol in the treatment of infantile haemangiomas: lessons from the European propranolol in the treatment of complicated haemangiomas (PITCH) taskforce survey. Br J Dermatol. 2016 Mar;174(3):594-601. doi:10.1111/bjd.14233. Epub 2015 Dec 26.

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oscar

Clinical Guideline

Oscar Clinical Guideline: Approved and Accepted Off-label Medical Necessity Criteria for Products, Drugs and Biologicals (PG136, Ver. 3)

Approved and Accepted Off-label Medical Necessity Criteria for Products, Drugs and Biologicals

Disclaimer

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Summary

The Plan aims to ensure appropriate and safe use of FDA-approved/cleared prescription products (i.e., drugs, biologicals, devices) when used for medically accepted indications. Coverage may be provided⇅ when the product is used for:

- Indications listed in the FDA-approved/cleared labeling.
  ⇅*Please note: the Plan may deem an FDA-approved/cleared product to be unproven or not medically necessary if a review of published medical literature suggests the use may be unsafe or ineffective.*
- Off-label uses that are supported by sufficient evidence⇄ in medical compendia, evidence-based guideline or peer-reviewed literature:
  - Off-label usage may be considered reasonable and necessary if supported by sufficient evidence. However, off-label use is not covered if:
    - The use is identified by the FDA as not indicated.

- The use is specifically identified as not indicated in one or more of the compendia listed**.**
- Evidence-based guideline and/or peer-reviewed literature deems the use as not safe and/or effective.

⇄*Please note: For off-label use, the provider must submit documentation fully supporting the proposed use when requested. Coverage decisions will consider high quality published evidence.*

This policy provides coverage criteria for products requiring prior authorization that:

- Lack specific Plan clinical guidelines or established criteria, including new products or those with recent major labeling changes***; or***
- Have been prescribed for an off-label indication.
    - Use must also be supported by high quality published evidence and not contradicted by other literature.

Please note: Other drug-specific or class-specific clinical guidelines may also be applicable. The Plan may review all requests made under the Medical or Pharmacy benefit against specific prior authorization criteria, as applicable and at its discretion.

Definitions

"**Biosimilar**" refers to copies of biologic drugs. They are similar to an FDA-approved biologic, known as the reference product.

"**Brand Name Drug**" means the first version of a particular medication to be developed or a medication that is sold under a pharmaceutical manufacturer's own registered trade name or trademark. The original manufacturer is granted a patent, which allows it to be the only company to make and sell the new drug for a certain number of years.

"**Compendia**" are summaries of drug information and medical evidence to support decision-making about the appropriate use of drugs and medical procedures. Examples include, but are not limited to:

1. American Hospital Formulary Service Drug Information
2. Elsevier Clinical Pharmacology
3. National Comprehensive Cancer Network Drugs and Biologics Compendium
4. Thomson Micromedex DrugDex
5. United States Pharmacopeia-National Formulary (USP-NF)

"Concurrent review" refers to authorization requests during active management of a condition. Most commonly, concurrent review refers to ongoing inpatient care, but can be requested and processed for outpatient services. The objective of concurrent review is to ensure timely and cost-effective utilization of ongoing services.

"Contraindication" is a specific situation or circumstance in which a medical procedure, medicine or surgery should not be used because it may harm the person.

"**Documentation**" refers to written information, including but not limited to:

1. Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses;
2. Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"**Evidence-based, peer-reviewed medical journals**" are publications that publish original research and scholarly articles related to the medical field. These journals use a peer-review process in which submitted articles are reviewed by independent experts in the same field to ensure their scientific accuracy, validity, and reliability before publication. The articles published in these journals are often based on research that use rigorous scientific methods to provide evidence for medical practices, therapies, and treatments. The goal of evidence-based medicine is to provide the most effective care to patients based on the best available scientific evidence.

"**FDA,**" or the Food and Drug Administration, is an agency of the United States federal government responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices, cosmetics, and veterinary products. The FDA's main goal is to ensure that these products are safe and effective for their intended use, and that their labeling and marketing are truthful and not misleading.

"**Formulary**" means a list of medications available to members with or without Prior Authorization.

"**Generic Drugs**" means prescription Drugs that have been determined by the Food and Drug Administration (FDA) to be equivalent to Brand Name Drugs, but are not made or sold under a registered trade name or trademark. Generic Drugs have the same active ingredients, meet the same FDA requirements for safety, purity, and potency and must be dispensed in the same dosage form (e.g., tablet, capsule, cream) as the Brand Name Drug.

"**High Strength/Quality Evidence**" is defined as at least one randomized, double-blind trial without significant limitations and with intent-to-treat analysis, confidence intervals reported, and consistent results from multiple trials or a meta-analysis with low heterogeneity. In some cancer-related cases, a non-blinded or single-blinded trial that meets the study objectives may also be considered as High Strength/Quality Evidence, such as in National Cancer Institute (NCI)-sponsored cooperative group studies or multicenter trials.

"**Low Strength/Quality Evidence**" is defined as evidence that includes observational studies, case reports, or case series, and in some cases, randomized clinical trials with significant limitations. It also encompasses evidence in the form of expert consensus panel reports or expert reviewer comments.

"**Moderate Strength/Quality Evidence**" is defined as at least one non-blinded or single-blinded, randomized or non-randomized clinical trial; a meta-analysis of randomized, controlled clinical trials with heterogeneous results if reasons for heterogeneity are adequately discussed; a randomized, controlled clinical trial with important methodological limitations; or inconsistent evidence from two or more randomized controlled trials with widely varying estimates of treatment effects. In some cancer-related cases, a non-blinded, non-randomized trial such as a phase II study may be considered as Moderate Strength/Quality Evidence for rare cancers or cancers with limited treatment options.

"Off-label" refers to a diagnosis, condition, age group, dose, frequency, dosage form (e.g., oral tablet, solution, capsules), duration, site or route of administration, or other factor related to prescribing, for which a product (e.g., prescription drug or over-the-counter product) has not been explicitly approved or cleared by the FDA.

"**Quantity Limit"** refers to the maximum available dosage or quantity a drug may be dispensed for during a designated period of time as indicated by the Plan.

Medical Necessity Criteria for Initial Authorization

If there is no product-specific Clinical Guideline or indication-specific clinical criteria, the Plan considers the requested FDA-approved or cleared product medically necessary if **ALL** the following criteria are met:

1. The product is being prescribed by or in consultation with a specialist or clinician with relevant specialty training **IF** accurate diagnosis and prescription, determination of risks and benefits of treatment, dosing, monitoring for side effects, or overall care coordination require specialist training to ensure safe and effective use of the product***; AND***

2. The safety and effectiveness of use for the indication is consistent with **ONE** of the following⇶:
    a. FDA approved labeling (i.e., product information) for indication, including age, dosing (dosage, frequency, duration of therapy, and site of administration), and contraindications; ***or***
    b. Use is supported with an appropriate level of evidence of efficacy by at least **ONE** of the following compendia, and not contraindicated or otherwise not recommended in the FDA labeling:
        i. American Hospital Formulary Service-Drug Information (AHFS-DI) and Grades of Recommendation is **EITHER** "Recommended" **OR** "Reasonable Choice"***; or***
        ii. American Medical Association (AMA) Drug Evaluations, or its successor publication***; or***
        iii. Clinical Pharmacology and the off-label use carries a Strong Recommendation "For" use, with any level of evidence***; or***
        iv. Lexi-Drugs AND the indication is listed as "Use: Off-Label" **AND** rated as "Evidence Level A"***; or***
        v. Micromedex DrugDex and the Strength of Recommendation for the indication is a Class I, Class IIa, or Class IIb***; or***
        vi. National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium and the level of evidence for the indication is Category 1, 2A, or 2B***; or***
    c. Evidence-based, peer-reviewed, recognized medical literature meeting **ALL** of the following:
        i. At least two articles from major peer-reviewed professional medical journals published in the United States, Canadian, European, or Great Britain, based on scientific or medical criteria, the product's safety and effectiveness for treatment of the indication for which the product has been prescribed***; and***
        ii. No article from a major peer-reviewed professional medical journal has concluded, based on scientific or medical criteria, that the product is unsafe or ineffective or that the product's safety and effectiveness cannot be determined for the treatment of the indication for which the product has been prescribed***; and***
        iii. The use is not listed as unsupported, not indicated, not recommended (or equivalent terms) in any of the medical reference compendia***; AND.***

⇶*<u>Please note:</u> the Plan may deem an FDA-approved/cleared product to be unproven or not medically necessary if a review of published medical literature suggests the use may be unsafe or ineffective.*

3. The member must have documented evidence of **ALL** of the following, if applicable:
    a. Failure of an adequate trial of at least three FDA-approved or cleared product (if available) that are considered the standard of care for the prescribed indication, unless:
        i. Clinically significant adverse effects are experienced***; or***
        ii. All FDA-approved or cleared alternatives are contraindicated***; or***
        iii. The request is for a product for treatment associated with cancer for a State with regulations against pre-requisite trial(s) of alternatives in certain oncology settings***; and***
    b. If the requested product is a Brand drug with a generic or biosimilar available, the member is unable to use or has tried and failed the corresponding generic or biosimilar product from two or more (≥ 2) manufacturers (if available)***; and***
    c. If the drug is to be used in combination with other drugs for a particular indication, the safety and efficacy of use of those drugs in combination must be supported by reliable evidence in peer-reviewed published medical literature***; AND***
4. The product being requested meets **BOTH** of the following:
    a. The prescribed dose, frequency, duration of therapy, and site of administration are consistent with FDA-approved labeling, compendia of current literature, practice guidelines, or peer-reviewed literature for the relevant indication***; and***
    b. If the requested dosage exceeds the Plan's quantity limit **AND** the prescribed dosage cannot be achieved using a different dose or formulation that is within the Plan's limit***; AND***
5. The member has no contraindications to the prescribed agent per FDA labeling***; AND***
6. Documentation (such as office chart notes, lab results or other clinical information) are provided for review to substantiate the above listed requirements.

<u>If the above medical necessity criteria are met, the initial prior authorization (including duration) approval may be considered medically necessary when one of the following applies:</u>

1. The duration of treatment requested is deemed medically necessary by the treating provider, when eligible for coverage per the member's benefits.
2. The initial prior authorization approval duration may be shortened or lengthened from the requested treatment duration in EITHER of the following cases:
    a. The nature of the service/treatment warrants a specific or different approval duration (e.g., 6-months, 12-months) based on the standards of care.
    b. The available clinical evidence or guideline recommendations support a specific approval period.

NOTE: Benefit, eligibility, or other applicable Plan restrictions may impact the length of the authorization period.

- *Ongoing prior authorization may be required after the initial approval period based on the service requested, clinical guidelines, and demonstration of continued medical necessity.*
- *Prior authorization does not guarantee payment or assure coverage, which is contingent on the member's eligibility and available benefits. Concurrent review may be required during the approval period to monitor ongoing medical necessity and appropriate use.*
- *Services must be delivered by plan-authorized providers and facilities, when applicable, and follow standards for evidence-based care delivery appropriate to the member's condition and goals of care.*

Medical Necessity Criteria for Reauthorization:

Prior authorization renewals will be reviewed on a case-by-case basis to determine medical necessity. Reauthorization requests will be considered medically necessary if **ALL** of the following criteria are met:

1. The member meets all applicable **Medical Necessity Criteria for Initial Authorization**, including:
    a. The prescribed use remains consistent with FDA-approved labeling or is supported by recognized compendia or high-quality published evidence***; and***
    b. The prescribed dose, frequency, duration of therapy, and site of administration remain consistent with FDA-approved labeling, nationally recognized compendia, or peer-reviewed medical literature for the relevant indication***; and***
    c. The member does not have any new contraindications to the prescribed product per FDA labeling***; AND***
2. The member has demonstrated a positive clinical response or benefit from therapy as evidenced by disease stability, disease improvement, or progress toward achievement of therapeutic goals as defined in the initial authorization***; AND***
3. The member has not experienced significant adverse effects, intolerable side effects, or unacceptable toxicity from the prescribed product that would necessitate discontinuation***; AND***
4. If the request is for a dose increase or change in dosing regimen, it must meet **BOTH** of the following criteria:
    a. The requested dosage, frequency, duration of therapy, and site of administration are supported by FDA-approved labeling, nationally recognized compendia, or peer-reviewed medical literature for the relevant indication (prescriber must submit supporting evidence)***; and***

b. If the requested dosage exceeds the Plan's quantity limit **AND** the prescribed dosage cannot be achieved using a different dose or formulation that is within the Plan's limit.

Table 1: Level of Evidence Definitions

AHFS Grades of Recommendation	
Recommended (Accepted)	The drug or biologic should be used, is recommended/indicated, or is useful/effective/beneficial in most cases.
Reasonable Choice (Accepted, with Possible Conditions) (e.g., treatment option)	The drug or biologic is reasonable to use under certain conditions (e.g., in certain patient groups), can be useful/effective/beneficial, or is probably recommended or indicated.
Not Fully Established (Unclear Risk/Benefit, Equivocal Evidence, Inadequate Data and/or Experience)	Usefulness and/or effectiveness is unknown, unclear, or uncertain or is not well established relative to the standard of care.
Not Recommended (Unaccepted)	The drug or biologic is considered inappropriate, obsolete, or unproven; is not recommended, is not indicated, or is not useful/effective/beneficial; or may be harmful.
Elsevier Clinical Pharmacology (quality of evidence rating and strength of recommendation)	
Strong Recommendation	An off-label use that carries a Strong Recommendation "For" or "Against" use, with any level of evidence, should be considered binding and reflect that Elsevier recommends or does not recommend, respectively, the use of the drug for that indication in the situation described. All off-label uses with a strong level of recommendation will appear in the referential database and be clearly identified as recommended or not recommended; however, a strong recommendation "Against use" will not be found within the clinical decision support data.
Equivocal/Weak Recommendation	Off-label uses that have inconclusive data "For" or "Against" use carry a Weak Recommendation. A Weak recommendation, with any level of evidence, reflects a neutral or equivocal position (i.e., neither for or against use) by Elsevier. All off-label uses with a weak level of recommendation will appear in the referential database and be clearly identified as equivocal; however, a weak recommendation "Against use" will not be found within the clinical decision support data.

Lexi-Drugs Level of Evidence Scale
A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit. B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate. C - Evidence from observational studies (eg, retrospective case series/reports providing significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain. G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Micromedex DrugDex Strength of Recommendation	
Class I - Recommended	The given test or treatment has been proven to be useful, and should be performed or administered.
Class IIa - Recommended, In Most Cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb - Recommended, In Some Cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III - Not Recommended	The given test, or treatment is not useful, and should be avoided.
Class Indeterminate	Evidence Inconclusive

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

Table 2: Peer-reviewed Professional Medical Journals

NOTE: The list of medical journals provided as an example is not intended to be an all-inclusive or comprehensive list. Numerous other credible medical journals exist that are not included here, and this list should not be considered a complete representation of the medical journal landscape.

Journal Name	Specialty	Publisher
Academic Emergency Medicine	emergency medicine	Wiley-Blackwell
American Journal of Respiratory and Critical Care Medicine	respiratory and critical care	American Thoracic Society
Annals of Emergency Medicine	emergency medicine	Elsevier
Annals of Internal Medicine	internal medicine	American College of Physicians; The American Heart Association
Annals of Oncology	oncology	Elsevier
Annals of Surgery	surgery	Lippincott Williams & Wilkins
Annals of Surgical Oncology	oncology	Springer
Archives of Disease in Childhood	pediatrics	BMJ Group
Biology of Blood and Marrow Transplantation	hematology/Oncology	Carden Jennings Publishing
Blood	hematology	American Society of Hematology
BMJ Open	general medicine	BMJ Group
Bone Marrow Transplantation	hematology/Oncology	Springer Nature
British Journal of Cancer	oncology	Springer Nature
Cancer	oncology	Wiley
Circulation	cardiology	American Heart Association
Clinical Cancer Research	oncology	American Association for Cancer Research

Clinical Infectious Diseases	infectious diseases	Oxford University Press
Diabetes Care	diabetes	American Diabetes Association
Drugs	Pharmacology	Springer
Emerging Infectious Diseases	infectious diseases	National Center for Infectious Diseases, Centers for Disease Control and Prevention
European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology	oncology	Elsevier
Gastroenterology	gastroenterology	Elsevier
Gynecologic Oncology	gynecologic oncology	Elsevier
International Journal of Cancer	oncology	Wiley-Blackwell
International Journal of Radiation Oncology, Biology, Physics	radiation oncology	Elsevier
JAMA: The Journal of the American Medical Association	general medicine	American Medical Association
Journal of Clinical Oncology	oncology	American Society of Clinical Oncology
Journal of Neurology, Neurosurgery, and Psychiatry	neurology and psychiatry	BMJ Publishing Group
Journal of the National Cancer Institute	oncology	Oxford University Press
Journal of the National Comprehensive Cancer Network	oncology	Harborside Press
Leukemia	hematology/oncology	Nature
Nature	multidisciplinary sciences	Nature Publishing Group
Nature Communications	multidisciplinary sciences	Nature Publishing Group
Nature Medicine	general medicine	Nature Publishing Group
Neurology	neurology	American Academy of Neurology

Neuropharmacology	pharmacology	Elsevier
New England Journal of Medicine	general medicine	Massachusetts Medical Society
Obstetrics and Gynecology	obstetrics and gynecology	Wolters Kluwer
Pediatrics	pediatrics	American Academy of Pediatrics
PLOS One	multidisciplinary sciences	PLOS
Radiation Oncology	oncology	BioMed Central Ltd.
Stroke	neurology	Wolters Kluwer
The American Journal of Clinical Dermatology	dermatology	Springer
The American Journal of Clinical Nutrition	nutrition	Elsevier
The American Journal of Gastroenterology	gastroenterology	Wolters Kluwer
The American Journal of Medicine	general medicine	Elsevier
The American Journal of Pathology	pathology	Elsevier
The American Journal of Physiology	physiology	American Physiological Society
The American Journal of Physiology - Endocrinology and Metabolism	physiology	American Physiological Society
The American Journal of Psychiatry	psychiatry	American Psychiatric Association
The American Journal of Sports Medicine	sports medicine	SAGE Publications
The American Journal of Transplantation	transplantation	Elsevier
The Annals of Thoracic Surgery	thoracic surgery	Elsevier
The BMJ (formerly the British Medical Journal)	general medicine	BMJ Publishing Group
The British Journal of Haematology	hematology	Wiley-Blackwell

The British Journal of Psychiatry	psychiatry	Royal College of Psychiatrists
The British Journal of Surgery	surgery	Oxford University Press
The Cochrane Database of Systematic Reviews	evidence-based medicine	Wiley-Blackwell
The Journal of Adolescent Health	adolescent health	Elsevier
The Journal of Allergy and Clinical Immunology	allergy and immunology	Elsevier
The Journal of the American Geriatric Society	Geriatric medicine	Wiley-Blackwell
The Journal of Bone and Joint Surgery	orthopedics	American Orthopaedic Association
The Journal of Cerebral Blood Flow & Metabolism	neurology	SAGE Publications
The Journal of Clinical and Aesthetic Dermatology	dermatology	Matrix Medical Communications
The Journal of Clinical and Experimental Neuropsychology	neuropsychology	Taylor & Francis
The Journal of Clinical Endocrinology and Metabolism	endocrinology	Oxford University Press
The Journal of Clinical Hypertension	hypertension	Elsevier
The Journal of Clinical Immunology	immunology	Springer
The Journal of Clinical Investigation	general medicine	American Society for Clinical Investigation
The Journal of Clinical Lipidology	lipidology	Elsevier
The Journal of Clinical Microbiology	microbiology	American Society for Microbiology
The Journal of Clinical Oncology	oncology	American Society of Clinical Oncology
The Journal of Clinical Pharmacology	pharmacology	Wiley-Blackwell
The Journal of Clinical Psychiatry	psychiatry	Physicians Postgraduate Press
The Journal of Clinical Psychology	clinical psychology	Wiley-Blackwell

The Journal of Clinical Sleep Medicine	sleep medicine	American Academy of Sleep Medicine
The Journal of Dental Research	dentistry	SAGE Publications
The Journal of Emergency Medicine	emergency medicine	Elsevier
The Journal of Geriatric Psychiatry and Neurology	geriatric psychiatry and neurology	SAGE Publications
The Journal of Hand Surgery	hand surgery	Elsevier
The Journal of Hospital Infection	infection control	Elsevier
The Journal of Hospital Medicine	hospital medicine	Wiley-Blackwell
The Journal of Infectious Diseases	infectious diseases	Oxford University Press
The Journal of Infectious Diseases and Therapy	infectious diseases	Springer
The Journal of Investigative Medicine	general medicine	SAGE Publications
The Journal of Medical Internet Research	medical informatics	JMIR Publications
The Journal of Medical Microbiology	microbiology	Microbiology Society
The Journal of Neuroscience Nursing	neuroscience nursing	American Association of Neuroscience Nurses
The Journal of Neurosurgery	neurosurgery	American Association of Neurological Surgeons
The Journal of Nuclear Medicine	nuclear medicine	Society of Nuclear Medicine
The Journal of Nuclear Medicine Technology	nuclear medicine	Society of Nuclear Medicine
The Journal of Pathology	pathology	Wiley-Blackwell
The Journal of Rheumatology	rheumatology	The Journal of Rheumatology Publishing Company
The Journal of the American Academy of Dermatology	dermatology	Elsevier

The Journal of the American Academy of Orthopaedic Surgeons	orthopedics	Wolters Kluwer
The Journal of the American Association of Nurse Practitioners	nursing	Wolters Kluwer
The Journal of the American College of Cardiology	cardiology	Elsevier
The Journal of the American College of Radiology	radiology	Elsevier
The Journal of the American College of Surgeons	surgery	Lippincott Williams & Wilkins, Inc.
The Journal of the American Dental Association	dentistry	American Dental Association
The Journal of the American Heart Association	cardiology	Wiley-Blackwell
The Journal of the American Medical Directors Association	geriatric medicine	Elsevier
The Journal of the American Medical Informatics Association	medical informatics	Oxford University Press
The Journal of the American Optometric Association	optometry	American Optometric Association
The Journal of the American Podiatric Medical Association	podiatry	American Podiatric Medical Association
The Journal of the American Society of Hypertension	hypertension	Elsevier
The Journal of the American Society of Nephrology	nephrology	Wolters Kluwer
The Journal of the National Cancer Institute	oncology	Oxford University Press
The Journal of Thoracic and Cardiovascular Surgery	thoracic and cardiovascular surgery	Elsevier
The Journal of Thoracic Oncology	thoracic oncology	Elsevier
The Journal of Urology	urology	Elsevier
The Journal of Vascular and Interventional Radiology	interventional radiology	Elsevier
The Journal of Vascular Surgery	vascular surgery	Elsevier

The Lancet	general medicine	Elsevier
The Lancet Diabetes & Endocrinology	diabetes and endocrinology	Elsevier
The Lancet Haematology	hematology	Elsevier
The Lancet Infectious Diseases	infectious diseases	Elsevier
The Lancet Neurology	neurology	Elsevier
The Lancet Oncology	oncology	Elsevier
The Lancet Public Health	public health	Elsevier
The Lancet Respiratory Medicine	respiratory medicine	Elsevier

Experimental or Investigational / Not Medically Necessary

The use of products, drugs and biologicals are considered contraindicated, experimental, investigational, unproven, or not medically necessary in the following cases:

1. The product, drug, or biologic has not received approval or clearance for any indication from the U.S. Food and Drug Administration (FDA).
2. The prescribed use is listed as a contraindication in FDA labeling.
3. The Pharmacy and Therapeutics (P&T) Committee classifies it as experimental, investigational, or unproven because the safety and/or efficacy cannot be established after reviewing the published scientific literature.
4. Indications or diagnoses in which the product has been shown to be unsafe or ineffective.
5. Continued therapy for members who have developed an absolute contraindication, significant intolerance, or have failed to achieve the intended therapeutic outcome after an adequate trial of the product.
6. The prescribed use is not supported by any of the recognized compendia :
    a. AHFS-DI or Clinical Pharmacology: The narrative text is "not supportive" (or equivalent term).
    b. DrugDex: The level of evidence for the indication is Class III in DrugDex.
    c. Lexi-Drugs: Indication is listed as "Use: Unsupported."
    d. NCCN: The level of evidence for the indication is Category 3 in NCCN.

7. There is insufficient published evidence to support the safety and efficacy of the product for the prescribed use. Evidence is considered insufficient if it primarily consists of:
    a. Observational studies, case reports, or case series.
    b. Non-randomized studies or studies with serious methodological limitations.
    c. Expert consensus panel reports or expert reviewers' comments without supporting empirical evidence.
8. The prescribed use has been shown to be unsafe or ineffective in well-designed, controlled clinical trials or meta-analyses published in peer-reviewed medical journals.

References

1. American Academy of Family Physicians. (2017, Dec). Clinical Practice Guideline Manual. https://www.aafp.org/family-physician/patient-care/clinical-recommendations/cpg-manual.html#ix
2. American College of Physicians. (n.d.). www.acponline.org. Clinical Practice Guidelines and Recommendations. https://www.acponline.org/clinical-information/clinical-guidelines-recommendations
3. American Hospital Formulary Service - Drug Information (AHFS-DI). Available at: http://www.ahfsdruginformation.com
4. Bowling F, Badrick T. Methods for determining clinical utility. Clin Biochem. 2023 Nov;121-122:110674. doi: 10.1016/j.clinbiochem.2023.110674. Epub 2023 Oct 14. PMID: 37844681.
5. Clair JS. A New Model of Tracheostomy Care: Closing the Research–Practice Gap. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 3: Implementation Issues). Rockville (MD): Agency for Healthcare Research and Quality (US); 2005 Feb. Table 1, AHRQ scale of research grades and levels. Available from: https://www.ncbi.nlm.nih.gov/books/NBK20542/table/A5857/
6. Elsevier Gold Standard Clinical Pharmacology Compendium (Clinical Pharmacology). EdElsevier Editorial Policy for Off-Label Data within Drug Information Products and Databases. Available at: https://www.elsevier.com/clinical-solutions/drug-information/editorial-policy/off-label-data
7. Halperin JL, Levine GN, Al-Khatib SM, et al. Further Evolution of the ACC/AHA Clinical Practice Guideline Recommendation Classification System, A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2016;133:1426–1428. Doi: https://doi.org/10.1161/CIR.0000000000000312
8. Hayes, Inc. What is a Hayes Rating? https://evidence.hayesinc.com/static/HRating

9. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.
10. IBM® Micromedex® DRUGDEX®. IBM Watson Health. IBM Micromedex Policy on Compendia Drug Content. Available at: https://www.ibm.com/downloads/cas/GXNB3ZG4
11. Institute for Clinical and Economic Review, Peterson Health Technology Institute. (2023, Sept). ICER-PHTI Assessment Framework for Digital Health Technologies. https://phti.com/wp-content/uploads/sites/3/2023/09/ICER-PHTI-Assessment-Framework-for-Digital-Health-Technologies.pdf
12. Micromedex. Recommendation, Evidence and Efficacy Ratings. https://www.micromedexsolutions.com/micromedex2/librarian/CS/6FDB05/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/938DAC/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=3198&contentSetId=50&title=Recommendation%2C+Evidence+and+Efficacy+Ratings&servicesTitle=Recommendation%2C+Evidence+and+Efficacy+Ratings
13. National Academies of Sciences, Engineering, and Medicine. 2011. Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press. https://doi.org/10.17226/13058.
14. National Comprehensive Cancer Network (NCCN). The NCCN Drugs and Biologics Compendium. NCCN Compendium®. Available at: https://www.nccn.org/compendia-templates/compendia/nccn-compendia
15. National Comprehensive Cancer Network. (n.d.). Development and Update of Guidelines. https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines
16. National Comprehensive Cancer Network. (n.d.). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) with NCCN Evidence Blocks™. https://www.nccn.org/guidelines/guidelines-with-evidence-blocks
17. National Institute for Health and Care Excellence. (2014, Oct). Developing NICE guidelines: the manual. Last updated: Nov 2023. https://www.nice.org.uk/process/pmg20/chapter/introduction
18. National Institute for Health and Care Excellence. (2014, Oct). Glossary. Last updated: Nov 2023. https://www.nice.org.uk/process/pmg20/chapter/glossary#randomised-controlled-trial
19. National Institute of Aging. (n.d.). NIA Glossary of Clinical Research Terms. https://www.nia.nih.gov/research/dgcg/nia-glossary-clinical-research-terms
20. National Institutes of Health. (April 2023). Glossary of Common Terms. https://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms
21. Schunemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of

GRADE - a statement by the GRADE Guidance Group. J Clin Epidemiol. 2023 May 19;159:79-84. doi: 10.1016/j.jclinepi.2023.05.010.

22. The American College of Obstetricians and Gynecologists. (2021, Sep). Clinical Consensus Methodology. https://www.acog.org/clinical/clinical-guidance/clinical-consensus/articles/2021/09/clinical-consensus-methodology
23. U.S. Department of Health and Human Service Food and Drug Administration (FDA). Center for Drug Evaluation and Research | CDER. Available at: https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder.
24. U.S. Department of Health and Human Service Food and Drug Administration (FDA). Understanding Unapproved Use of Approved Drugs "Off Label". Available at: https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label.
25. U.S. Food & Drug Administration. (2018, Jan). Step 3: Clinical Research. https://www.fda.gov/patients/drug-development-process/step-3-clinical-research
26. U.S. Food & Drug Administration. (2023, Dec). 510(k) Premarket Notification. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm
27. U.S. Food & Drug Administration. (2023, Dec). Device Classification Under Section 513(f)(2)(De Novo). https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm
28. U.S. Food & Drug Administration. (2023, Sept). In Vitro Diagnostics Emergency Use Authorizations (EUAs) - Serology and Other Adaptive Immune Response Tests for SARS-CoV-2. https://www.fda.gov/medical-devices/covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-emergency-use-authorizations-euas-serology-and-other-adaptive-immune-response
29. U.S. Food and Drug Administration (FDA). Off-label and investigational use of marketed drugs, biologics, and medical devices. Available at: https://www.fda.gov/regulatoryinformation/guidances/ucm126486.htm
30. U.S. Food and Drug Administration. Drugs@FDA. U.S. Department of Health & Human Services. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda.
31. U.S. Preventive Services Task Force. (2018, Oct). Grade Definitions. https://www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions
32. U.S. Preventive Services Task Force. (2022). A and B recommendations. https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics/uspstf-a-and-b-recommendations

33. U.S. Preventive Services Task Force. (n.d.). STANDARDS FOR GUIDELINE DEVELOPMENT. https://www.uspreventiveservicestaskforce.org/uspstf/sites/default/files/inline-files/standards-guideline-dev%20%281%29.pdf
34. Wolters Kluwer Lexi-Drugs®. Clinical Drug Information. Available at: http://www.wolterskluwercdi.com/lexicomp-online/

Clinical Guideline Revision / History Information

Original Date: 3/23/2023 Reviewed/Revised: 3/21/2024, 7/1/2025

Oscar Clinical Guideline: Xarelto (rivaroxaban) 1mg/mL Granules for Suspension (PG137, Ver. 3)

Xarelto (rivaroxaban) 1mg/mL Granules for Suspension

Disclaimer

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Summary

Xarelto (Rivaroxaban) is a medication utilized to treat or prevent blood clots. It has been designed to lower the risk of heart attack, stroke, and death in certain individuals. Additionally, Xarelto has been shown to decrease the likelihood of decreased blood flow to the legs, amputation, and serious heart problems in some patients.

Xarelto is available in two forms: tablets and granules for suspension. The tablets are taken orally, usually once daily with food, while the granules for suspension are mixed with a liquid and taken orally. The recommended dose of Xarelto may vary based on the indication and the patient's individual characteristics, such as weight, renal function, and concomitant medications.

Xarelto (Rivaroxaban) is indicated:

- to reduce the risk of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (AF).

There are limited data on the relative effectiveness of Xarelto (Rivaroxaban) and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well controlled.

- for the treatment of deep vein thrombosis (DVT).
- for the treatment of pulmonary embolism (PE).
- for the reduction in the risk of recurrence of DVT and/or PE in adult patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months.
- for the prophylaxis of DVT, which may lead to PE in adult patients undergoing knee or hip replacement surgery.
- for the prophylaxis of venous thromboembolism (VTE) and VTE-related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE, and not at high risk of bleeding.
- in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular death, myocardial infarction, and stroke) in adult patients with coronary artery disease (CAD).
- in combination with aspirin, to reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major amputation of a vascular etiology) in adult patients with peripheral artery disease (PAD), including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD.
- for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment.
- for thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

Definitions

"**Congenital heart disease**" refers to a range of conditions that are present at birth and affect the structure and function of the heart. Congenital heart disease can range from minor abnormalities to serious conditions that require ongoing medical care.

"**Coronary artery disease (CAD)**" is a condition in which the blood vessels that supply blood to the heart become narrow or blocked, reducing the flow of oxygen and nutrients to the heart. CAD can lead to chest pain (angina), heart attack, and other serious health problems.

"**Deep vein thrombosis (DVT)**" is a condition in which a blood clot forms in one of the deep veins, usually in the legs. DVT can cause swelling, pain, and redness in the affected leg, and can lead to serious complications if the clot travels to the lungs (pulmonary embolism).

"**Fontan procedure**" is a surgical treatment for certain types of congenital heart disease. It is used to redirect the flow of blood from the right side of the heart to the lungs, bypassing the heart's right ventricle and reducing the workload on the heart.

"**Nonvalvular atrial fibrillation (AF)**" is a type of irregular heartbeat in which the two upper chambers of the heart (the atria) beat in a fast and irregular manner. This can increase the risk of blood clots and stroke.

"**Parenteral**" refers to the administration of a medication or other substance into the body through a route other than the digestive tract, such as injection or infusion.

"**Prophylaxis**" refers to the use of measures to prevent the development of a disease or condition. In the context of medication, prophylaxis refers to the use of a drug to prevent the occurrence of a disease or condition.

"**Pulmonary embolism (PE)**" is a condition in which a blood clot travels to the lungs and blocks one or more blood vessels, causing chest pain, shortness of breath, and other symptoms. PE can be life-threatening if left untreated.

"**Recurrent**" refers to the occurrence of a disease, condition, or event more than once.

A "**Stroke**" is a medical condition in which the blood supply to the brain is interrupted, causing brain cells to die. Strokes can have a range of effects, including weakness or paralysis on one side of the body, difficulty speaking or understanding speech, and vision loss.

"**Systemic embolism**" refers to the obstruction of a blood vessel by an embolus, a clot or other material that has broken off from another part of the body and traveled through the bloodstream. Systemic emboli can cause serious health problems, including heart attack, stroke, and organ damage.

"**Venous thromboembolism (VTE)**" is a term used to describe a condition in which a blood clot forms in a vein and causes a blockage. VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

Medical Necessity Criteria for Authorization

The Plan considers **Xarelto (Rivaroxaban) granules for suspension** medically necessary when **ONE** of the following criteria are met:

1. The member is 18 years of age or older and there is documented evidence that the member cannot take or have Xarelto tablets appropriately administered***; OR***
2. The member is a pediatric patient <18 years of age and Xarelto (Rivaroxaban) is being prescribed for **ANY** of the following:
    a. thromboprophylaxis in members with congenital heart disease following the Fontan procedure***; or***
    b. reduce risk of recurrent venous thromboembolism (VTE) after ≥5 days of initial treatment with a parenteral anticoagulant***; or***
    c. treatment of venous thromboembolism (VTE) after ≥5 days of initial treatment with a parenteral anticoagulant.

If the above prior authorization criteria are met, Xarelto (Rivaroxaban) will be authorized for the following time frame based on its intended use:

- **60-days** for:
    - superficial vein thrombosis (acute symptomatic)***; or***
    - venous thromboembolism prophylaxis in acutely ill medical patients, nonmajor orthopedic surgery of the lower limb, or total hip or knee arthroplasty***; or***
- **6-months** for heparin-induced thrombocytopenia (treatment)***; or***
- **12-months** for all other indications.

Experimental or Investigational / Not Medically Necessary

Xarelto (Rivaroxaban) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

References

1. Alikhan R, Gomez K, Maraveyas A, et al. Cancer-associated venous thromboembolism in adults (Second edition): A British society for haematology guideline. Br J Haemetol. 2024 Jul;205(1):71-87. doi: 10.1111/bjh.19414. Epub 2024 Apr 25.
2. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 196: Thromboembolism in pregnancy. Obstet Gynecol. 2018;132(1):e1-e17. doi:10.1097/AOG.0000000000002706.
3. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med. 2018;378(8):699-707. doi:10.1056/NEJMoa1712746.
4. Barnes GD, Burnett A, Allen A, et al. Thromboembolic prevention and anticoagulant therapy during the COVID-19 pandemic: updated clinical guidance from the anticoagulation forum. J Thromb Thrombolysis. 2022 Aug;54(2):197-210. Doi: 10.1007/s11239-022-02643-3. Epub 2022 May 17.

5. Beyer-Westendorf J, Schellong SM, Gerlach H, et al; SURPRISE investigators. Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. Lancet Haematol. 2017;4(3):e105-e113. doi: 10.1016/S2352-3026(17)30014-5.
6. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020;382(21):1994-2004. doi:10.1056/NEJMoa2000052.
7. By the 2023 American Geriatrics Society Beers Criteria Update Expert Panel. American geriatrics society 2023 updated AGS Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023 Jul;71(7):2052-2081. doi:10.1111/jgs.18372. Epub 2023 May 4.
8. Crowther M. Management of heparin-induced thrombocytopenia. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
9. Crowther MA, Cuker A. Reduced-intensity rivaroxaban for the prevention of recurrent venous thromboembolism. N Engl J Med. 2017;376(13):1279-1280. doi:10.1056/NEJMe1701628.
10. Cuker A, Arepally GM, Chong BH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia. Blood Adv. 2018;2(22):3360-3392. doi:10.1182/bloodadvances.2018024489.
11. Dager WE, Gulseth MP, Nutescu EA, eds. Anticoagulation Therapy: A Clinical Practice Guide. 2nd ed. Bethesda, MD: American Society of Health-System Pharmacists; 2018.
12. Davis KA, Davis DO. Direct acting oral anticoagulants for the treatment of suspected heparin-induced thrombocytopenia. Eur J Haematol. 2017;99(4):332-335. doi:10.1111/ejh.12921.
13. Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation: a report of the American College of Cardiology Clinical Expert Consensus Document Task Force. J Am Coll Cardiol. 2017;69(7):871-898. doi:10.1016/j.jacc.2016.11.024.
14. Douketis JD, Mithoowani S. Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
15. Douketis JD, Mithoowani S. Prevention of venous thromboembolism (VTE) in adults undergoing non-major extremity orthopedic surgery. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
16. Douketis JD, Spyropoulos AC, Murad MH, et al. Perioperative management of antithrombotic therapy: an American College of Chest Physicians clinical practice guideline. Chest. 2022c;162(5):e207-e243. doi:10.1016/j.chest.2022.07.025.
17. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017;377(14):1319-1330. doi:10.1056/NEJMoa1709118.
18. European Association for the Study of the Liver. EASL clinical practice guidelines on prevention and management of bleeding and thrombosis in patients with cirrhosis. J Hepatol. 2022 May; 76(5):1151-1184. doi:10.1016/j.jhep.2021.09.003. Epub 2022 Mar 15.
19. Falanga A, Ay C, Di Nisio M, et al. Venous thromboembolism in cancer patients: ESMO clinical practice guideline. Ann Oncol. 2023 May;34(5):452-467. doi:10.1016/j.annonc.2022.12.014. Epub 2023 Jan 10.
20. Falanga A, Leader A, Ambaglio C, et al. EHA guideline on management of antithrombotic treatments in thrombocytopenic patients with cancer. Hemasphere. 2022 Jul 13;6(8):e750. doi:10.1097/HS9.0000000000000750. eCollection 2022 Aug.
21. Hull RD. Venous thromboembolism: anticoagulation after initial management. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.

22. Joglar JA, Chung MK, Armbruster AL, et al. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American college of cardiology/American heart association joint committee on clinical practice guidelines. J Am Coll Cardiol. 2024 Jan 2; 83(1):109-279. doi:10.1016/j.jacc.2023.08.017. Epub 2023 Nov 30.
23. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol. 2020;38(5):496-520. doi:10.1200/JCO.19.01461.
24. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO guideline update. J Clin Oncol. 2023 Jun 1;41(16):3063-3071. doi:10.1200/JCO.23.00294. Epub Apr 19.
25. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021;77(5):629-658. doi:10.1016/j.jacc.2020.09.011.
26. Leung LLK. Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
27. Lip GYH. Acute coronary syndrome: Anticoagulation in medically treated patients. Post TW, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com.
28. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. CHEST. 2018 Nov; 154(5):1121-1201. doi:10.1016/j.chest.2018.07.040. Epub 2018 Aug 22.
29. Lyman GH, Carrier M, Ay C, et al. American society of hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer. Blood Adv. 2021 Apr 13;5(7):1953. doi:10.1182/bloodadvances.2021004734.
30. Male C, Lensing AWA, Palumbo JS, et al. Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. Lancet Haematol. 2020;7(1):e18-e27.
31. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19. doi:10.1056/NEJMoa1112277.
32. Middeldorp S, Nieuwlaat R, Kreuziger LB, et al. American society of hematology 2023 guidelines for management of venous thromboembolism: thrombophilia testing. Blood Adv. 2023 Nov 28;7(22):7101-7138. doi:10.1182/bloodadvances.2023010177.
33. Moores LK, Tritschler T, Brosnahan S, et al. Thromboprophylaxis in patients with COVID-19: a brief update to the CHEST guideline and expert panel report. Chest. 2022 Jul;162(1):213-225. doi:10.1016/j.chest.2022.02.006. Epub 2022 Feb 12.
34. Ntaios G, Swaminathan B, Berkowitz SD, et al. Efficacy and safety of rivaroxaban versus aspirin in embolic stroke of undetermined source and carotid atherosclerosis. Stroke. 2019 Sep;50(9):2477-2485. doi:10.1161/STROKEAHA.119.025168. Epub 2019 Aug 12.
35. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):e72-e227. doi:10.1161/CIR.0000000000000923.
36. Patel SV, Liberman SA, Burgess PL. The American society of colon and rectal surgeons clinical practice guidelines for the reduction of venous thromboembolism disease in

colorectal surgery. Dis Colon Rectum. 2023 Sep 1;66(9):1162-1173. doi:10.1097/DCR.0000000000002975. Epub 2023 Jun 12.
37. Powers WJ, Rabinstein AA, Ackerson T, et al; American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):46-110. doi:10.1161/STR.0000000000000158.
38. Rosovsky RP, Kline-Rogers E, Lake L, et al. Direct oral anticoagulants in obese patients with venous thromboembolism: results of an expert consensus panel. Am J Med. 2023;136(6):523-533. doi:10.1016/j.amjmed.2023.01.010[PubMed 36803697]
39. Samama CM, Afshari A, Grønlykke L, Madsen MH, Wiberg S, Romero CS. European guidelines on peri-operative venous thromboembolism prophylaxis: first update. Eur J Anaesthesiol. 2024 Aug 1;41(8):561-569. doi:10.1097/EJA.0000000000002025. Epub 2024 Jul 10.
40. Samama CM, Laporte S, Rosencher N, et al; PRONOMOS Investigators. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. N Engl J Med. 2020;382(20):1916-1925. doi:10.1056/NEJMoa1913808.
41. Schutgens REG, Jimenez-Yuste V, Escobar M, et al. Antithrombotic treatment in patients with hemophilia: an EHA-ISTH-EAHAD-ESO clinical practice guideline. Hemasphere. 2023 Jun 5;7(6):e900. doi:10.1097/HS9.0000000000000900. eCollection 2023 Jun.
42. Sharifi M, Bay C, Vajo Z, Freeman W, Sharifi M, Schwartz F. New oral anticoagulants in the treatment of heparin-induced thrombocytopenia. Thromb Res. 2015;135(4):607-9. doi:10.1016/j.thromres.2015.01.009.
43. Shatzel JJ, Crapster-Pregont M, Deloughery TG. Non-vitamin K antagonist oral anticoagulants for heparin-induced thrombocytopenia. A systematic review of 54 reported cases. Thromb Haemost. 2016;116(2):397-400. doi:10.1160/TH16-02-0101.
44. Siegal DM, Tseng EK, Schunemann HJ, et al. ASH living guidelines on use of anticoagulation for thromboprophylaxis in patients with COVID-19: executive summary. Blood Adv 2024 Oct 22; bloodadvances.2024014219. doi:10.1182/bloodadvances.2024014219. Online ahead of print.
45. Spyropoulos AC, Ageno W, Albers GW, et al; MARINER Investigators. Rivaroxaban for thromboprophylaxis after hospitalization for medical illness. N Engl J Med. 2018;379(12):1118-1127. doi:10.1056/NEJMoa1805090.
46. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and expert panel report. Chest. 2021;160(6):e545-e608. doi:10.1016/j.chest.2021.07.055.
47. Tran PN, Tran MH. Emerging role of direct oral anticoagulants in the management of heparin-induced thrombocytopenia. Clin Appl Thromb Hemost. 2018;24(2):201-209. doi:10.1177/1076029617696582.
48. Weitz JI, Lensing AWA, Prins MH, et al; EINSTEIN CHOICE Investigators. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med. 2017;376(13):1211-1222. doi:10.1056/NEJMoa1700518.
49. Willeford A, Zhu W, Stevens C, Thomas IC. Direct oral anticoagulants versus warfarin in the treatment of left ventricular thrombus. Ann Pharmacother. 2021;55(7):839-845. doi:10.1177/1060028020975111.
50. Xarelto (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc; February 2023.

51. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36(20):2017-2023. doi:10.1200/JCO.2018.78.8034[PubMed 29746227]
52. Young G, Lensing AWA, Monagle P, et al. Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. J Thromb Haemost. 2020;18(7):1672-1685. doi:10.1111/jth.14813.
53. Yuan Z, Levitan B, Deng H, et al. Quantitative benefit-risk evaluation of rivaroxaban in patients after peripheral arterial revascularization: the VOYAGER PAD trial. J AM Heart Assoc. 2024 Apr 16;13(8):e032782. doi:10.1161/JAHA.123.032782. Epub 2024 Apr 2.

Clinical Guideline Revision / History Information

Original Date: 3/23/2023

Reviewed/Revised: 3/21/2024, 7/1/2025

Vyjuvek (beremagene geperpavec-svdt)

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Summary

Epidermolysis Bullosa (EB) is a group of inherited skin disorders characterized by exceedingly fragile skin that blisters, erodes, and scars in response to minimal friction or trauma. Four main types are EB simplex, dystrophic EB (DEB), junctional EB, and Kindler syndrome. The severity and presentation of symptoms, typically starting at birth or during infancy, differ significantly across types and subtypes. The US sees an estimated birth of 200 children per year with EB.

Dystrophic EB (DEB), caused by mutations in the COL7A1 gene that diminish or obstruct the production of type VII collagen (C7), is one such subtype. C7 is crucial for skin strength and stability, primarily constituting anchoring fibrils, structures attaching the epidermal basement membrane to the dermis. In the absence of functional C7, skin fragility intensifies and separates easily. DEB can be inherited as a dominant or recessive trait, with recessive types (RDEB) being the most severe due to mutations in both copies of the COL7A1 gene. Dominant DEB (DDEB) is milder, resulting from mutations in a single COL7A1 gene copy. It is estimated that fewer than 5000 individuals in the US live with DEB.

EB management is generally supportive, with wound care, protective bandaging, pain management, therapy, nutritional regulation, infection control, and carcinoma monitoring. Treatment usually takes place at specialized EB centers. However, there is a pressing need for treatments to improve outcomes for EB patients, especially those with dystrophic types.

Vyjuvek (beremagene geperpavec-svdt or B-VEC), a product by Krystal Biotech Inc., is the first FDA-approved treatment for wounds linked with DEB. It was approved by the FDA on 05/19/2023 for the treatment of DEB in patients aged six months or older, with either recessive or dominant DEB. Vyjuvek holds the distinction of being the first approved product in the DEB space and the first approved topical redosable gene therapy. It delivers functional human COL7A1 genes directly to the skin of affected patients, expressing functional collagen VII to form anchoring fibrils and stabilize the fragile skin.

Definitions

"**Anchoring fibrils**" are structural components of the skin that connect the epidermal basement membrane to the dermis, thereby maintaining skin integrity.

"**Beremagene geperpavec-svdt (Vyjuvek)**" is a gene therapy medication used to treat DEB. Vyjuvek introduces a functional version of the COL7A1 gene into the patient's skin cells, aiming to enable the production of collagen VII.

"**Collagen VII (C7)**" is a protein that is integral to skin strength and stability. It forms the major part of anchoring fibrils, which attach the epidermal basement membrane to the dermis.

"**COL7A1 gene**" is the gene responsible for the production of collagen VII. Mutations in this gene cause dystrophic epidermolysis bullosa.

"**Dominant DEB (DDEB)**" is a less severe form of DEB, resulting from mutations in a single copy of the COL7A1 gene.

"**Dystrophic Epidermolysis Bullosa (DEB)**" is one of the four main types of EB. It occurs due to mutations in the COL7A1 gene, which cause a reduction or absence of collagen VII production.

"**Epidermolysis Bullosa (EB)**" is a group of rare, inherited skin conditions that cause skin to become incredibly fragile, resulting in blisters and tears even from minor friction or trauma.

"**Gene therapy**" is a type of treatment that involves introducing, altering, or suppressing a gene to treat a disease.

"Geneticist"is an expert in the field of genes, hereditable diseases, and the managment and treatment of hereditable diseases.

"Genetic testing" is a general term for medical procedures aimed at analyzing a person's DNA for mutations or alterations in one's genes. Genetic tests may include, but are not limited to, targeted gene sequencing (testing for only specific genes or regions of the genome), multigene panel testing (testing multiple genes or multiple regions of the genome simultaneously), or exome sequencing (or "whole exome sequencing" assessing for gene alterations or mutations amongst only protein-coding DNA/genome).

"**Immunofluorescence Mapping (IFM)**" is a diagnostic technique used to visualize the presence and location of proteins in skin tissue. In the context of DEB, it can identify alterations or absence of type VII collagen along the basement membrane zone (BMZ).

"**Pathogenic variant**": This term refers to changes in the DNA sequence of a gene that has been confirmed to increase the risk of disease. In the context of DEB, pathogenic variants in the COL7A1 gene result in dysfunctional collagen VII production.

"**Recessive DEB (RDEB)**" is a more severe form of DEB, caused by mutations in both copies of the COL7A1 gene.

"**Squamous cell carcinoma**" is a type of skin cancer that can develop in severe cases of RDEB.

"**Transmission Electron Microscopy (TEM)**" is a microscopy technique that provides detailed, high-resolution images of cellular structures. It can be used to observe the structure of anchoring fibrils and detect subepidermal blistering in DEB patients.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Vyjuvek (beremagene geperpavec-svdt)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a geneticist, dermatologist, or pathologist who is experienced in the diagnosis and treatment of epidermolysis bullosa (EB); ***AND***
2. The member is 6 months of age or older; ***AND***
3. The member has a clinical diagnosis of dystrophic epidermolysis bullosa (DEB) confirmed by at least **ONE** of the following methods:
    a. Genetic testing techniques, such as targeted gene sequencing, multigene panel testing, exome sequencing, or other genomic methods that identify **EITHER**:
        i. recessive DEB (RDEB), confirmed by two copies of pathogenic variants (biallelic) in the collagen type VII alpha 1 chain (COL7A1) gene. The type of mutations (e.g., nonsense, missense, splice-site mutations, or small insertions/deletions) should be specified; ***or***
        ii. dominant DEB (DDEB), confirmed by a single copy of a pathogenic variant (heterozygous) in the COL7A1 gene. The specific type of mutation should be defined; ***or***
    b. Immunofluorescence Mapping (IFM) indicating altered or missing type VII collagen along the basement membrane zone (BMZ); ***or***
    c. Transmission Electron Microscopy (TEM) displaying either underdeveloped or rudimentary anchoring fibrils or subepidermal blistering; ***AND***
4. Documentation of **ALL** of the following:
    a. Measurements of wound size at baseline; ***and***
    b. A comprehensive treatment plan inclusive of wound care, pain management, nutritional support, and physical therapy as required; ***and***
    c. Vyjuvek (beremagene geperpavec-svdt) will be administered by a healthcare professional, either in a professional healthcare setting (e.g., clinic) or the home setting; ***AND***
5. The prescribed dosage meets **ONE** of the following:
    a. For members aged 6 months to <3 years, up to 0.8 mL per week (i.e., a maximum weekly dose of 1.6×10^9 plaque forming units [PFU]); ***or***
    b. For members aged 3 years and older, up to 1.6 mL per week (i.e., a maximum weekly dose of 3.2×10^9 PFU).

NOTE: *Vyjuvek (beremagene geperpavec-svdt) must be used within the aforementioned limits unless a higher quantity has been approved based on a review of a medication exception request. The prescribing provider must offer a clinical rationale for any request exceeding these dosage limits.*

If the above prior authorization criteria are met, the requested medication will be approved for an initial approval duration of 12 weeks (3 months).

Medical Necessity Criteria for Reauthorization

Reauthorization for 6 months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The requested medication is prescribed by or in consultation with a geneticist, dermatologist, or pathologist; ***AND***
2. The member has experienced a documented improvement in wound healing while on Vyjuvek (beremagene geperpavec-svdt). This improvement must be validated by clinical documentation showing a reduction in wound size, with measurements taken at baseline and at each follow-up visit, demonstrating consistent progress in healing; ***AND***
3. The member has demonstrated adherence to the Vyjuvek treatment protocol, with applications conducted regularly according to instructions, i.e., applied by a healthcare professional once a week; ***AND***
4. There is no recorded evidence of unacceptable toxicity or adverse reactions to Vyjuvek (beremagene geperpavec-svdt) that would necessitate discontinuation of treatment. Routine monitoring for common adverse events such as pruritus, chills, and skin squamous-cell carcinoma (SCC) should be reflected in the clinical chart; ***AND***
5. There is no clinical evidence indicating disease progression, as defined by a significant exacerbation of existing wounds that have been treated. This should be confirmed by clinical evaluations and documented in the member's medical record.

Experimental or Investigational / Not Medically Necessary

Vyjuvek (beremagene geperpavec-svdt) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, treatment of other skin disorders caused by genetic mutations.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
99202-99205	Office or other outpatient visit for the evaluation and management of a new patient.
99211-99215	Office or other outpatient visit for the evaluation and management of an established patient.
J3401	Beremagene geperpavec-svdt for topical administration, containing nominal 5 x 109 PFU/ml vector genomes, per 0.1 ml
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
Q81.2	Epidermolysis bullosa dystrophica
Z48.00	Encounter for change or removal of nonsurgical wound dressing
Z48.01	Encounter for change or removal of surgical wound dressing
Z48.02	Encounter for removal of sutures

Appendix

Clinical Studies

The efficacy and safety of Vyjuvek were assessed in two key clinical trials, Phase III GEM-3 and Phase I/II GEM-1, studying the effectiveness of beremagene geperpavec-svdt (B-VEC) in the treatment of dystrophic epidermolysis bullosa (DEB).

In the Phase III GEM-3 trial, the double-blind randomized placebo-controlled study included 31 participants, predominantly aged 18 years or younger, suffering from DEB. Each participant had two wounds treated weekly – one with B-VEC, and one with placebo, for a period of 26 weeks. The primary endpoint was complete wound healing at 6 months. Results indicated significantly higher wound healing in wounds treated with B-VEC) compared to those treated with placebo (67% vs. 22%, 95% CI [24-68]

p=0.002, number needed to treat [NNT]=3). The secondary end point, complete healing at 3 months, was significantly higher in those exposed to B-VEC versus placebo (71% vs. 20%, 95% CI [29-73], p<0.001, NNT=2). A total of 18 patients experienced at least 1 adverse event, most of which were mild or moderate.

The Phase I/II GEM-1 trial was a single-center open-label trial with intra-patient comparison, conducted over 12 weeks. Nine patients with RDEB were enrolled, with three enrolling twice for treatment of a new set of target wounds. The primary outcome was wound closure, defined as a reduction in wound surface area of ≥ 95% from baseline by study week 12. Results revealed that all but one target wound treated with B-VEC achieved closure after 3 months. B-VEC was found to be significantly superior to placebo for wound closure, and the time to and duration of wound closure numerically favored B-VEC over placebo.

References

1. Chen H, Marinkovich P, Gonzalez M, et al. GEM-3: Phase 3 study of beremagene geperpavec, an investigational, topical gene therapy, for the treatment of dystrophic epidermolysis bullosa. Pediatr Dermatol. 2022;39(Suppl. 1):9-10. doi:10.1111/pde.14998
2. Fine J.D., Mellerio J.E.: Epidermolysis bullosa. In Bolognia J.L., et al. (eds): Dermatology., ed 4 2018. Elsevier, Philadelphia pp. 538-553.
3. Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. N Engl J Med. 2022;387(24):2211-2219. doi:10.1056/NEJMoa2206663
4. Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. Nat Med. 2022;28(4):780-788. doi:10.1038/s41591-022-01737-y
5. Mariath LM, Santin JT, Schuler-Faccini L, Kiszewski AE. Inherited epidermolysis bullosa: update on the clinical and genetic aspects. An Bras Dermatol. 2020;95(5):551-569. doi:10.1016/j.abd.2020.05.001
6. Marinkovich M, Gonzalez M, Guide S, et al. GEM-3: phase 3 safety and immunogenicity results of beremagene geperpavec (B-VEC), an investigational, topical gene therapy for dystrophic epidermolysis bullosa (DEB). J Invest Dematol. 2022;142(8 Suppl):S79. doi:10.1016/j.jid.2022.05.474
7. Vyjuvek (beremagene geperpavec) [prescribing information]. Pittsburgh, PA: Krystal Biotech, Inc; May 2023.

Clinical Guideline Revision / History Information

Original Date: 06/29/2023
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Clinical Guideline

Oscar Clinical Guideline: Antidiabetic Agents - Glucagon-like Peptide-1 (GLP-1) Receptor Agonists (PG152, Ver. 5)

Antidiabetic Agents - Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Summary

Incretin mimetics, also known as glucagon-like peptide-1 (GLP-1) receptor agonists, are an important class of antidiabetic agents that potentiate glucose-dependent insulin secretion, suppress glucagon secretion, slow gastric emptying, and promote satiety. They are used to manage diabetes, a long-term medical condition characterized by high blood sugar levels due to the pancreas not producing enough insulin, or the body not responding effectively to insulin.

- Tirzepatide (Mounjaro) is a unique dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist. Clinical trials, including the SURPASS series, have demonstrated that tirzepatide significantly reduces hemoglobin A1c (HbA1c) levels (up to 2.8%) and body weight (up to 14.8 kg) compared to placebo, semaglutide, insulin degludec, and insulin glargine. Cardiovascular outcome studies are ongoing to assess its impact on major adverse cardiovascular events (MACE). A new single-dose vial formulation of tirzepatide is now available, offering additional administration options.
- Other notable GLP-1 receptor agonists include:
    - Exenatide extended-release (Bydureon BCise)
    - Exenatide immediate-release (Byetta)
    - Semaglutide injection (Ozempic)
    - Semaglutide oral (Rybelsus)
    - Dulaglutide (Trulicity)
    - Liraglutide (Victoza)

Several of these medications, particularly dulaglutide, liraglutide, and injectable semaglutide, have demonstrated cardiovascular benefits. They have been shown to reduce the risk of MACE in adults with T2DM and established cardiovascular disease or multiple cardiovascular risk factors, aligning with the 2025 American Diabetes Association (ADA) Standards of Medical Care in Diabetes and the 2022 American Association of Clinical Endocrinology (AACE) guidelines.

Ozempic (semaglutide) demonstrated reno-protective effects in adults with type 2 diabetes mellitus and chronic kidney disease, aligning with the 2025 American Diabetes Association (ADA) Standards of Medical Care in Diabetes.

A noteworthy safety update includes a recent warning for Ozempic (semaglutide) regarding increased reports of ileus, a potentially life-threatening intestinal blockage. Clinicians should monitor patients for signs of gastrointestinal obstruction and manage accordingly.

Management of T2DM typically involves lifestyle modifications such as diet, exercise, and weight loss. Pharmacologic therapy is often necessary to achieve glycemic control. Metformin is generally preferred for initial treatment; however, GLP-1 receptor agonists with proven cardiovascular benefits are recommended for patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk.

<u>NOTE:</u>

1. The Plan requires that members either be unable to use, or have tried and failed preferred medication(s) first. Requests for non-formulary medications are subject to Non-Formulary Products Criteria (PG069).
2. Coverage for prescription medications intended for obesity treatment, weight loss, weight reduction, or dietary control varies depending on a member's specific benefit policy. Please refer to the member's benefit plan document for information on benefit eligibility and terms of coverage. This clinical guideline specifically addresses the use of GLP-1 receptor agonists for type 2 diabetes mellitus. Other indications are managed under separate guidelines.
    a. For coverage criteria related to the use of GLP-1 receptor agonists for weight management, please refer to the Oscar Clinical Guideline: Weight Loss Agents (PG070).
    b. For coverage criteria related to Wegovy (semaglutide) for cardiovascular risk reduction in adults with established cardiovascular disease and obesity or overweight, please refer to the Oscar Clinical Guideline: Wegovy for Cardiovascular Risk Reduction (PG194).
    c. For coverage criteria related to Zepbound (tirzepatide) for the treatment of moderate-to-severe obstructive sleep apnea in adults with obesity, please refer to the Oscar Clinical Guideline: Zepbound (tirzepatide) for the Treatment of Obstructive Sleep Apnea (PG255).

Table 1: Glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics)

Classification	Drug[#]	FDA-Approved Indications
Dual Glucose-dependent Insulinotropic Polypeptide (GIP) and GLP-1 Receptor Agonists	Mounjaro (tirzepatide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1 2]
Incretin mimetics Antidiabetics	Bydureon BCise (exenatide)	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus [1 2 4 5]
	Byetta (exenatide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1 2 5]
	Ozempic (semaglutide)	Diabetes mellitus, type 2, treatment: [1 2] ● as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. ● to reduce the risk of major adverse cardiovascular

		events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease. ● to reduce the risk of sustained eGFR decline, end-stage kidney disease and cardiovascular death in adults with type 2 diabetes mellitus and chronic kidney disease.
	Rybelsus (semaglutide)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. [1] [2]
	Trulicity (dulaglutide)	Diabetes mellitus, type 2, treatment: [1] [2] ● As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus; ● risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors.
	Victoza (liraglutide)	Diabetes mellitus, type 2, treatment: [1] [6] ● As an adjunct to diet and exercise to improve glycemic control in children ≥10 years of age, adolescents, and adults with type 2 diabetes mellitus; ● risk reduction of major cardiovascular events (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease.

[#] *include both brand and generic and all dosage forms and strengths unless otherwise stated*

<u>Limitations of Use:</u>

[1] has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis

[2] is not indicated for use in patients with type 1 diabetes mellitus

[3] has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.

[4] is not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of the rat thyroid C-cell tumor findings to humans

[5] should not be used with other products containing the active ingredient exenatide.

[6] should not be coadministered with other liraglutide-containing products.

Definitions

"**Insulin**" is a hormone produced by the beta cells in the pancreas. It facilitates the entry of glucose into cells for energy production. Insufficient insulin leads to a high blood glucose level, a condition known as diabetes. Oral and injectable medications can help increase insulin production, enhance the body's sensitivity to insulin, and decrease blood sugar levels.

"**Incretin Mimetics**" are a class of medications that imitate the function of incretins, natural hormones in the body that help lower post-meal blood sugar levels. These medications, also known as glucagon-like peptide-1 (GLP-1) receptor agonists, slow digestion, prevent the liver from making too much glucose, and help the pancreas produce more insulin when needed.

"**Type 1 Diabetes**" is an autoimmune condition where the pancreas's beta cells are unable to produce sufficient insulin, leading to elevated blood glucose levels. Patients with Type 1 diabetes often require daily insulin injections to regulate their blood glucose.

"**Type 2 Diabetes**" is a metabolic disorder characterized by insufficient insulin production or insulin resistance in the body cells. It is more common than Type 1 and often managed through lifestyle changes, non-insulin medications, and, if necessary, insulin injections.

"**Blood Glucose**" is the primary sugar found in the bloodstream, serving as the body's main energy source. Chronic high blood glucose levels can lead to complications from blood vessel damage.

"**Hemoglobin A1c (HbA1c)**" is a blood test that measures average blood glucose levels over the past 2 to 3 months. It is also referred to as the A1C or glycosylated hemoglobin test. Various factors, such as age, ethnicity, certain conditions, and pregnancy, can affect A1C results.

"**Hyperglycemia**" is the medical term for high blood glucose. It can occur due to inadequate fasting (fasting hyperglycemia) or post-meal (postprandial hyperglycemia).

"**Hypoglycemia**" is a condition characterized by abnormally low blood glucose, typically less than 70 mg/dL. Symptoms include hunger, nervousness, dizziness, confusion, and in severe cases, unconsciousness. Immediate treatment involves consuming carbohydrate-rich foods or using injectable glucagon for severe cases.

"**Cardiovascular Disease**" refers to a class of diseases involving the heart and blood vessels. It is a common complication in individuals with long-term Type 2 diabetes and is often a key consideration when selecting an appropriate diabetes medication.

Medical Necessity Criteria for Initial Authorization

The Plan considers **glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics)** medically necessary when **ALL** the following criteria are met:

1. The medication is age-appropriate for the member as per the FDA-approved indications***; AND***
    - ➢ *For Bydureon BCise, Trulicity, and Victoza, the member must be 10 years of age or older.*
    - ➢ *For other glucagon-like peptide-1 (GLP-1) receptor agonists, the member must be 18 years of age or older.*
2. The member has a diagnosis of type 2 diabetes mellitus based on at least **ONE** of the following diagnostic criteria:
    a. A fasting glucose level of greater than 126 mg/dL (7.0 mmol/L)****; and/or***
    b. A 2-hour glucose tolerance test result of greater than 200 mg/dL (11.1 mmol/L)****; and/or***
    c. A hemoglobin A1c (HbA1c) level of 6.5% (48 mmol/mol) or higher****; and/or***
    d. Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia (e.g., frequent urination, extreme thirst, and unexplained weight loss) or hyperglycemic crisis***; AND***

    Important Notes: **The American Diabetes Association (ADA) "Standards of Care in Diabetes" recommends, in the absence of unequivocal hyperglycemia, diagnosis requires two abnormal results from different tests which may be obtained at the same time (e.g., A1C and FPG), or the same test at two different time points.*
        - ➢ *If two different tests are above diagnostic thresholds, this confirms the diagnosis without need for further testing.*
        - ➢ *If two different tests are used and results are discordant, the test with a result above the diagnostic cut point should be repeated.*
        - ➢ *For the Random Plasma Glucose test, a confirmatory test is not required if accompanied by classic symptoms of hyperglycemia or hyperglycemic crisis.*
3. The member has **ONE** of the following:
    a. is unable to use, or has adequately tried and failed metformin at a minimum effective dose of 1500 mg daily for at least 90 days***; or***
    b. requires combination therapy to achieve glycemic control **AND** has an HbA1c of 7.5 percent or greater***; or***

c. has established Atherosclerotic Cardiovascular Disease (ASCVD) (e.g., coronary artery disease, cerebrovascular disease, peripheral arterial disease), **AND** the request is for **ONE** of the following:
    i. Liraglutide (Victoza)***; or***
    ii. Ozempic (semaglutide)***; or***
    iii. Trulicity (dulaglutide)***; or***
d. has presence of multiple cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking, obesity, family history of premature ASCVD), **AND** the request is for Trulicity (dulaglutide)***; or***
e. has CKD with an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m^2 or greater **AND** the request is for **ONE** of the following:
    i. Liraglutide (Victoza)***; or***
    ii. Ozempic (semaglutide)***; or***
    iii. Trulicity (dulaglutide)***.***

If the above prior authorization criteria are met, the requested drug will be approved for 12-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if the member has been using the requested **GLP-1 receptor agonist** and demonstrates an ongoing clinical need for continued therapy, as evidenced by **ONE** of the following:

1. A reduction in Hemoglobin A1c (HbA1c) since initiation of therapy, documented within the past 6 months***; or***
2. Maintenance of target HbA1c levels (e.g., HbA1c less than 7% or as determined by the treating provider based on member-specific goals)***; or***
3. Improvement in fasting plasma glucose levels since initiation of therapy***; or***
4. Presence of established ASCVD, multiple cardiovascular risk factors, or Chronic Kidney Disease (CKD) **AND** the requested GLP-1 receptor agonist is **ONE** of the following agents with proven benefits in these conditions:
    a. Liraglutide (Victoza)***; or***
    b. Ozempic (semaglutide)***; or***
    c. Trulicity (dulaglutide)***.***

Experimental or Investigational / Not Medically Necessary

Glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., incretin mimetics) for any other indication is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven.

***NOTE** - This clinical guideline specifically addresses the use of GLP-1 receptor agonists for type 2 diabetes mellitus. For other indications, such as weight management and cardiovascular risk reduction, please refer to the respective clinical guidelines:*

- *Weight Loss Agents (PG070), for coverage criteria related to the use of GLP-1 receptor agonists for weight management.*
- *Wegovy for Cardiovascular Risk Reduction (PG194), for coverage criteria related to Wegovy (semaglutide) for cardiovascular risk reduction in adults with established cardiovascular disease and obesity or overweight.*

Appendix

Metformin in Type 2 Diabetes

The recommendation for a minimum effective dose of 1500 milligrams daily of metformin is derived from clinical findings which show that this dosage effectively regulates both fasting blood glucose and glycosylated hemoglobin levels - crucial markers of long-term glucose control.

Metformin functions by decreasing glucose production in the liver and enhancing insulin sensitivity in both the liver and peripheral tissues. This enhancement in turn improves the uptake and usage of glucose. The efficacy of metformin is dose-dependent, with the most clinically meaningful responses usually not seen at doses below 1500 milligrams per day.

The strategy of starting metformin treatment at a lower dose and gradually stepping up the dose over time (typically over a period of weeks) is useful in reducing the occurrence and intensity of gastrointestinal side effects. These side effects are the most common adverse reactions linked with metformin therapy and can include symptoms such as nausea, vomiting, diarrhea, abdominal cramping, and bloating. Commencing therapy at a lower dose (for instance, 500 mg twice daily or 850 mg once daily) and progressively increasing the dosage over time allows patients to better tolerate metformin. This results in improved medication adherence and ultimately, superior glycemic control.

- For patients who need further glycemic control beyond what can be achieved with a total daily dose of 2000 mg, the dosage of metformin can be boosted up to a maximum of 2550 mg per day, given in divided doses. This upper limit is based on clinical trials that show doses above this

level do not provide an additional glycemic control benefit but may increase the risk of adverse effects.

- For pediatric patients, the same principle of beginning at a lower dose and incrementally increasing applies, with a maximum limit of 2000 mg per day given in divided doses.

Table 2: Metformin in Diabetes Treatment

Clinical Consideration	Recommendation
Understanding Metformin	Metformin is frequently used due to its efficacy, cost-effectiveness, and cardiovascular benefits. However, GI adverse effects are common and could limit its use.
Managing Patient Expectations	Inform patients that side effects are often temporary and encourage patience during the dosage adjustment period.
Choosing Metformin Type	Extended-release (ER) versions are generally preferred due to fewer daily doses and reduced discontinuation rates. However, consider cost and insurance coverage.
Initiating Metformin	Start at a low dose (500 mg for ER/IR or 250 mg for those with GI intolerance history). Consider using liquid formulations or single-ingredient products for easier titration.
Dosage Increase	Gradually up titrate dosage every one to two weeks. Decrease back to the last tolerated dose if GI symptoms occur, and then try to increase more slowly.
Dosage Titration (Adults)	Dosage may be increased by 500 mg at weekly intervals until desired response or a maximum dosage is reached (2.55 g daily for immediate-release, 2.5 g for certain extended-release tablets, and 2 g for others).
Dosage Titration (Children 10–16 years)	Dosage may be increased by 500 mg at weekly intervals until desired response or a maximum dosage of 2 g daily in 2 divided doses is reached.
Maximizing Tolerance	Advice patients to take metformin during or immediately after meals. Consider dividing doses if tolerability is an issue.
Addressing Complaints	Manage common complaints such as diarrhea and nausea by temporary dose reduction. If odor of the drug is a problem, consider switching brands or generics.

GI Tolerance Issues	If GI symptoms persist, consider using 5-HT3-antagonists like ondansetron or treating underlying Helicobacter pylori infection.
Insufficient Dose Tolerance	Even lower doses can improve glucose control. Consider combining metformin with another agent if necessary.
Interrupted Therapy	If therapy is interrupted, consider a full titration when restarting. Lower the dose and increase slowly if adverse effects occur upon restarting.

References

1. American College of Obstetricians and Gynecologists (ACOG) Committee on Practice Bulletins—Obstetrics. ACOG Practice Bulletin No. 190: Gestational diabetes mellitus. Obstet Gynecol. 2018;131(2):e49-e64.
2. American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin No. 201: Pregestational diabetes mellitus. Obstet Gynecol. 2018;132(6):e228-e248. doi:10.1097/AOG.0000000000002960
3. American Diabetes Association (ADA). Standards of medical care in diabetes–2021. Diabetes Care. 2021;44(suppl 1):S1-S232.
4. American Diabetes Association Professional Practice Committee; 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S27–S49. https://doi.org/10.2337/dc25-S002
5. American Diabetes Association Professional Practice Committee; 6. Glycemic Goals and Hypoglycemia: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S128–S145. https://doi.org/10.2337/dc25-S006
6. American Diabetes Association Professional Practice Committee; 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S167–S180. https://doi.org/10.2337/dc25-S008
7. American Diabetes Association Professional Practice Committee; 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S181–S206. https://doi.org/10.2337/dc25-S009
8. American Diabetes Association Professional Practice Committee; Summary of Revisions: Standards of Care in Diabetes—2025. Diabetes Care 1 January 2025; 48 (Supplement_1): S6–S13. https://doi.org/10.2337/dc25-SREV
9. American Diabetes Association Professional Practice Committee, Draznin, B., Aroda, V. R., Bakris, G., Benson, G., Brown, F. M., Freeman, R., Green, J., Huang, E., Isaacs, D., Kahan, S., Leon, J., Lyons, S. K., Peters, A. L., Prahalad, P., Reusch, J., & Young-Hyman, D. (2022). 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Diabetes care, 45(Suppl 1), S125–S143. https://doi.org/10.2337/dc22-S009
10. American Diabetes Association Professional Practice Committee. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes-2024. Diabetes Care. 2024 Jan 1;47(Suppl 1):S145-S157. doi: 10.2337/dc24-S008. PMID: 38078578; PMCID: PMC10725806.
11. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. Diabetes Care. 2024 Jan

1;47(Suppl 1):S158-S178. doi: 10.2337/dc24-S009. Erratum in: Diabetes Care. 2024 Jul 1;47(7):1238. doi: 10.2337/dc24-er07a. PMID: 38078590; PMCID: PMC10725810.
12. American Diabetes Association Professional Practice Committee. 11. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes-2025. Diabetes Care. 2025 Jan 1;48(Supplement_1):S239-S251.
13. Anderson SL, Marrs JC. Tirzepatide for type 2 diabetes. Drugs Context. 2023 Aug 22;12:2023-6-1. doi: 10.7573/dic.2023-6-1. PMID: 37664792; PMCID: PMC10470858.
14. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, Chandrasekaran S, DeFronzo RA, Einhorn D, Galindo RJ, Gardner TW, Garg R, Garvey WT, Hirsch IB, Hurley DL, Izuora K, Kosiborod M, Olson D, Patel SB, Pop-Busui R, Sadhu AR, Samson SL, Stec C, Tamborlane WV Jr, Tuttle KR, Twining C, Vella A, Vellanki P, Weber SL. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. 2022 Oct;28(10):923-1049. doi: 10.1016/j.eprac.2022.08.002. Epub 2022 Aug 11. Erratum in: Endocr Pract. 2023 Jan;29(1):80-81. doi: 10.1016/j.eprac.2022.12.005. PMID: 35963508; PMCID: PMC10200071.
15. Blumer I, Hadar E, Hadden DR, et al. Diabetes and pregnancy: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2013;98(11):4227-4249.
16. Bosch C, Carriazo S, Soler MJ, Ortiz A, Fernandez-Fernandez B. Tirzepatide and prevention of chronic kidney disease. Clin Kidney J. 2022 Dec 23;16(5):797-808. doi: 10.1093/ckj/sfac274. PMID: 37151412; PMCID: PMC10157759.
17. Bydureon (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2022.
18. Bydureon (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2024.
19. Bydureon BCise (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2024.
20. Bydureon BCise (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2022.
21. Byetta (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; November 2024.
22. Byetta (exenatide) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; December 2022.
23. Conlin PR, Burke BV, Hobbs C, Hurren KM, Lang AE, Morrison JW, Spacek L, Steil EN, Watts SA, Weinreb JE, Pogach LM. Management of Type 2 Diabetes Mellitus: Synopsis of the Department of Veterans Affairs and Department of Defense Clinical Practice Guideline. Mayo Clin Proc. 2024 Jul 5:S0025-6196(24)00210-6. doi: 10.1016/j.mayocp.2024.04.014. Epub ahead of print. PMID: 39093266.
24. David B Sacks, Mark Arnold, George L Bakris, David E Bruns, Andrea R Horvath, Åke Lernmark, Boyd E Metzger, David M Nathan, M Sue Kirkman, Guidelines and Recommendations for Laboratory Analysis in the Diagnosis and Management of Diabetes Mellitus, Clinical Chemistry, Volume 69, Issue 8, August 2023, Pages 808–868, https://doi.org/10.1093/clinchem/hvad080
25. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2018;41(12):2669-2701. doi:10.2337/dci18-0033
26. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and Diagnosis of Diabetes: Standards of Care in Diabetes-2023. Diabetes Care 2023; 46:S19.

27. France NL, Syed YY. Tirzepatide: A Review in Type 2 Diabetes. Drugs. 2024 Feb;84(2):227-238. doi: 10.1007/s40265-023-01992-4. Epub 2024 Feb 23. PMID: 38388874.
28. Garber AJ, Handelsman Y, Grunberger G et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm 2020 executive summary. Endocr Pract. 2020; 26:107-139. [PubMed 32022600]
29. Grunberger G, Sherr J, Allende M, Blevins T, Bode B, Handelsman Y, Hellman R, Lajara R, Roberts VL, Rodbard D, Stec C, Unger J. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocr Pract. 2021 Jun;27(6):505-537. doi: 10.1016/j.eprac.2021.04.008. PMID: 34116789.
30. He L, Wang J, Ping F, et al. Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: a systematic review and meta-analysis of randomized clinical trials. JAMA Intern Med. 2022;182(5):513-519. doi:10.1001/jamainternmed.2022.0338
31. Honigberg MC, Chang LS, McGuire DK, Plutzky J, Aroda VR, Vaduganathan M. Use of Glucagon-Like Peptide-1 Receptor Agonists in Patients With Type 2 Diabetes and Cardiovascular Disease: A Review. JAMA Cardiol. 2020 Oct 1;5(10):1182-1190. doi: 10.1001/jamacardio.2020.1966. PMID: 32584928; PMCID: PMC7744318.
32. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2020;98(supp 4):S1-S115. doi:10.1016/j.kint.2020.06.019
33. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2022 Nov;102(5S):S1-S127.
34. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314.
35. LeRoith D, Biessels GJ, Braithwaite SS, et al. Treatment of diabetes in older adults: an Endocrine Society* clinical practice guideline. J Clin Endocrinol Metab. 2019;104(5):1520-1574. doi:10.1210/jc.2019-00198
36. Michos ED, Bakris GL, Rodbard HW, Tuttle KR. Glucagon-like peptide-1 receptor agonists in diabetic kidney disease: A review of their kidney and heart protection. Am J Prev Cardiol. 2023 May 24;14:100502. doi: 10.1016/j.ajpc.2023.100502. PMID: 37313358; PMCID: PMC10258236.
37. Mounjaro (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; November 2024.
38. Mounjaro (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; September 2022.
39. Ozempic (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; January 2025.
40. Ozempic (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; November 2024.
41. Ozempic (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; October 2022.
42. Qaseem A, Obley AJ, Shamliyan T, Hicks LA, Harrod CS, Crandall CJ; Clinical Guidelines Committee of the American College of Physicians; Balk EM, Cooney TG, Cross JT Jr, Fitterman N, Lin JS, Maroto M, Miller MC, Shekelle P, Tice JA, Tufte JE, Etxeandia-Ikobaltzeta I, Yost J. Newer Pharmacologic Treatments in Adults With Type 2 Diabetes: A Clinical Guideline From the

American College of Physicians. Ann Intern Med. 2024 May;177(5):658-666. doi: 10.7326/M23-2788. Epub 2024 Apr 19. PMID: 38639546; PMCID: PMC11614146.
43. Romera I, Cebrián-Cuenca A, Álvarez-Guisasola F, Gomez-Peralta F, Reviriego J. A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes. Diabetes Ther. 2019 Feb;10(1):5-19.
44. Rybelsus (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; November 2024.
45. Samson, Susan L. et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update. Endocrine Practice. Volume 29, Issue 5, 305 - 340.
46. Sattar N, McGuire DK, Pavo I, Weerakkody GJ, Nishiyama H, Wiese RJ, Zoungas S. Tirzepatide cardiovascular event risk assessment: a pre-specified meta-analysis. Nat Med. 2022 Mar;28(3):591-598. doi: 10.1038/s41591-022-01707-4. Epub 2022 Feb 24. PMID: 35210595; PMCID: PMC8938269.
47. Saxenda (liraglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; April 2023.
48. Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; November 2024.
49. Trulicity (dulaglutide) [prescribing information]. Indianapolis, IN: Eli Lilly and Company; December 2022.
50. Vaughan EM, Santiago-Delgado ZM. Management of Type 2 Diabetes Mellitus With Noninsulin Pharmacotherapy. Am Fam Physician. 2024 Apr;109(4):333-342. PMID: 38648832.
51. Victoza (liraglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; November 2024.
52. Victoza (liraglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; June 2022.
53. Wegovy (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; March 2024.
54. Wegovy (semaglutide) [prescribing information]. Plainsboro, NJ: Novo Nordisk Inc; February 2023.
55. Weinberg Sibony R, Segev O, Dor S, Raz I. Drug Therapies for Diabetes. Int J Mol Sci. 2023 Dec 5;24(24):17147. doi: 10.3390/ijms242417147. PMID: 38138975; PMCID: PMC10742594.
56. Writing Committee Members; ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure. J Card Fail. 2022 May;28(5):e1-e167.
57. Zepbound (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; October 2024.

Clinical Guideline Revision / History Information

Original Date: 06/29/2023

Reviewed/Revised: 07/31/2023, 12/19/2024, 01/30/2025, 07/01/2025

Oscar Clinical Guideline: Ycanth (cantharidin) (PG162, Ver.3)

Ycanth (cantharidin)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Molluscum contagiosum (molluscum) is a widespread skin infection caused by the molluscum virus, a dermatotropic DNA poxvirus. This condition predominantly affects children and is common worldwide. The infection results in small, flesh-colored papules and papulovesicles, measuring 1-4 mm across, which usually have a distinct umbilicated or dimpled center. These papules are typically not accompanied by much inflammation; however, when an inflammatory response is observed, it often signals the start of disease resolution.

- Although molluscum lesions are generally painless, they might itch or become irritated. Scratching or picking at the bumps can lead to autoinoculation, scarring, or secondary bacterial infections.
- The primary mode of molluscum transmission is through direct person-to-person contact or by autoinoculation. Indirect transmission can occur through touching contaminated items like towels, clothes, or toys.

- In immunocompetent individuals, molluscum contagiosum often resolves spontaneously within 6 to 12 months. Treatment may be warranted to decrease spread, relieve symptoms, or reduce duration.
- Immunocompromised individuals are at a higher risk of extensive and persistent disease.

Molluscum contagiosum is often self-limiting in immunocompetent individuals, but decision to treat may be based on risk of inoculation (to self or others via open lesion or sexual transmission in the case of genital lesions). If one chooses to treat molluscum contagiosum, management options include cryotherapy, curettage, Ycanth (cantharidin) topical solution, or podophyllotoxin. Limited data is available for other therapies (e.g., imiquimod, potassium hydroxide, topical retinoids).

Ycanth (cantharidin 0.7% topical solution) is indicated for the topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older.

- Ycanth is administered to patients only by health care providers who have received instruction and training prior to preparation and administration of Ycanth. Providers apply a single application of Ycanth to each lesion every 3 weeks as needed. The topical solution can be removed with soap and water 24 hours after treatment.
- Ycanth is for topical use only. Ycanth is not for oral, mucosal, or ophthalmic use.
- The safety and efficacy in pediatric patients below the age of 2 years have not been established.
- The safety and efficacy of drug use for longer than 12 weeks has not been established.

Definitions

"**Central Umbilication**" refers to a characteristic dimple or depression at the center of a lesion or papule.

"**Immunocompetent**" means having a functional immune system, not weakened by disease or medication.

"**Immunosuppression**" refers to a state where the immune system is suppressed, either by specific conditions like HIV, medications, or malignancies.

"**Molluscum Contagiosum**" is a viral skin infection caused by the molluscipox virus resulting in small, raised, typically painless bumps on the skin.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Ycanth (cantharidin)** medically necessary when **ALL** of the following criteria are met:

1. The member is 2 years of age or older; ***AND***
2. The member has a diagnosis of molluscum contagiosum; ***AND***
3. IF the member is immunocompetent[‡], documentation does **NOT** indicate that the member has uncomplicated, mild, molluscum contagiosum amenable to expectant observation; ***AND***

   [‡]*i.e., the member does NOT have immunosuppression caused by HIV, medications, and/or malignancy*
4. The member is unable to use (e.g., member is less than 18 years of age, as safety and efficacy has not been well established in the pediatric population), or has tried and failed Podofilox 0.5% Topical Solution.

If the above prior authorization criteria are met, Ycanth (cantharidin) will be approved for 12-weeks, up to 4 applications, with repeat applications no more frequently than every 3 weeks.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 4 additional applications (up to 4 total) will be granted if the member has recent (within the last 6 weeks) clinical documentation demonstrating:

1. Partial response evidenced by reduction in number or size of lesions but with some remaining; ***AND***
2. At least 3 weeks have passed since the last application; ***AND***
3. Total duration of therapy has not exceeded 4 applications.

   NOTE: In clinical trials, patients received up to 4 applications of Ycanth at intervals of approximately 21 days. Reauthorization requires evidence of continued benefit and allows retreatment within studied limits.

Experimental or Investigational / Not Medically Necessary

Ycanth (cantharidin) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Condylomata Acuminata, another term for genital warts, referring specifically to the raised, cauliflower-like appearance that these warts can have. They are caused by HPV and are not the same as molluscum contagiosum.
- Genital Warts, warts that appear on the genitalia and are caused by certain strains of HPV. They are not the same as molluscum contagiosum.

- Papilloma Viral Infection, benign tumors that arise from epithelial tissues and are caused by various types of the human papillomavirus (HPV).
- Sexually Transmitted Disease (STD), a broad category of diseases that are primarily transmitted through sexual contact. Both molluscum contagiosum and genital warts (caused by HPV) can be considered STDs, but the term STD includes many other diseases as well, such as chlamydia, gonorrhea, and HIV, to name a few.
- Verruca (Warts), another term for warts. These are caused by HPV and are distinct from molluscum contagiosum.
- Verruca Vulgaris, i.e., common warts, typically seen on the hands and fingers. They are caused by the human papillomavirus (HPV) and are not the same as molluscum contagiosum.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
17110	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; up to 14 lesions
17111	Destruction (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery, surgical curettement), of benign lesions other than skin tags or cutaneous vascular proliferative lesions; 15 or more lesions
46900	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; chemical
46924	Destruction of lesion(s), anus (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
54050	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), simple; chemical
54065	Destruction of lesion(s), penis (eg, condyloma, papilloma, molluscum contagiosum, herpetic vesicle), extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)

56501	Destruction of lesion(s), vulva; simple (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
56515	Destruction of lesion(s), vulva; extensive (eg, laser surgery, electrosurgery, cryosurgery, chemosurgery)
J7354	Cantharidin for topical administration, 0.7%, single unit dose applicator (3.2 mg)
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
B08.1	Molluscum contagiosum

ICD-10 codes‡ considered experimental or investigational or *not* considered medically necessary

‡*not all-inclusive*

Code	*Description*
A51	Early syphilis
A51.3	Secondary syphilis of skin and mucous membranes
A54	Gonococcal infection
A54.0	Gonococcal infection of lower genitourinary tract without periurethral or accessory gland abscess
A54.6	Gonococcal infection of anus and rectum
A56	Other sexually transmitted chlamydial diseases
A56.3	Chlamydial infection of anus and rectum
A60	Anogenital herpesviral [herpes simplex] infections
A60.0	Herpesviral infection of genitalia and urogenital tract
A60.1	Herpesviral infection of perianal skin and rectum
A60.9	Anogenital herpesviral infection, unspecified
A63	Other predominantly sexually transmitted diseases, not elsewhere classified
A63.0	Anogenital (venereal) warts
A63.8	Other specified predominantly sexually transmitted diseases
A64	Unspecified sexually transmitted disease
A66	Yaws
A66.1	Multiple papillomata and wet crab yaws
B00	Herpesviral [herpes simplex] infections

B00.8	Other forms of herpesviral infections
B00.9	Herpesviral infection, unspecified
B07	Viral warts
B07.0	Plantar wart
B07.8	Other viral warts
B07.9	Viral wart, unspecified
C51	Malignant neoplasm of vulva
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, unspecified
C60	Malignant neoplasm of penis
C60.0	Malignant neoplasm of prepuce
C60.1	Malignant neoplasm of glans penis

References

1. Eichenfield LF, McFalda W, Brabec B, et al. Safety and efficacy of VP-102, a proprietary, drug-device combination product containing cantharidin, 0.7% (w/v), in children and adults with molluscum contagiosum: two phase 3 randomized clinical trials. JAMA Dermatol. 2020;156(12):1315-1323. doi:10.1001/jamadermatol.2020.3238
2. Basdag H et al: Molluscum contagiosum: to treat or not to treat? Experience with 170 children in an outpatient clinic setting in the northeastern United States. Pediatr Dermatol. 32(3):353-7, 2015
3. Edwards S, Boffa MJ, Janier M, Calzavara-Pinton P, Rovati C, Salavastru CM, Rongioletti F, Wollenberg A, Butacu AI, Skerlev M, Tiplica GS. 2020 European guideline on the management of genital molluscum contagiosum. J Eur Acad Dermatol Venereol 2021;35;17-26.
4. Eichenfield LF et al: Safety and efficacy of VP-102 (cantharidin, 0.7% w/v) in molluscum contagiosum by body region: post hoc pooled analyses from two phase III randomized trials. J Clin Aesthet Dermatol. 14(10):42-7, 2021
5. Eichenfield LF, McFalda W, Brabec B, Siegfried E, Kwong P, McBride M, Rieger J, Willson C, Davidson M, Burnett P. Safety and Efficacy of VP-102, a Proprietary, Drug-Device Combination Product Containing Cantharidin, 0.7% (w/v), in Children and Adults With Molluscum Contagiosum: Two Phase 3 Randomized Clinical Trials. JAMA Dermatol. 2020 Dec 1;156(12):1315-1323. doi: 10.1001/jamadermatol.2020.3238.
6. Eichenfield LF, Siegfried E, Kwong P, McBride M, Rieger J, Glover D, Willson C, Davidson M, Burnett P, Olivadoti M. Pooled Results of Two Randomized Phase III Trials Evaluating VP-102, a

Drug-Device Combination Product Containing Cantharidin 0.7% (w/v) for the Treatment of Molluscum Contagiosum. Am J Clin Dermatol. 2021 Mar;22(2):257-265. doi: 10.1007/s40257-020-00570-8. Epub 2021 Feb 18.
7. Hanna D, Hatami A, Powell J, Marcoux D, Maari C, Savard P, Thibeault H, McCuaig C. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. Pediatr Dermatol. 2006 Nov-Dec;23(6):574-9. doi: 10.1111/j.1525-1470.2006.00313.x.
8. Heo JY et al: The efficacy and safety of topical 10% potassium hydroxide for molluscum contagiosum: a systematic review and meta-analysis. J Dermatolog Treat. 33(3):1682-90, 2022
9. James WD et al: Viral diseases. In: James WD et al, eds: Andrews' Diseases of the Skin: Clinical Dermatology. 13th ed. Elsevier; 2020:362-420.e8
10. Petersen BW et al: Other poxviruses that infect humans: parapoxviruses (including orf virus), molluscum contagiosum, and Yatapoxviruses. In: Bennett JE et al, eds: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Elsevier; 2020:1818-21.
11. Silverberg NB, Sidbury R, Mancini AJ. Childhood molluscum contagiosum: experience with cantharidin therapy in 300 patients. J Am Acad Dermatol. 2000 Sep;43(3):503-7. doi: 10.1067/mjd.2000.106370. PMID: 10954663.
12. Syed TA, Lundin S, Ahmad M. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. A placebo-controlled, double-blind study. Dermatology. 1994;189(1):65-68.
13. Vakharia PP et al: Efficacy and safety of topical cantharidin treatment for molluscum contagiosum and warts: a systematic review. Am J Clin Dermatol. 19(6):791-803, 2018
14. van der Wouden JC et al: Interventions for nongenital molluscum contagiosum in persons without immune deficiency. JAMA Dermatol. 154(2):203-4, 2018
15. Ycanth (cantharidin) [prescribing information]. West Chester, PA: Verrica Pharmaceuticals Inc; October 2024.

Clinical Guideline Revision / History Information

Original Date: 9/21/2023
Reviewed/Revised: 4/26/2024, 7/1/2025

Oscar Clinical Guideline: Izervay (avancincaptad pegol) (PG168, Ver. 3)

Izervay (avancincaptad pegol)

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Summary

Age-related macular degeneration (AMD) is a common progressive eye condition and a leading cause of vision loss in those over 65 years old. The most common form is dry AMD, affecting about 70-90% of AMD patients. As dry AMD advances, the risk of geographic atrophy increases. Geographic atrophy (GA), characterized by irreversible loss of retinal cells, leading to progressive vision difficulties like blurred areas or missing spots when reading, accounts for ~15% of all AMD cases. Geographic atrophy impacts daily functioning and can ultimately cause severe central vision loss or blindness.

Despite the significant burden of GA, effective treatment options have been lacking until recently. On August 4, 2023, the FDA granted approval to Izervay (avacincaptad pegol) as the first C5 complement inhibitor for GA secondary to AMD. As an overactive complement system contributes to AMD pathology, inhibiting C5 may reduce this damaging effect.

1. The monthly intravitreal injections of Izervay were studied in two phase 3 trials, GATHER1 and GATHER2, which showed significantly reduced GA lesion growth rates compared to sham

injections over 12 months. However, no differences in visual acuity were observed between the treatment and placebo groups.

2. A post-hoc analysis of the GATHER1 and GATHER2 study assessed the impact of Izervay (avancincaptad pegol) 2 mg versus sham on the impact on visual acuity measured by letter loss from baseline. There was a significant difference between Izerkay (avancincaptad pegol) and sham for loss of ≥15 works (3.4% vs. 78%) by 12 months. This difference was consistently seen for ≥10 word and ≥20 word loss. This post-hoc analysis also found a reduction in the loss of visual acuity to below driving eligibility threshold, which is a clinically meaningful outcome. However, this study is significantly limited by its post-hoc design, limited statistical analysis and power (despite pooling the GATHER1 and GATHER2 study sample to increase total size).
3. While Izervay represents an important advance as the first approved pharmacotherapy for GA, concerns exist regarding its benefit-risk profile. Increased adverse events like endophthalmitis and conversion to wet AMD were seen with Izervay versus placebo. Additionally, the lack of efficacy on visual acuity, a key goal in managing AMD, raises uncertainty about its clinical value.

Definitions

"**Age-related macular degeneration (AMD)**" is a common progressive eye disease that results in damage to the macula and central vision loss. It has two main forms - dry and wet AMD.

"**Drusen**"is yellow extracellular deposits that accumulate under the retinal pigment epithelium characterizing early AMD.

"**Dry AMD**" is the most common form of AMD (~90% cases) characterized by drusen deposits and abnormalities in the retinal pigment epithelium in the macula.

"**Endophthalmitis**" is a serious inflammation of the interior of the eye that can lead to vision loss.

"**Geographic atrophy (GA)**" is an advanced form of dry AMD defined by irreversible atrophy and loss of retinal cells leading to progressive vision impairment. Also known as atrophic AMD.

"**Idiopathic Polypoidal Choroidal Vasculopathy (IPCV)**" is a condition characterized by the presence of polypoidal, saccular dilations of blood vessels located beneath the RPE. It can lead to serous and hemorrhagic detachments of the RPE. While IPCV shares some similarities with nAMD, it's a distinct entity.

"**Intravitreal injection**" refers to injection of a medication into the vitreous humor of the eye to directly deliver the drug to the retina.

"**Macula**" is the small central area of the retina responsible for sharp, detailed central vision.

"**Neovascular Age-Related Macular Degeneration (nAMD)**" is the wet form of AMD. It is characterized by the growth of abnormal blood vessels under the retina, which can leak fluid and blood. This leads to rapid and severe central vision loss if not treated.

"**Stargardt Disease**" is an inherited form of juvenile macular degeneration. It typically begins in childhood or adolescence and is caused by mutations in specific genes. Over time, there's a progressive loss of central vision.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Izervay (avacincaptad pegol)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with an ophthalmologist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a diagnosis of geographic atrophy secondary to age-related macular degeneration supported by clinical documentation; ***AND***
4. The member does **NOT** have **ANY** of the following:
    a. active ocular or periocular infections; ***or***
    b. active intraocular inflammation; ***AND***
5. Izervay (avacincaptad pegol) is being prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, Izervay (avancincaptad pegol) will be approved for up to 12-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 12 months for **Izervay (avacincaptad pegol)** will be reviewed on a case-by-case basis and may be granted based on **BOTH** of the following:

1. The medication is prescribed by or in consultation with an ophthalmologist***; AND***
2. Clinical documentation is provided showing **ALL** of the following:

a. Continued disease stability or slowing in the growth rate of geographic atrophy lesions***; AND***
b. No evidence of unacceptable toxicity or adverse events, such as endophthalmitis, retinal detachment, or conversion to wet AMD***; AND***
c. If applicable, clinical rationale and supporting evidence for extended Izervay treatment beyond 24 months of total use.

Experimental or Investigational / Not Medically Necessary

Izervay (avacincaptad pegol) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Neovascular Age-Related Macular Degeneration (nAMD)
- Stargardt Disease
- Idiopathic Polypoidal Choroidal Vasculopathy

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
Healthcare Common Procedure Coding System (HCPCS) code	
J2782	Injection, avacincaptad pegol, 0.1 mg
CPT code for injections	
67028	Intravitreal injection of a pharmacologic agent (separate procedure)
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
H35.3113	Nonexudative age-related macular degeneration, right eye, advanced atrophic without subfoveal involvement

H35.3123	Nonexudative age-related macular degeneration, left eye, advanced atrophic without subfoveal involvement
H35.3133	Nonexudative age-related macular degeneration, bilateral, advanced atrophic without subfoveal involvement
H35.3114	Nonexudative age-related macular degeneration, right eye, advanced atrophic with subfoveal involvement
H35.3124	Nonexudative age-related macular degeneration, left eye, advanced atrophic with subfoveal involvement
H35.3134	Nonexudative age-related macular degeneration, bilateral, advanced atrophic with subfoveal involvement
H35.3193	Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic without subfoveal involvement
H35.3194	Nonexudative age-related macular degeneration, unspecified eye, advanced atrophic with subfoveal involvement

References

1. American Academy of Ophthalmology. Geographic atrophy. Accessed August 29, 2023. https://eyewiki.aao.org/Geographic_Atrophy
2. Apte R.S., et al.: Age related macular degeneration. N Engl J Med 2021; 385: pp. 539-547.
3. Cabral de Guimaraes TA, Daich Varela M, Georgiou M, Michaelides M: Treatments for dry age-related macular degeneration: therapeutic avenues, clinical trials and future directions. Br J Ophthalmol. 2022 Mar;106(3):297-304. doi: 10.1136/bjophthalmol-2020-318452. Epub 2021 Mar 19.
4. Colijn JM, et al. Enlargement of geographic atrophy from first diagnosis to end of life. JAMA Ophthalmol. 2021;139(7):743-750.
5. Danzig CJ, Khanani AM, Kaiser PK, et al. Vision loss reduction with avacincaptad pegol for geographic atrophy: a 12-month post hoc analysis of the GATHER1 and GATHER2 trials. Opthamol Retina. 2024 Nov;8(11):1052-1060. doi:10.1016/j.oret.2024.04.023. Epub 2024 May 7.
6. Flaxel C.J., et al.: American Academy of Ophthalmology preferred practice patterns: age related macular degeneration. Ophthalmology 2020; 127: pp. P1-P65.
7. Izervay (avacincaptad pegol) [prescribing information]. Parsippany, NJ: Iveric bio, Inc; February 2025.
8. Jaffe GJ, et al. C5 inhibitor avacincaptad pegol for geographic atrophy due to age-related macular degeneration. Ophthalmology. 2021;128(4):576-586.
9. Khanani AM, Patel SS, Staurenghi G, et al. Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial. The Lancet. Oct 2023;402(10411):1449-1458. doi:10.1016/s0140-6736(23)01583-0.

10. Kim BJ, Mastellos DC, Li Y, Dunaief JL, Lambris JD. Targeting complement components C3 and C5 for the retina: key concepts and lingering questions. Prog Retin Eye Res. 2021;83:100936. doi:10.1016/j.preteyeres.2020.100936
11. Tzoumas N, Riding G, Williams MA, Steel DHW. Complement inhibitors for age-related macular degeneration. Cochrane Database of Systematic Reviews 2023, Issue 6. Art. No.: CD009300. DOI: 10.1002/14651858.CD009300.pub3.

Clinical Guideline Revision / History Information

Original Date: 9/21/2023

Reviewed/Revised: 4/26/2024, 7/1/2025

Oscar Clinical Guideline: Soliris (eculizumab) (PG188, Ver. 2)

Soliris (eculizumab)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Soliris (eculizumab) is a recombinant humanized monoclonal antibody that specifically binds to the complement protein C5, inhibiting its cleavage into C5a and C5b and preventing the generation of the terminal complement complex C5b-9. Soliris (eculizumab) is FDA-approved for the following conditions:

1. Treatment of paroxysmal nocturnal hemoglobinuria (PNH)
2. Atypical hemolytic uremic syndrome (aHUS)
3. Anti-acetylcholine receptor antibody positive generalized myasthenia gravis (gMG) in adults
4. Anti-aquaporin-4 antibody positive neuromyelitis optica spectrum disorder (NMOSD) in adults.

By inhibiting terminal complement activity, Soliris (eculizumab) reduces intravascular hemolysis in PNH, complement-mediated thrombotic microangiopathy in aHUS, anti-AChR antibody-mediated neuromuscular damage in gMG, and complement-mediated injury to the central nervous system in NMOSD.

Definitions

"Acute Kidney Injury" refers to an acute condition in which there is a sudden decline in kidney function.

"**Anti-acetylcholine receptor (anti-AChR) antibodies**" are autoantibodies directed against the nicotinic acetylcholine receptor found at the neuromuscular junction.

"**Atypical hemolytic uremic syndrome (aHUS)**" is an ultra-rare, life-threatening genetic disorder caused by chronic, uncontrolled activation of the alternative complement pathway, resulting in complement-mediated thrombotic microangiopathy (TMA).

"Cholinesterase inhibitors" refer to a class of drugs that prevent the breakdown of acetylcholine, a neurotransmitter which plays a major role in memory and muscle movement and contraction.

"Expanded Disability Status Scale (EDSS)" is a clinical tool used in patients with multiple sclerosis (MS), to assess level of disability. The scale ranges from 0 to 10, with higher values associated with greater disability. See appendix, ***table 1***.

"Flow cytometry" is a tool used to rapidly assess the characteristics of a single cell using lasers in a buffered salt solution.

"**Generalized myasthenia gravis (gMG)**" is an autoimmune neuromuscular disease caused by antibodies that attack components of the neuromuscular junction (NMJ), impairing transmission between nerve and muscle, resulting in muscle weakness and fatigue.

"Immunomodulatory biologics" are large molecule drugs used to change one's immune response.

"Immunosuppressives," or immunosuppressive therapies, are any agent aimed at reducing the body's immune response, which may be used to treat conditions characterized by overactive immune systems, or to avoid rejection of bone marrow or organ transplant.

"**Myasthenia Gravis Activities of Daily Living (MG-ADL) score**" is a validated, 8-item patient-reported scale that assesses the impact of myasthenia gravis on daily functions.

"**Myasthenia Gravis Foundation of America (MGFA) Clinical Classification**" is a commonly used classification system that defines myasthenia gravis severity based on the degree and distribution of muscle weakness.

"**Neuromyelitis optica spectrum disorder (NMOSD)**" is a chronic inflammatory disorder of the central nervous system characterized by severe, immune-mediated demyelination and axonal damage predominantly targeting the optic nerves and spinal cord. The majority of patients have autoantibodies to aquaporin-4 (AQP4).

"**Paroxysmal nocturnal hemoglobinuria (PNH)**" refers to a rare, acquired, life-threatening disease of the blood characterized by complement-mediated hemolysis, thrombosis, and bone marrow failure.

"**Quantitative Myasthenia Gravis (QMG) score**" is a 13-item physician-administered scale that measures the severity of myasthenia gravis based on muscle weakness assessment.

"Relapse" refers to a deterioration or recurrence of a disease state after a temporary improvement.

"Thrombocytopenia" is a condition characterized by very low platelets in the blood.

"Thrombotic microangiopathy" refers to a group of rare disorders which is characterized by blood clots in small blood vessels, low platelet count, and the destruction of red blood cells.

"Thrombotic thrombocytopenic purpura" is a rare condition characterized by small blood clots in small blood vessels throughout the body, limiting or blocking the flow of blood to important areas of the body such as the heart, kidneys or brain.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Soliris (eculizumab)** medically necessary when ALL the following criteria are met for the applicable indication listed below:

1. Prescribed by, or in consultation with, a physician who specializes in the treatment of the specific condition:
    a. Atypical hemolytic uremic syndrome (aHUS) - hematologist or nephrologist; ***or***
    b. Generalized myasthenia gravis (gMG) - neurologist or neuromuscular disease specialist; ***or***
    c. Paroxysmal Nocturnal Hemoglobinuria (PNH) - hematologist; ***or***

d. Neuromyelitis Optica Spectrum Disorder (NMOSD) - neurologist or neuro-ophthalmologist; ***AND***

2. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., efgartigimod alfa, ravulizumab, rituximab, rozanolixizumab, zilucoplan, inebilizumab, etc.); ***AND***
3. Dosing is consistent with FDA-approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines based on indication, weight, and age; ***AND***
4. The member meets the medical necessity criteria for the applicable indication listed below:

<u>Atypical hemolytic uremic syndrome (aHUS)</u>

5. The member is at least 1 month of age; ***AND***
6. The member has a diagnosis of aHUS confirmed by ruling out:
    a. Thrombotic thrombocytopenic purpura (TTP), e.g., ADAMTS13 activity level above 5%; ***and***
    b. Shiga toxin E. coli-related HUS (STEC-HUS), e.g., STEC-test negative in members with a history of bloody diarrhea in the preceding 2-weeks; ***AND***
7. The member has documented presence of thrombotic microangiopathy, as evidenced by ALL of the following:
    a. Microangiopathic hemolytic anemia (e.g., anemia, increased LDH, decreased haptoglobin, increased indirect bilirubin, increased AST, elevated reticulocyte count, presence of schistocytes, helmet cells, and burr cells on peripheral blood smear)***; and***
    b. Thrombocytopenia, defined as a platelet count below 150,000/microliter***; and***
    c. Acute kidney injury (e.g., elevated serum creatinine, oliguria, presence of hematuria, proteinuria, pyuria, casts on urinalysis) or member requires dialysis.

<u>Generalized myasthenia gravis (gMG)</u>

5. The member is 18 years of age or older; ***AND***
6. The member has a confirmed diagnosis of generalized myasthenia gravis (gMG) **AND** documentation of **ALL** of the following:
    a. Positive serologic test for anti-acetylcholine receptor (anti-AChR) antibodies; ***and***
    b. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IV (*see* Appendix*, **Table 1***); ***and***
    c. Baseline Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of at least (≥) 6; ***AND***
7. The member is unable to use, limited by toxicity, or has adequately tried and failed or experienced insufficient response to at least **TWO** standard therapies for gMG, such as:
    a. Cholinesterase inhibitors (eg, pyridostigmine); ***and/or***

b. Corticosteroids (e.g., prednisone) or inability to taper steroids below a reasonably acceptable level without return of symptoms; ***and/or***
c. Immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, tacrolimus).

<u>Neuromyelitis Optica Spectrum Disorder (NMOSD)</u>

5. The member is 18 years of age or older; ***AND***
6. The member has confirmed diagnosis of NMOSD, as evidenced by a positive serologic test for anti-aquaporin-4 (AQP4) antibodies; ***AND***
7. The member must have experienced at least **ONE** of the following:
    a. 2 or more relapses in the 12 months prior; ***or***
    b. 3 or more relapses in the 24 months prior, with at least 1 relapse occurring within the last 12 months; ***AND***
8. The member has an Expanded Disability Status Scale (EDSS) score of ≤ 7 (i.e., presence of at least limited ambulation with aid) (*see* Appendix*, **Table 2***); ***AND***
9. Soliris (eculizumab) will NOT be initiated during a NMOSD relapse episode.

<u>Paroxysmal Nocturnal Hemoglobinuria (PNH)</u>

5. The member is at least 1 month of age; ***AND***
6. Diagnosis of PNH confirmed by flow cytometry demonstrating a deficiency of glycosylphosphatidylinositol-anchored proteins (GPI-APs) with EITHER of the following:
    a. at least 5% PNH cells (i.e., cells lacking GPI-AP expression); ***or***
    b. at least 51% of GPI-deficient poly-morphonuclear cells (e.g., neutrophils deficient in GPI-APs); ***AND***
7. The member has documentation of one or more of the following:
    a. Hemoglobin ≤ 9 g/dL with symptomatic anemia, or hemoglobin ≤ 7 g/dL; ***and/or***
    b. Absolute reticulocyte count ≥ 2 times the upper limit of normal; ***and/or***
    c. Thrombosis; ***and/or***
    d. Transfusion dependence (≥ 2 transfusions in the last 12 months).

<u>**If the above prior authorization criteria are met, Soliris (eculizumab) will be authorized for up to 6-months.**</u>

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 12-months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. Prescribed by, or in consultation with, a physician who specializes in the treatment of the specific condition:
    a. Atypical hemolytic uremic syndrome (aHUS) - hematologist or nephrologist; ***or***
    b. Generalized myasthenia gravis (gMG) - neurologist or neuromuscular disease specialist; ***or***
    c. Neuromyelitis Optica Spectrum Disorder (NMOSD) - neurologist or neuro-ophthalmologist; ***or***
    d. Paroxysmal Nocturnal Hemoglobinuria (PNH) - hematologist; ***AND***
2. There is no unacceptable toxicity or adverse reaction to therapy, such as:
    a. Serious infections (e.g. serious respiratory or urinary tract infections); ***and/or***
    b. Severe hypersensitivity reactions; ***and/or***
    c. Severe immunosuppression; ***and/or***
    d. Other intolerable side effects or reactions; ***AND***
3. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., efgartigimod alfa, ravulizumab, rituximab, rozanolixizumab, zilucoplan, etc.); ***AND***
4. Dosing is consistent with FDA-approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines based on indication, weight, and age; ***AND***
5. Ongoing therapy is required to maintain disease stability and control; ***AND***
6. Documentation of positive clinical response to therapy, such as ANY of the following:
    a. Atypical Hemolytic Uremic Syndrome (aHUS)
        i. Improvement or normalization of lactate dehydrogenase (LDH) levels and/or haptoglobin; ***and/or***
        ii. Improvement or normalization of platelet counts; ***and/or***
        iii. Improvement in serum creatinine from baseline and/or stabilization of renal function; ***and/or***
        iv. Reduction or absence of schistocytes or fragmented red blood cells on peripheral blood smear; ***and/or***
        v. Improvement in hemoglobin levels from baseline; ***or***
    b. Generalized Myasthenia Gravis
        i. Improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) **OR** Quantitative Myasthenia Gravis (QMG) score from baseline; ***and/or***
        ii. Achievement of minimal symptom expression or pharmacological remission; ***and/or***

iii. Lack of relapses or reduced frequency/severity of relapses compared to baseline; ***or***

c. Neuromyelitis Optica Spectrum Disorder
   i. Reduction in the frequency and/or severity of relapses***; and/or***
   ii. Stabilization or improvement in disability scores***; and/or***
   iii. Absence of new lesions on MRI; ***or***

d. Paroxysmal Nocturnal Hemoglobinuria (PNH)
   i. Stabilization of hemoglobin levels; ***and/or***
   ii. Decreased transfusion requirements; ***and/or***
   iii. Reduced hemolysis; ***and/or***
   iv. Improvement in PNH symptoms; ***and/or***
   v. Improvement or normalization of lactate dehydrogenase (LDH) levels.

Experimental or Investigational / Not Medically Necessary

Soliris (eculizumab) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Antibody-mediated transplant rejection (excluding cardiac and renal transplants)
- Post-transplant recurrence of atypical hemolytic uremic syndrome (aHUS)
- Shiga toxin Escherichia coli-related hemolytic uremic syndrome (STEC-HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- Concomitant use with other targeted immunomodulating biologics.
- Other complement-mediated diseases or conditions not listed above as medically necessary.
- Use in patients who have unresolved serious *Neisseria meningitidis* infection or are not adequately vaccinated against *Neisseria meningitidis.*

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)
J1300	Injection, eculizumab, 10 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
D59.3	Hemolytic-uremic syndrome
D59.30	Hemolytic-uremic syndrome, unspecified
D59.31	Infection-associated hemolytic-uremic syndrome
D59.32	Hereditary hemolytic-uremic syndrome
D59.39	Other hemolytic-uremic syndrome
D59.5	Paroxysmal nocturnal hemoglobinuria
G36.0	Neuromyelitis optica
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.2	Congenital and developmental myasthenia

Appendix

Table 1: Summary of Myasthenia Gravis Foundation of America (MGFA) Disease Clinical Classification

Class	*Description*
I	Ocular muscle weakness; All other muscles - normal strength
II	Mild generalized weakness

IIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
III	Moderate generalized weakness
IIIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
IV	Severe generalized weakness
IVa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IVb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
V	Intubation, with or without ventilation; Not for routine postoperative care

NOTE: The preceding table summarizes key aspects of the Myasthenia Gravis Foundation of America (MGFA) Disease Classifications. This is provided only for quick reference. For the exact definitions and details on the MGFA Disease Classifications, please refer to the original MGFA Classification document available at https://myasthenia.org/Portals/0/MGFA%20Classification.pdf.

Table 2: Expanded Disability Status Scale (EDSS)

Score	Description
0	Normal neurological examination, no disability in any functional system
1.0	No disability, minimal signs in one functional system
1.5	No disability, minimal signs in more than one functional system
2.0	Minimal disability in one functional system
2.5	Mild disability in one functional system or minimal disability in two functional systems
3.0	Moderate disability in one functional system, or mild disability in three or four functional systems. No walking impairment
3.5	Moderate disability in one functional system and more than minimal disability in

	several others. No walking impairment
4.0	Significant disability but self-sufficient and up and about some 12 hours a day. Able to walk without aid or rest for 500m
4.5	Significant disability but up and about much of the day. Able to work a full day. May otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200m
5.5	Disability severe enough to prevent full daily activities. Able to walk without aid or rest for 100m
6.0	Requires a walking aid – cane, crutch, etc. – to walk about 100m with or without resting
6.5	Requires two walking aids – pair of canes, crutches, etc. – to walk about 20m without resting
7.0	Unable to walk beyond approximately 5m even with aid. Essentially restricted to a wheelchair; though wheels a standard wheelchair and able to get in and out alone. Up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps. Restricted to a wheelchair and may need help getting in and out. Can wheel but cannot carry on in a standard wheelchair for a full day and may require a motorised wheelchair
8.0	Essentially restricted to a bed or chair or being pushed in wheelchair. May be out of bed much of the day. Retain many self-care functions. Generally has effective use of arms
8.5	Essentially restricted to a bed for much of the day. Has some effective use of arms, retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

NOTE: The preceding table summarizes key aspects of the Expanded Disability Status Scale (EDSS). This is provided only for quick reference. For the exact definitions and details on the EDSS, please refer to the original EDSS document available at https://mstrust.org.uk/a-z/expanded-disability-status-scale-edss

References

1. Cancado RD, Araujo AS, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematol Transfus Cell Ther. 2020 Jul 6; 43(3):341-348. doi:10.1016/j.htct.2020.05.006.
2. Cofiell R, Kukreja A, Bedard K, Yan Y, Mickle AP, Ogawa M, Bedrosian CL, Faas SJ. Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. Blood. 2015 May 21;125(21):3253-62. doi: 10.1182/blood-2014-09-600411. Epub 2015 Apr 1. PMID: 25833956; PMCID: PMC4449039.
3. Gruppo RA, Rother RP. Eculizumab for congenital atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 360:544-6. [PubMed 19179329]
4. Hillmen P, Young NS, Schubert J et al. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006; 355:1233-43. [PubMed 16990386].
5. Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. Lancet Neurol. 2017 Dec; 16(12):976-986. doi:10.1016/S147404422(17)30369-1. Epub 2017 Oct 20.
6. Kittleson MM, Patel N, Chang DH, Kransdorf EP, Kobashigawa JA, Patel JK. Eculizumab for antibody-mediated rejection in heart transplantation: a case-control study. Clin Transplant. 2021;35(12):e14454. doi:10.1111/ctr.14454[PubMed 34402096]
7. Kulkarni S, Kirkiles-Smith NC, Deng YH, et al. Eculizumab therapy for chronic antibody-mediated injury in kidney transplant recipients: a pilot randomized controlled trial. Am J Transplant. 2017;17(3):682-691. doi:10.1111/ajt.14001[PubMed 27501352]
8. Lapeyraque AL, Malina M, Fremeaux-Bacchi V et al. Eculizumab in severe Shiga-toxin-associated HUS. N Engl J Med. 2011; 364:2561-3. [PubMed 21612462]
9. Legendre CM, Licht C, Muus P et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. N Engl J Med. 2013; 368:2169-81. [PubMed 23738544].
10. Lee JW, Sicre de Fontbrune F, Wong Lee Lee L, Pessoa V, Gualandro S, Füreder W, Ptushkin V, Rottinghaus ST, Volles L, Shafner L, Aguzzi R, Pradhan R, Schrezenmeier H, Hill A. Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study. Blood. 2019 Feb 7;133(6):530-539. doi: 10.1182/blood-2018-09-876136. Epub 2018 Dec 3. PMID: 30510080; PMCID: PMC6367644.
11. Licht C, Greenbaum LA, Muus P, Babu S, Bedrosian CL, Cohen DJ, Delmas Y, Douglas K, Furman RR, Gaber OA, Goodship T, Herthelius M, Hourmant M, Legendre CM, Remuzzi G, Sheerin N, Trivelli A, Loirat C. Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. Kidney Int. 2015 May;87(5):1061-73. doi: 10.1038/ki.2014.423. Epub 2015 Feb 4. PMID: 25651368; PMCID: PMC4424817.
12. Marks WH, Mamode N, Montgomery RA, et al; C10-001 Study Group. Safety and efficacy of eculizumab in the prevention of antibody-mediated rejection in living-donor kidney transplant recipients requiring desensitization therapy: a randomized trial. Am J Transplant. 2019;19(10):2876-2888. doi:10.1111/ajt.15364[PubMed 30887675]
13. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114-122. doi:10.1212/WNL.0000000000011124[PubMed 33144515]
14. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 361:1676-87. [PubMed 19846853]

15. Nürnberger J, Philipp T, Witzke O et al. Eculizumab for atypical hemolytic-uremic syndrome. N Engl J Med. 2009; 360:542-4. [PubMed 19179328]
16. Patel JK, Coutance G, Loupy A, et al. Complement inhibition for prevention of antibody-mediated rejection in immunologically high-risk heart allograft recipients. Am J Transplant. 2021;21(7):2479-2488. doi:10.1111/ajt.16420[PubMed 33251691].
17. Pittock SJ, Berthele A, Fujihara K, Kim HJ, Levy M, Palace J, Nakashima I, Terzi M, Totolyan N, Viswanathan S, Wang KC, Pace A, Fujita KP, Armstrong R, Wingerchuk DM. Eculizumab in Aquaporin-4-Positive Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019 Aug 15;381(7):614-625. doi: 10.1056/NEJMoa1900866. Epub 2019 May 3. PMID: 31050279.
18. Pittock SJ, Fujihara K, Palace J, et al. Eculizumab monotherapy for NMOSD: data from PREVENT and its open-label extension. Mult Scler. 2022 Mar;28(3):480-486. doi:10.1177/13524585211038291. Epub 2021 Sep 9.
19. Pugh D, O'Sullivan ED, Duthie FA, Masson P, Kavanagh D. Interventions for atypical haemolytic uraemic syndrome. Cochrane Database Syst Rev. 2021 Mar 23;3(3):CD012862. doi: 10.1002/14651858.CD012862.pub2. PMID: 33783815; PMCID: PMC8078160.
20. Rees L. Atypical HUS: time to take stock of current guidelines and outcome measures?. Pediatr Nephrol. 2013; 28:675-7. [PubMed 23389238].
21. Risitano AM, Marotta S, Ricci P, Marano L, Frieri C, Cacace F, Sica M, Kulasekararaj A, Calado RT, Scheinberg P, Notaro R, Peffault de Latour R. Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT. Front Immunol. 2019 Jun 14;10:1157. doi: 10.3389/fimmu.2019.01157. PMID: 31258525; PMCID: PMC6587878.
22. Schinstock CA, Bentall AJ, Smith BH, et al. Long-term outcomes of eculizumab-treated positive crossmatch recipients: allograft survival, histologic findings, and natural history of the donor-specific antibodies. Am J Transplant. 2019;19(6):1671-1683. doi:10.1111/ajt.15175[PubMed 30412654]
23. Schmidtko J, Peine S, El-Housseini Y et al. Treatment of atypical hemolytic uremic syndrome and thrombotic microangiopathies: a focus on eculizumab. Am J Kidney Dis. 2013; 61:289-99. [PubMed 23141475]
24. Socié G, Caby-Tosi MP, Marantz JL, et al. Eculizumab in paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome: 10-year pharmacovigilance analysis. Br J Haematol. 2019;185(2):297-310. doi:10.1111/bjh.15790[PubMed 30768680]
25. Soliris (eculizumab) [prescribing information]. Boston, MA: Alexion Pharmaceuticals Inc; September 2024.
26. Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. Am J Transplant. 2011;11(11):2405-2413. doi:10.1111/j.1600-6143.2011.03757.x[PubMed 21942930]
27. Tan EK, Bentall A, Dean PG, Shaheen MF, Stegall MD, Schinstock CA. Use of eculizumab for active antibody-mediated rejection that occurs early post-kidney transplantation: a consecutive series of 15 cases. Transplantation. 2019;103(11):2397-2404. doi:10.1097/TP.0000000000002639[PubMed 30801549]
28. Tschumi S, Gugger M, Bucher BS et al. Eculizumab in atypical hemolytic uremic syndrome: long-term clinical course and histological findings. Pediatr Nephrol. 2011; 26:2085-8. [PubMed 21877169]
29. Ultomiris (ravulizumab-cwvz) [prescribing information]. Boston, MA: Alexion Pharmaceuticals Inc.; September 2024.

30. Velleca A, Shullo MA, Dhital K, et al. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2023;42(5):e1-e141. doi:10.1016/j.healun.2022.10.015[PubMed 37080658]
31. Vilalta R, Lara E, Madrid A et al. Long-term eculizumab improves clinical outcomes in atypical hemolytic uremic syndrome. Pediatr Nephrol. 2012; 27:2323-6. [Free Fulltext PMC][PubMed 22890512]
32. Wingerchuk DM, Fujihara K, Palace J, et al. Long-term safety and efficacy of eculizumab in Aquaporin-4 IgG-positive NMOSD. Ann Neurol. 2021 Jun;89(6):1088-1098. doi:10.1002/ana.26049. Epub 2021 Feb 27.
33. Yerly P, Rotman S, Regamey J, et al. Complement blockade with eculizumab to treat acute symptomatic humoral rejection after heart transplantation. Xenotransplantation. 2022;29(1):e12726. doi:10.1111/xen.12726[PubMed 35001433]
34. Young NS, Antonioli E, Rotoli B et al. Safety and efficacy of the terminal complement inhibitor eculizumab in patients with paroxysmal nocturnal hemoglobinuria: SHEPHERD phase III clincial study results. Paper presented at American Society of Hematology Annual Meeting. Orlando, FL: 2006 Dec 9.

Clinical Guideline Revision / History Information

Original Date: 3/21/2024
Reviewed/Revised: 7/1/2025

Oscar Clinical Guideline: Rystiggo (rozanolixizumab-noli) (PG190, Ver. 2)

Rystiggo (rozanolixizumab-noli)

Disclaimer

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Summary

Generalized myasthenia gravis (gMG) is a chronic autoimmune neuromuscular disorder characterized by muscle weakness and fatigue. It is caused by the production of autoantibodies that target components of the neuromuscular junction, such as the acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK). The condition leads to a breakdown in communication between nerves and muscles, resulting in weakness and fatigue of voluntary muscles.

Symptoms of gMG can vary but commonly include weakness of the eye muscles (ocular myasthenia), drooping eyelids (ptosis), blurred or double vision (diplopia), changes in facial expressions, difficulty swallowing, and shortness of breath. The severity of gMG is often classified using the Myasthenia Gravis Foundation of America (MGFA) Clinical Classification, which categorizes the disease into five main classes (I-V) based on signs, symptoms, and degree of impairment. This classification helps guide treatment decisions and assess disease progression.

Rystiggo (rozanolixizumab-noli), a neonatal Fc receptor blocker, is a prescription medicine indicated for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-AChR or anti-MuSK antibody positive. It is administered through weekly subcutaneous infusions and is designed to target the underlying autoimmune mechanisms of gMG. Management of gMG includes but is not limited to: surgical approaches, cholinesterase inhibitors (e.g., pyridostigmine), immunotherapy (e.g., corticosteroids, azathioprine, mycophenolate mofetil), and intravenous immune globulin. Those with anti-MuSK have been shown to be less responsive to cholinesterase inhibitors, and once started on corticosteroids, often find themselves steroid-dependent despite addition of other therapies. Rystiggo (rozanolixizumab-noli) is the first and only FDA-approved agent for anti-MuSK gMG.

Definitions

"**Generalized myasthenia gravis (gMG)**" is a chronic autoimmune neuromuscular disorder characterized by fluctuating weakness of voluntary muscles.

"**Anti-acetylcholine receptor (anti-AChR) antibodies**" are autoantibodies directed against the nicotinic acetylcholine receptor found at the neuromuscular junction.

"**Anti-muscle specific tyrosine kinase (anti-MuSK) antibodies**" are autoantibodies directed against the muscle-specific tyrosine kinase protein.

"Cholinesterase inhibitors" refer to a class of drugs that prevent the breakdown of acetylcholine, a neurotransmitter which plays a major role in memory and muscle movement and contraction.

"**Myasthenia Gravis Foundation of America (MGFA) Clinical Classification**" is a system that categorizes disease severity into five main classes (I-V) with subclasses based on signs, symptoms, and degree of impairment.

"**Myasthenia Gravis Activities of Daily Living (MG-ADL)**" is an 8-item patient-reported questionnaire that assesses daily functions often impacted by myasthenia gravis. Total score ranges from 0 to 24, with a higher score indicating more disability. A positive change in the score indicates worsening and a negative change indicates improvement.

"**Quantitative Myasthenia Gravis (QMG)**" is a comprehensive 13-item scale specifically designed to accurately assess the severity of myasthenia gravis. It evaluates various aspects such as endurance, fatigability, and fluctuations in symptoms. The scale assigns scores ranging from 0 to 39, with higher

scores indicating a more severe manifestation of the disease. A positive change in the score indicates worsening and a negative change indicates improvement.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Rystiggo (rozanolixizumab-noli)** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with a neurologist or neuromuscular disease specialist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a confirmed diagnosis of generalized myasthenia gravis (gMG) **AND** documentation of **ALL** of the following:
    a. Positive serologic test for anti-acetylcholine receptor (anti-AChR) OR anti-muscle specific tyrosine kinase (anti-MuSK) antibodies; ***and***
    b. Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class II to IVa (*see* Appendix, ***Table 1***); ***and***
    c. Baseline Myasthenia Gravis-Activities of Daily Living (MG-ADL) total score of at least 3 (with at least 3 points from non-ocular symptoms); ***AND***
4. **IF** anti-AChR antibody positive, the member is unable to use, limited by toxicity, or has adequately tried and failed or experienced insufficient response to at least **TWO** standard therapies for gMG, such as:
    a. Cholinesterase inhibitors (eg, pyridostigmine); ***and/or***
    b. Corticosteroids (e.g., prednisone) or inability to taper steroids below a reasonably acceptable level without return of symptoms; ***and/or***
    c. Immunosuppressive therapies (e.g., azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide, tacrolimus); ***AND***
5. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., efgartigimod alfa, rituximab, ravulizumab, zilucoplan, etc.); ***AND***
6. Prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, the requested product will be authorized for up to 16-weeks.

Medical Necessity Criteria for Reauthorization

Reauthorization for up to 6 months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. Prescribed by or in consultation with a neurologist or neuromuscular disease specialist; ***AND***
2. Documentation of positive clinical response to therapy, such as ANY of the following:
    a. Improvement in Myasthenia Gravis-Activities of Daily Living (MG-ADL) **OR** Quantitative Myasthenia Gravis (QMG) score from baseline; ***and/or***
    b. Achievement of minimal symptom expression or pharmacological remission; ***and/or***
    c. Lack of relapses or reduced frequency/severity of relapses compared to baseline; ***AND***
3. Ongoing therapy is required to maintain disease stability and control; ***AND***
4. There is no unacceptable toxicity or adverse reaction to therapy, such as:
    a. Serious infections (e.g. serious respiratory or urinary tract infections); ***and/or***
    b. Severe hypersensitivity reactions; ***and/or***
    c. Severe immunosuppression; ***and/or***
    d. Other intolerable side effects or reactions; ***AND***
5. Will not be used concomitantly with other immunomodulatory biologic therapies (e.g., efgartigimod alfa, rituximab, rozanolixizumab, ravulizumab, zilucoplan, etc.); ***AND***
6. Prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

Experimental or Investigational / Not Medically Necessary

Rystiggo (rozanolixizumab-noli) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Chronic Inflammatory Demyelinating Polyradiculoneuropathy
- Fibromyalgia
- Leucine-Rich Glioma Inactivated 1 Autoimmune Encephalitis
- Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease (MOG-AD)
- Primary Immune Thrombocytopenia (ITP)
- Thrombocytopenia

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name
CPT/HCPCS Codes considered medically necessary if criteria are met:

Code	*Description*
96369	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); initial, up to 1 hour, including pump set-up and establishment of subcutaneous infusion site(s)
96371	Subcutaneous infusion for therapy or prophylaxis (specify substance or drug); additional pump set-up with establishment of new subcutaneous infusion site(s) (List separately in addition to code for primary procedure)
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96401	Chemotherapy administration, subcutaneous or intramuscular; non-hormonal anti-neoplastic
J9333	Injection, rozanolixizumab-noli, 1 mg
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
G70.0	Myasthenia gravis
G70.00	Myasthenia gravis without (acute) exacerbation
G70.01	Myasthenia gravis with (acute) exacerbation
G70.2	Congenital and developmental myasthenia

Appendix

Table 1: Summary of Myasthenia Gravis Foundation of America (MGFA) Disease Clinical Classification

Class	*Description*
I	Ocular muscle weakness; All other muscles - normal strength
II	Mild generalized weakness
IIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible

III	Moderate generalized weakness
IIIa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IIIb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
IV	Severe generalized weakness
IVa	Predominantly limb/axial weakness; Lesser oropharyngeal involvement possible
IVb	Predominantly oropharyngeal/respiratory weakness; Lesser limb/axial involvement possible
V	Intubation, with or without ventilation; Not for routine postoperative care

NOTE: The preceding table summarizes key aspects of the Myasthenia Gravis Foundation of America (MGFA) Disease Classifications. This is provided only for quick reference. For the exact definitions and details on the MGFA Disease Classifications, please refer to the original MGFA Classification document available at https://myasthenia.org/Portals/0/MGFA%20Classification.pdf.

References

1. Bril V, Benatar M, Andersen H, MG0002 Investigator Study Group, et al. Efficacy and Safety of Rozanolixizumab in Moderate to Severe Generalized Myasthenia Gravis A Phase 2 Randomized Control Trial. Neurology Feb 2021, 96 (6) e853-e865; DOI: 10.1212/WNL.0000000000011108.
2. Bril V, Drużdż A, Grosskreutz J, and MG0003 study team. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. Lancet Neurol. 2023 May;22(5):383-394. doi: 10.1016/S1474-4422(23)00077-7. PMID: 37059507. https://pubmed.ncbi.nlm.nih.gov/37059507
3. Bril V, Druzdz A, Grosskreutz J, et al. Long-term Efficacy and Safety of Symptom-driven Cyclic Rozanolixizumab Treatment in Patients with Generalized Myasthenia Gravis: A Pooled Analysis of a Phase 3 Study and Two Open-label Extension Studies (P1-5.012). Neurology Apr 2023, 100 (17 Supplement 2) 3747; DOI: 10.1212/WNL.0000000000203497
4. Farrugia ME et al: A practical approach to managing patients with myasthenia gravis-opinions and a review of the literature. Front Neurol. 11:604, 2020
5. Gronseth GS et al: Practice advisory: thymectomy for myasthenia gravis (practice parameter update): report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 94(16):705-9, 2020
6. Guidon AC, Muppidi S, Nowak RJ, et al. Telemedicine visits in myasthenia gravis: expert guidance and the Myasthenia Gravis Core Exam (MG-CE). Muscle Nerve 2021; 64:270-276.
7. Habib AA, Sacconi S, Antonini G, et al. Efficacy and safety of rozanolixizumab in patients with muscle-specific tyrosine kinase autoantibody-positive generalised myasthenia gravis: a subgroup analysis of the randomised, double-blind, placebo-controlled, adaptive phase III MycarinG study. Ther Adv Neurol Disord. 2024 Sep 12:17:17562864241273036. doi:10.1177/17562864241273036. eCollection 2024.

8. Jaretzki A 3rd et al: Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology. 55(1):16-23, 2000
9. Jayam-Trouth A, Dabi A, Solieman N, Kurukumbi M, Kalyanam J. Myasthenia gravis: a review. Autoimmune Dis. 2012;2012:874680. doi:10.1155/2012/874680.
10. Li J, Wu X, Chu T, et al. The effiacay and safety of FcRN inhibitors in patients with myasthenia gravis: a systematic review and meta-analysis. J Neurol. 2024 May; 271(5):2298-2308. doi:10.1007/s00415-024012247-x. Epub 2024 Mar 3.
11. Ma Y, Nie X, Zhu G, et al. The efficacy and safety of different targetted drugs for the treatment of generalized Myasthenia Gravis: a systematic review and bayesian network meta-analysis. CNS Drugs. 2024 Feb;38(2):93-104. doi:10.1007/s40263-024-01062-7. Epub 2024 Feb 1.
12. Narayanaswami P, Sanders D, Wolfe G, Benatar M, et al. International consensus guidance for management of myasthenia gravis, 2020 update. Neurology® 2021;96:114-122. doi:10.1212/WNL.0000000000011124.
13. Rystiggo (rozanolixizumab) [prescribing information]. Smyrna, GA: UCB Inc; June 2024.
14. Sacca F, Pane C, Espinosa PE, et al. Efficacy and innovative therapies in myasthenia gravis: a systematic review, meta-analysis and network meta-analysis. Eur J Neurol. 2023 Dec;30(12):3854-3867. doi:10.1111/ene.15872. Epub 2023 May 30.
15. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419-425. doi:10.1212/WNL.0000000000002790
16. Smith AG, Wolfe GI, Habib AI, et al. Risk-benefit analysis of novel treatments for patients with generalized myasthenia gravis. Adv Ther. 2024 Dec; 41(12):4628-4647. doi:10.1007/s12325-024-03014-5. Epub 2024 Oct 29.
17. Sussman J et al: The Association of British Neurologists' myasthenia gravis guidelines. Ann N Y Acad Sci. 1412(1):166-9, 2018
18. Sussman J, Farrugia ME, Maddison P, et al. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015; 15: 199-206.
19. Zhong H, Li Z, Li X, et al. Initiation response, maximized therapeutic efficacy and post-treatment effects of biological targeted therapies in myasthenia gravis: a systematic review and network meta-analysis. Front Neurol. 2024 Oct 28;15:1479685. doi:10.3389/fneur.2024.1479685. eCollection 2024.

Clinical Guideline Revision / History Information

Original Date: 1/26/2024
Reviewed/Revised: 7/1/2025

Oscar Clinical Guideline: Adakveo (crizanlizumab) (PG193, Ver. 2)

Adakveo (crizanlizumab)

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Summary

Sickle cell disease (SCD) is an inherited blood disorder caused by mutations in the beta-globin gene, resulting in production of abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped. This leads to vaso-occlusion, hemolysis, and endothelial dysfunction, causing acute complications like painful vaso-occlusive crises (VOCs), acute chest syndrome (ACS), and stroke, as well as chronic organ damage. Standard preventative treatment includes hydroxyurea to increase fetal hemoglobin; l-glutamine, for regulating and preventing red blood cell oxidative damage; pain management, for both acute and chronic pain; red blood cell transfusions; and more recently, targeted therapies like voxelotor (which was withdrawn from the market in September, 2024) and Adakveo (crizanlizumab). However, many patients continue to experience recurrent severe crises despite available therapies. Allogeneic hematopoietic stem cell transplant (HSCT) can be curative but is limited by donor availability and transplant-related risks.

Adakveo (crizanlizumab), administered as a monthly intravenous infusion, is a humanized IgG2 monoclonal antibody developed by Novartis for the prevention of VOCs in patients with SCD in adults and pediatric patients aged 16 and older. It works by binding to P-selectin, a cell adhesion protein that plays a key role in the pathogenesis of VOCs. By inhibiting P-selectin, Adakveo (crizanlizumab) aims to reduce the frequency of these painful episodes.

Adakveo (crizanlizumab) received FDA approval in November 2019 based on the results of the phase 2 SUSTAIN trial[3] (NCT01895361), which showed a significant reduction in the annual rate of VOCs compared to placebo. However, the drug's efficacy and safety have been called into question following the recent phase 3 STAND trial[1] (NCT03814746), which failed to demonstrate superiority over placebo in reducing VOCs. In August 2023, the European Medicines Agency (EMA) revoked the conditional marketing authorization for crizanlizumab[7], citing concerns about its benefit-risk profile in light of the STAND trial[1] results.

Definitions

"**Sickle cell disease**" refers to a group of inherited blood disorders caused by a mutation in the beta-globin gene, resulting in abnormal hemoglobin S that polymerizes under deoxygenated conditions, causing red blood cells to become sickle-shaped and prone to hemolysis and vaso-occlusion, leading to a complex pathophysiology involving chronic inflammation, endothelial dysfunction, and end-organ damage.

"**Vaso-occlusive crisis**" refers to the hallmark acute complication of sickle cell disease caused by obstruction of blood flow in the microcirculation by sickled red blood cells, leading to tissue ischemia and severe pain, often requiring hospitalization for pain management, intravenous fluids, and other supportive care.

Policy Statement on Adakveo (crizanlizumab) Efficacy Information

Based on a review of the available evidence, including the FDA label, clinical trial data, treatment guidelines, and real-world data, the Plan considers Adakveo (crizanlizumab) unproven and not medically necessary for the prevention of vaso-occlusive crises (VOCs) in patients with sickle cell disease (SCD) at this time.

The pivotal phase 2 SUSTAIN trial[3] (NCT01895361) showed a statistically significant reduction in VOCs with high-dose crizanlizumab compared to placebo. However, the confirmatory phase 3 STAND trial[1] (NCT03814746) failed to demonstrate superiority of either crizanlizumab 5 mg/kg or 7.5 mg/kg over placebo in reducing VOCs leading to healthcare visits or managed at home. The lack of benefit seen in

STAND[1], a larger and more robust study, suggests Adakveo (crizanlizumab) may not provide a clinically meaningful benefit.

Additionally, real-world data on the use of Adakveo (crizanlizumab) is limited but conflicting. One single-center study found that while Adakveo (crizanlizumab) decreased acute care visits for VOCs in high utilizers, the discontinuation rate was extremely high, with only 1 out of 9 patients remaining on treatment by the end of the study period. Reasons for discontinuation included inability to adhere to monthly infusion appointments, perceived lack of efficacy, worsening of pain, and lack of transportation. These findings raise doubts about the real-world effectiveness and feasibility of Adakveo (crizanlizumab). Another small study looked at real-world data from 2018-2023, and found that amongst 112 patients, Adakveo (crizanlizumab) there was both a reduction in home and health-care managed VOCs, a reduction in a significant reduction in opioid use.

There are also unanswered questions regarding the long-term efficacy and safety of Adakveo (crizanlizumab). The SUSTAIN trial[3] only lasted 52 weeks, which is considered short for evaluating the impact on outcomes in a chronic disease like SCD. The effect of chronic blockade of P-selectin is unknown. Serious adverse events such as infections and infusion-related reactions have been reported.

Medical Necessity Criteria for Adakveo (crizanlizumab)

Evidence is insufficient to conclude that Adakveo (crizanlizumab) provides a clinically meaningful benefit that outweighs the risks for patients with SCD. Well-designed studies demonstrating a clear efficacy and safety advantage over existing therapies are needed. Therefore, Adakveo (crizanlizumab) is considered unproven and not medically necessary at this time. Coverage will be re-evaluated as new evidence becomes available.

Experimental or Investigational / Not Medically Necessary

Adakveo (crizanlizumab) for any indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Sickle Cell Disease (SCD),
    - The phase 3 STAND trial (n=252) failed to show a statistically significant difference in the annualized rates of VOCs leading to healthcare visits between crizanlizumab 5 mg/kg and 7.5 mg/kg vs placebo (rate ratio [RR] 1.08, 95% CI 0.76-1.55, P>.999). There was also no significant difference in the rate of VOCs managed at home or leading to healthcare visits (RR 0.83, 95% CI 0.59-1.17). These results contrast with the earlier phase

2 SUSTAIN trial and suggest crizanlizumab may not provide a clinically meaningful benefit.

- Advanced Glioblastoma / Metastatic Melanoma in the Central Nervous System / MGMT-unmethylated Glioblastoma (GBM),
- Myelofibrosis,
- Priapism, ***and***
- Retinal Vasculopathy Cerebral Leukoencephalopathy.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
J0791	Injection, crizanlizumab-tmca, 5 mg
ICD-10 Codes considered experimental or investigational or not considered medically necessary:	
Code	*Description*
D57.00	Hb-SS disease with crisis, unspecified
D57.01	Hb-SS disease with acute chest syndrome
D57.02	Hb-SS disease with splenic sequestration
D57.03	Hb-SS disease with cerebral vascular involvement
D67.04	Hb-SS disease with dactylitis
D57.09	Hb-SS disease with crisis with other specified complication
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome
D57.212	Sickle-cell/Hb-C disease with splenic sequestration

D57.213	Sickle-cell/Hb-C disease with cerebral vascular information.
D57.214	Sickle-cell HbC disease with dactylitis
D57.218	Sickle- cell/Hb disease with cerebral vascular disease
D57.219	Sickle-cell/Hb-C disease with crisis, unspecified
D.57.40	Sickle-cell thalaaemia without crisis
D57.411	Sickle-Cell Thalassemia, Unspecified, With Acute Chest Syndrome
D57.412	Sickle-Cell Thalassemia, Unspecified, With Splenic Sequestration
D57.413	Sickle-cell thalassemia, unspecified, with cerebral vascular involvement
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.418	Sickle-cell thalassemia, unspecified, with crisis with other specified complication
D57.419	Sickle-Cell Thalassemia, Unspecified, With Crisis
D57.42	Sickle-cell thalassemia beta zero without crisis
D57.431	Sickle-cell thalassemia beta zero with acute chest syndrome
D57.432	Sickle-cell thalassemia beta zero with splenic sequestration
D57.433	Sickle-cell thalassemia beta zero with cerebral vascular involvement
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.438	Sickle-cell thalassemia beta zero with crisis with other specified complication
D57.439	Sickle-cell thalassemia beta zero with crisis, unspecified
D57.44	Sickle-cell thalassemia beta plus without crisis
D57.451	Sickle-cell thalassemia beta plus with acute chest syndrome
D57.452	Sickle-cell thalassemia beta plus with splenic sequestration
D57.453	Sickle-cell thalassemia beta plus with cerebral vascular involvement
D57.454	Sickle-cell thalassemia beta plus with dactylitis
D57.458	Sickle-cell thalassemia beta plus with crisis with other specified complication
D57.459	Sickle-cell thalassemia beta plus with crisis, unspecified
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.813	Other sickle-cell disorders with cerebral vascular involvement

D57.814	Other sickle-cell disorders with dactylitis
D57.819	Other sickle-cell disorders with crisis, unspecified
H36.811	Nonproliferative sickle-cell retinopathy, right eye
H36.812	Nonproliferative sickle-cell retinopathy, left eye
H36.813	Nonproliferative sickle-cell retinopathy, bilateral
H36.819	Nonproliferative sickle-cell retinopathy, unspecified eye
H36.821	Proliferative sickle-cell retinopathy, right eye
H36.822	Proliferative sickle-cell retinopathy, left eye
H36.823	Proliferative sickle-cell retinopathy, bilateral
H36.829	Proliferative sickle-cell retinopathy, unspecified eye
O35.2XX0	Maternal care for (suspected) hereditary disease in fetus, not applicable or unspecified
O99.019	Anemia complicating pregnancy, unspecified trimester
P09.3	Abnormal findings on neonatal screening for congenital hematological disorders

References

1. Abboud MR, Cançado RD, De Montalembert M, Smith WR, Rimawi H, et. al. Efficacy, Safety, and Biomarker Analysis of 5 Mg and 7.5 Mg Doses of Crizanlizumab in Patients with Sickle Cell Disease: Primary Analyses from the Phase III STAND Study. Paper presented at 2023 American Society of Hematology (ASH) Annual Meeting in San Diego, California. December 9 - 12, 2023. Available online at: https://ash.confex.com/ash/2023/webprogram/Paper185429.html
2. Adakveo (crizanlizumab) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2022.
3. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. N Engl J Med. 2017; 376(5): 429-439. doi:10.1056/NEJMoa1611770
4. Cheplowitz H, Block S, Groesbeck J, Sacknoff S, Nguyen AL, Gopal S. Real-world data of Crizanlizumab in sickle cell disease: a single-center analysis. J Hematol. 2023; 12(3): 105-108. doi:10.14740/jh1127.
5. DeBonnett L, Joshi V, Silva-Pinto AC, et al. Real-world evidence of crizanlizumab showing reductions in vaso-occlusive and opioid usage in sick cell disease. Eur J Haematol. 2025 Feb; 114(2): 293-302. Doi: 10.1111/ejh,14323. Epub 2024 Oct 29.
6. Dick MH, Abdelgadir A, Kulkarni VV, Akram H, Chatterjee A, Pokhrel S, Khan S. Comparing the Safety and Efficacy of L-Glutamine, Voxelotor, and Crizanlizumab for Reducing the Frequency of Vaso-Occlusive Crisis in Sickle Cell Disease: A Systematic Review. Cureus. 2022 May 11;14(5):e24920. doi: 10.7759/cureus.24920. PMID: 35706735; PMCID: PMC9187358.

7. European Medicines Agency. Adakveo – Referral. https://www.ema.europa.eu/en/medicines/human/referrals/adakveo#:~:text=professional%20communications%20(DHPC)-,Overview,older%20with%20sickle%20cell%20disease
8. "European Commission (EC) Adopts Decision Endorsing CHMP Recommendation to Revoke the Conditional Marketing Authorization for Adakveo® (Crizanlizumab)." Novartis, www.novartis.com/news/european-commission-ec-adopts-decision-endorsing-chmp-recommendation-revoke-conditional-marketing-authorization-adakveo-crizanlizumab. Accessed 8 Mar. 2024.
9. Kutlar A, Kanter J, Liles DK, et al. Effect of crizanlizumab on pain crises in subgroups of patients with sickle cell disease: A SUSTAIN study analysis. Am J Hematol. 2019 Jan;94(1):55-61. doi: 10.1002/ajh.25308. Epub 2018 Nov 25. PMID: 30295335.
10. Iapoce C. STAND trial: Crizanlizumab shows no superiority over placebo for sickle cell disease. HCP Live December 9, 2023. https://www.hcplive.com/view/stand-trial-crizanlizumab-no-superiority-placebo-sickle-cell-disease
11. Sickle Cell Disease Association of America Medical and Research Advisory Committee. MARAC Statement About Crizanlizumab (Adakveo). 2023. Available online at: https://www.sicklecelldisease.org/wp-content/uploads/2023/07/H-4147-MARAC-Statement-Adaveko.pdf

Clinical Guideline Revision / History Information

Original Date: 3/21/2024
Reviewed/Revised: 7/1/2025

Oscar Clinical Guideline: Winrevair (sotatercept-csrk) (PG207, Ver. 2)

Winrevair (sotatercept-csrk)

Disclaimer

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Summary

Pulmonary arterial hypertension (PAH) is a rare, progressive disorder characterized by abnormally high blood pressure in the pulmonary arteries due to pathologic remodeling and narrowing of the small pulmonary arteries. This increased pulmonary vascular resistance strains the right side of the heart, eventually leading to right ventricular failure and premature death. PAH is classified as World Health Organization (WHO) Group 1 within the broader pulmonary hypertension categorization.

Current treatments for PAH target the prostacyclin, endothelin, and nitric oxide pathways to promote vasodilation and slow disease progression. These include endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, and prostacyclin pathway agents. However, despite combination therapy with these medications, PAH still carries high morbidity and mortality. Median survival is only 5-7 years after diagnosis, highlighting the need for novel treatment options.

Winrevair (sotatercept-csrk) is a first-in-class fusion protein that acts as a ligand trap to bind and inhibit activins and growth differentiation factors involved in the pathogenesis of PAH. By modulating signaling in the TGF-**β**/BMP pathway, Winrevair (sotatercept-csrk) has the potential to rebalance vascular homeostasis and inhibit or reverse pulmonary vascular remodeling. In the pivotal phase 3 STELLAR trial, Winrevair (sotatercept-csrk) significantly improved exercise capacity, hemodynamics, and clinical outcomes when added to standard combination therapy in patients with PAH. Winrevair (sotatercept-csrk) is indicated to improve exercise capacity, WHO functional class, and reduce the risk of clinical worsening events in adults with PAH.

Definitions

"**Pulmonary arterial hypertension (PAH)**" refers to a rare, progressive disorder characterized by abnormally high blood pressure in the pulmonary arteries that supply blood to the lungs. It is caused by pathologic narrowing and obstruction of the small pulmonary arteries. PAH is classified as WHO Group 1 pulmonary hypertension.

"**WHO functional class (FC)**" is a system to categorize the severity of functional impairment in patients with PAH based on symptom burden and activity limitation. WHO FC ranges from I to IV, with higher classes reflecting more severe symptoms and limitations.

"**6-minute walk distance (6MWD)**" is an objective measure of submaximal exercise capacity. It quantifies the distance an individual is able to walk on a flat, hard surface over a period of 6 minutes.

"**Right heart catheterization (RHC)**" refers to the gold standard diagnostic test used to definitively diagnose PAH and differentiate it from other types of pulmonary hypertension. RHC directly measures pressures in the right side of the heart and pulmonary arteries. PAH is defined hemodynamically by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg, pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 3 Wood units.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Winrevair (sotatercept-csrk)** medically necessary when **ALL** of the following criteria are met:

1. Prescribed by or in consultation with a cardiologist or pulmonologist with expertise in treating PAH; ***AND***
2. The member is 18 years of age or older; ***AND***

3. The member has a confirmed diagnosis of WHO Group 1 pulmonary arterial hypertension (PAH) that is classified as **ANY** of the following:
    a. Idiopathic; ***or***
    b. Heritable; ***or***
    c. Drug- or toxin-induced; ***or***
    d. Associated with connective tissue disease; ***or***
    e. Associated with corrected congenital systemic-to-pulmonary shunts (≥1 year after repair); ***AND***
4. The member's diagnosis has been confirmed by right catheterization showing **ALL** of the following:
    a. Mean pulmonary artery pressure (mPAP) > 20 mmHg at rest; ***and***
    b. Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg; ***and***
    c. Pulmonary vascular resistance (PVR) > 2 Wood units; ***AND***
5. The member has a World Health Organization (WHO) functional classification of either:
    a. Class II [Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.]; ***or***
    b. Class III [Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.]; ***AND***
6. The member is currently receiving a stable dose of at least two PAH-specific medications from **TWO** of the following drug classes for at least 90 days:
    a. Endothelin receptor antagonist (ERA) [e.g. bosentan, ambrisentan, macitentan]; ***and/or***
    b. Phosphodiesterase-5 inhibitor (PDE5i) [e.g. sildenafil, tadalafil]; ***and/or***
    c. Soluble guanylate cyclase (sGC) stimulator [e.g. riociguat]; ***AND***
7. The member does **NOT** have ANY of the following:
    a. HIV-associated PAH; ***or***
    b. Portopulmonary hypertension; ***or***
    c. Schistosomiasis-associated PAH; ***or***
    d. Pulmonary veno-occlusive disease; ***or***
    e. WHO Group 2, 3, 4 or 5 pulmonary hypertension; ***or***
        i. *Group 2: PH due to left heart disease.*
        ii. *Group 3: PH due to lung diseases and/or hypoxia.*
        iii. *Group 4: PH due to pulmonary artery obstructions.*
        iv. *Group 5: PH with unclear and/or multifactorial mechanisms.*
    f. Platelet count < 50,000/mm3 (50×10^9/L); ***AND***

8. Winrevair (sotatercept-csrk) is being prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.
    - *Starting dose: 0.3 mg/kg subcutaneously every 3 weeks*
    - *Target maintenance dose: 0.7 mg/kg subcutaneously every 3 weeks*

If the above prior authorization criteria are met, the requested product will be authorized for 6-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12-months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. Continues to meet the Initial Authorization criteria; ***AND***
2. Documentation of positive clinical response as demonstrated by at least **ONE** of the following:
    a. Improvement or maintenance in 6-minute walk distance; ***or***
    b. Improvement in WHO functional class; ***or***
    c. Reduction in hospitalizations for PAH; ***or***
    d. Improvement in hemodynamic parameters; ***AND***
3. There is no recorded evidence of unacceptable toxicity or adverse reactions from the drug (e.g. severe thrombocytopenia, serious bleeding).

Experimental or Investigational / Not Medically Necessary

Winrevair (sotatercept-csrk) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Pulmonary hypertension (PH) classified in WHO Groups 2-5, including:
    - PH due to left heart disease (Group 2).
    - PH due to lung diseases and/or hypoxia (Group 3).
    - Chronic thromboembolic PH (CTEPH) (Group 4).
    - PH with unclear or multifactorial etiologies (Group 5).
- Specific PAH etiologies/subgroups that were excluded from or not evaluated in the pivotal clinical trials, including:
    - PAH associated with portal hypertension.

    - HIV-associated PAH.
    - Schistosomiasis-associated PAH.
    - Pulmonary veno-occlusive disease (PVOD).
- Treatment of pediatric PAH (patients <18 years old).
- Patients with WHO functional class I or IV symptoms.

Rationale: Winrevair (sotatercept-csrk) has not been adequately studied for safety and efficacy in the above patient populations and clinical scenarios. Its FDA approval and pivotal trial data are limited to use in adults with WHO Group 1 PAH classified as idiopathic, heritable, drug-induced, or associated with connective tissue diseases or congenital heart disease. Patients had WHO FC II or III symptoms despite combination therapy with two or more PAH-specific drug classes.

- There is a lack of robust clinical trial data supporting the use of Winrevair (sotatercept-csrk) for non-Group 1 PH etiologies or the specific PAH subgroups listed above that were excluded from the STELLAR trial. Pediatric PAH patients were not included in the clinical development program. Winrevair (sotatercept-csrk) has not been evaluated in FC I or IV patients.
- The above Plan position is based on the best currently available clinical evidence for Winrevair (sotatercept-csrk) in PAH. As additional trials are published, the Plan will modify these policy statements accordingly to reflect any relevant changes in the evidence base and/or guideline recommendations. Until such time, Winrevair (sotatercept-csrk) use outside of its FDA-approved indication and pivotal trial population is considered experimental, investigational and unproven.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
96372	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
C9399	Unclassified drugs or biologicals
J3590	Unclassified biologics
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*

I27.0	Primary Pulmonary Hypertension

Appendix

Table 1: Clinical Classification of Pulmonary Hypertension

Group 1: PAH 1.1 Idiopathic 1.1.1 Long-term responders to calcium channel blockers 1.2 Heritable# 1.3 Associated with drugs and toxins# 1.4 Associated with: 1.4.1 connective tissue disease 1.4.2 HIV infection 1.4.3 portal hypertension 1.4.4 congenital heart disease 1.4.5 schistosomiasis 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement 1.6 Persistent PH of the newborn
Group 2: PH associated with left heart disease 2.1 Heart failure: 2.1.1 with preserved ejection fraction 2.1.2 with reduced or mildly reduced ejection fraction 2.1.3 cardiomyopathies with specific aetiologies¶ 2.2 Valvular heart disease: 2.2.1 aortic valve disease 2.2.2 mitral valve disease 2.2.3 mixed valvular disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
Group 3: PH associated with lung diseases and/or hypoxia 3.1 COPD and/or emphysema 3.2 Interstitial lung disease 3.3 Combined pulmonary fibrosis and emphysema 3.4 Other parenchymal lung diseases+ 3.5 Nonparenchymal restrictive diseases: 3.5.1 hypoventilation syndromes 3.5.2 pneumonectomy 3.6 Hypoxia without lung disease (e.g. high altitude) 3.7 Developmental lung diseases
Group 4: PH associated with pulmonary artery obstructions 4.1 Chronic thromboembolic PH 4.2 Other pulmonary artery obstructions§

Group 5: PH with unclear and/or multifactorial mechanisms 5.1 Haematological disorders*ƒ* 5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1 5.3 Metabolic disorders## 5.4 Chronic renal failure with or without haemodialysis 5.5 Pulmonary tumour thrombotic microangiopathy 5.6 Fibrosing mediastinitis 5.7 Complex congenital heart disease

PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis. #: patients with heritable PAH or PAH associated with drugs and toxins might be long-term responders to calcium channel blockers; ¶: hypertrophic, amyloid, Fabry disease and Chagas disease; +: parenchymal lung diseases not included in group 5; §: other causes of pulmonary artery obstructions include sarcomas (high- or intermediate-grade or angiosarcoma), other malignant tumours (e.g. renal carcinoma, uterine carcinoma, germ-cell tumours of the testis), nonmalignant tumours (e.g. uterine leiomyoma), arteritis without connective tissue disease, congenital pulmonary arterial stenoses and hydatidosis; ƒ: including inherited and acquired chronic haemolytic anaemia and chronic myeloproliferative disorders; ##: including glycogen storage diseases and Gaucher disease.

References

1. Hassoun, P. (2021). Pulmonary Arterial Hypertension.. The New England journal of medicine, 385 25, 2361-2376 . https://doi.org/10.1056/NEJMra2000348.
2. Hoeper MM et al. Phase 3 trial of sotatercept for treatment of pulmonary arterial hypertension. N Engl J Med. 2023;388(16):1478-1490.
3. Humbert M, Kovacs G, Hoeper MM, et al.: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022, 43:3618-731. 10.1093/eurheartj/ehac237
4. Humbert M, Kovacs G, Hoeper MM, et al.: 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2023, 61:10.1183/13993003.00879-2022
5. Humbert M, McLaughlin V, Gibbs JS, et al.: Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med. 2021, 384:1204-15. 10.1056/NEJMoa2024277
6. Karlyn A. Martin, Michael J. Cuttica; Chronic thromboembolic pulmonary hypertension: anticoagulation and beyond. Hematology Am Soc Hematol Educ Program 2021; 2021 (1): 478–484. doi: https://doi.org/10.1182/hematology.2021000282
7. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, Frantsve-Hawley J, Kawut SM, Ryan JJ, Rosenzweig EB, Sederstrom N, Steen VD, Badesch DB. Therapy for Pulmonary Arterial Hypertension in Adults: Update of the CHEST Guideline and Expert Panel Report. Chest. 2019 Mar;155(3):565-586. doi: 10.1016/j.chest.2018.11.030. Epub 2019 Jan 17. Erratum in: Chest. 2021 Jan;159(1):457. doi: 10.1016/j.chest.2020.11.021. PMID: 30660783.
8. Kovacs G, Bartolome S, Denton CP, et al. Definition, classification and diagnosis of pulmonary hypertension. Eur Respir J. 2024;64(4):2401324.
9. Rajagopal S, Ruetzler K, Ghadimi K, Horn EM, Kelava M, Kudelko KT, Moreno-Duarte I, Preston I, Rose Bovino LL, Smilowitz NR, Vaidya A; American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, and the Council on

Cardiovascular and Stroke Nursing. Evaluation and Management of Pulmonary Hypertension in Noncardiac Surgery: A Scientific Statement From the American Heart Association. Circulation. 2023 Apr 25;147(17):1317-1343. doi: 10.1161/CIR.0000000000001136. Epub 2023 Mar 16. PMID: 36924225.
10. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan 24;53(1):1801913. doi: 10.1183/13993003.01913-2018. PMID: 30545968; PMCID: PMC6351336.
11. Souza R, Badesch DB, Ghofrani HA, et al.: Effects of sotatercept on haemodynamics and right heart function: analysis of the STELLAR trial. Eur Respir J. 2023, 62:10.1183/13993003.01107-2023
12. Winrevair (sotatercept) [prescribing information]. Rahway, NJ: Merck Sharp & Dohme LLC; March 2024.

Clinical Guideline Revision / History Information

Original Date: 06/27/2024
Reviewed/Revised: 07/01/2025

Oscar Clinical Guideline: Lumryz (sodium oxybate) (PG246, Ver. 2)

Lumryz (sodium oxybate)

Disclaimer

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Summary

Narcolepsy is a chronic neurological sleep disorder characterized by excessive daytime sleepiness (EDS) with or without cataplexy (sudden loss of muscle tone). Current treatment options aim to manage symptoms and improve quality of life. Stimulants, wake-promoting agents like modafinil and armodafinil, and antidepressants are often used as first-line therapies. Sodium oxybate, a central nervous system depressant, is recommended for patients with narcolepsy who have an inadequate response to these treatments. Lumryz is an extended-release formulation of sodium oxybate approved for the treatment of cataplexy or EDS in adults with narcolepsy. It offers a once-nightly dosing option as an alternative to the twice-nightly immediate-release formulations.

Definitions

"**Cataplexy**" refers to a sudden, transient episode of muscle weakness accompanied by full conscious awareness, typically triggered by emotions such as laughing, crying, or terror.

"**Excessive daytime sleepiness (EDS)**" is the inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep.

"Hypocretin-1" is a natural chemical in the brain that helps regulate wakefulness.

"**Multiple Sleep Latency Test (MSLT)**" is a sleep study that measures how quickly a person falls asleep during the day and whether they enter rapid eye movement (REM) sleep.

"**Narcolepsy**" is a chronic neurological sleep disorder characterized by excessive daytime sleepiness, cataplexy, sleep paralysis, and hypnagogic hallucinations.

"Polysomnography (PSG)" is a sleep study used to diagnose sleep disorders by measuring certain components such as brain activity, oxygen levels, heart rate, breathing, eye movements, and leg movements.

"Sleep latency" is the amount of time it takes to fall asleep.

"**Sleep-onset REM periods (SOREMPs)**" are periods of rapid eye movement sleep that occur within 15 minutes of falling asleep, which are characteristic of narcolepsy.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Lumryz (sodium oxybate)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a sleep medicine specialist, neurologist, psychiatrist, or pulmonologist with expertise in treating sleep disorders; ***AND***
2. The member is 7 years of age or older; ***AND***
3. The member has a diagnosis of narcolepsy that has been confirmed by sleep lab testing or documented clinical symptoms including excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** at least **ONE** of the following:
    a. Cataplexy episodes (for narcolepsy type 1); ***or***
    b. Hypocretin-1 (orexin A) deficiency (≤110 pg/mL or <1/3 of mean values of healthy individuals tested using the same standardized assay); ***or***
    c. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency ≤ 15 minutes, or a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency ≤ 8

minutes and ≥ 2 sleep-onset REM periods (SOREMPs). A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT; ***AND***

4. The member has tried and failed prior treatments as follows:
    a. For members 18 years of age and older, the member is unable to use, or has tried and failed **ALL** of the following for at least 30-days duration each:
        i. Sunosi (solriamfetol); ***and***
        ii. Either modafinil or armodafinil; ***and***
        iii. At least **ONE** CNS stimulant, such as:
            1. amphetamine-dextroamphetamine; ***or***
            2. dextroamphetamine; ***or***
            3. methylphenidate; ***and***
        iv. For members with cataplexy - at least **ONE** antidepressant, such as:
            1. SSRIs (such as fluoxetine); ***or***
            2. SNRIs (such as venlafaxine); ***or***
            3. Tricyclic Antidepressants (such as clomipramine); ***or***
    b. For members 7 to 17 years of age, the member is unable to use, or has tried and failed the following for at least 30-days duration of at least **ONE** CNS stimulant, such as:
        i. methylphenidate***; or***
        ii. Amphetamine-based stimulant***; AND***
5. The member does **NOT** have **ANY** of the following:
    a. Succinic semialdehyde dehydrogenase (SSADH) deficiency; ***or***
    b. Documentation indicating concomitant use with, or inability to abstain from, any of the following while taking Lumryz (sodium oxybate):
        i. Alcohol (e.g., beer, wine, whisky); ***or***
        ii. Sedative hypnotics (e.g., alprazolam, diazepam, lorazepam, zolpidem); ***or***
        iii. Xyrem, Xywav, Wakix, or sodium oxybate products***; or***
    c. A condition that better explains the hypersomnolence and/or MSLT findings, such as:
        i. Insufficient sleep***; or***
        ii. Obstructive sleep apnea***; or***
        iii. Delayed sleep phase disorder***; or***
        iv. The effect of medication or substances or their withdrawal***; AND***
6. Lumryz (sodium oxybate) is being prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, the requested product will be authorized for 12-months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12-months will be granted if the member has recent (within the last 3-months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The member has experienced a positive clinical response to Lumryz (sodium oxybate) therapy as demonstrated by a reduction in symptoms of cataplexy and/or EDS; ***AND***
2. The member continues to abstain from alcohol and sedative hypnotics; ***AND***
3. Lumryz will not be used in combination with Xyrem, Xywav, Wakix, or sodium oxybate products; ***AND***
4. Lumryz continues to be prescribed at a dose and frequency that is within FDA approved labeling OR is supported by compendia or evidence-based published dosing guidelines for the requested indication.

Experimental or Investigational / Not Medically Necessary

Lumryz (sodium oxybate) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- When used in combination with alcohol, sedative hypnotics, or other medications containing sodium oxybate, gamma-hydroxybutyrate (GHB), or GHB precursors.
- When used in members with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
- For members under 7 years of age, safety and efficacy have not been established in pediatric populations.

References

1. Aurora RN, Lamm CI, Zak RS, Kristo DA, Bista SR, Rowley JA, Casey KR. Practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing for children. Sleep. 2012 Nov 1;35(11):1467-73. doi: 10.5665/sleep.2190. PMID: 23115395; PMCID: PMC3466793.
2. Howell M, Avidan AY, Foldvary-Schaefer N, Malkani RG, During EH, Roland JP, McCarter SJ, Zak RS, Carandang G, Kazmi U, Ramar K. Management of REM sleep behavior disorder: an American

Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2023 Apr 1;19(4):759-768. doi: 10.5664/jcsm.10424. PMID: 36515157; PMCID: PMC10071384.
3. Lumryz (sodium oxybate) [prescribing information]. Chesterfield, MO: Avadel CNS Pharmaceuticals, LLC; May 2023.
4. Lumryz (sodium oxybate) [prescribing information]. Chesterfield, MO: Avadel CNS Pharmaceuticals, LLC; October 2024.
5. Maski K, Trotti LM, Kotagal S, Robert Auger R, Rowley JA, Hashmi SD, Watson NF. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Sep 1;17(9):1881-1893. doi: 10.5664/jcsm.9328. PMID: 34743789; PMCID: PMC8636351.

Clinical Guideline Revision / History Information

Original Date: 09/18/2024
Reviewed/Revised: 07/01/2025

Xywav (calcium, magnesium, potassium, and sodium oxybates)

Summary

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness (EDS) and abnormal rapid eye movement (REM) sleep manifestations, including cataplexy, sleep paralysis, and hypnagogic hallucinations. It affects approximately 1 in 2,000 people in the United States. Idiopathic hypersomnia (IH) is a neurological sleep disorder characterized by excessive daytime sleepiness despite adequate or prolonged nighttime sleep.

First-line treatments for narcolepsy typically include central nervous system stimulants (e.g., modafinil, armodafinil, methylphenidate, amphetamines) for EDS, and sodium oxybate or antidepressants (e.g., SSRIs, SNRIs, TCAs) for cataplexy. For idiopathic hypersomnia, similar wake-promoting medications are used as first-line treatments.

Xywav (calcium, magnesium, potassium, and sodium oxybates) is a central nervous system depressant approved by the FDA for the treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy, and for the treatment of idiopathic hypersomnia in adults. It offers a lower-sodium alternative to Xyrem (sodium oxybate) and is typically considered after other treatments have failed or are contraindicated.

Definitions

"**Cataplexy**" refers to a sudden, transient episode of muscle weakness accompanied by full conscious awareness, typically triggered by emotions such as laughing, crying, or terror.

"**Excessive daytime sleepiness (EDS)**" is the inability to stay awake and alert during the day, resulting in unintended lapses into drowsiness or sleep.

"**Hypnagogic hallucinations**" are vivid, often frightening, dreamlike experiences that occur while falling asleep.

"Hypocretin-1" is a natural chemical in the brain that helps regulate wakefulness.

"**Idiopathic hypersomnia (IH)**" is a neurological disorder characterized by excessive daytime sleepiness that is not caused by disturbed sleep at night, other medical conditions, or medications.

"**Multiple Sleep Latency Test (MSLT)**" is a sleep study that measures how quickly a person falls asleep during the day and whether they enter rapid eye movement (REM) sleep.

"**Narcolepsy**" is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles.

"Polysomnography (PSG)" is a sleep study used to diagnose sleep disorders by measuring certain components such as brain activity, oxygen levels, heart rate, breathing, eye movements, and leg movements.

"Sleep latency" is the amount of time it takes to fall asleep.

"**Sleep-onset REM periods (SOREMPs)**" are periods of rapid eye movement sleep that occur within 15 minutes of falling asleep, which are characteristic of narcolepsy.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Xywav (calcium, magnesium, potassium, and sodium oxybates)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a sleep medicine specialist, neurologist, psychiatrist, or pulmonologist with expertise in treating sleep disorders***; AND***
2. The member meets the age requirement for the intended use:
    a. For treatment of cataplexy or excessive daytime sleepiness (EDS) in narcolepsy - the member is 7 years of age or older***; or***
    b. For treatment of idiopathic hypersomnia (IH) - the member is 18 years of age or older***; AND***
3. The member has a diagnosis of narcolepsy or idiopathic hypersomnia that has been confirmed by sleep lab testing or documented clinical symptoms:
    a. For narcolepsy - excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** at least **ONE** of the following:
        i. Cataplexy episodes (for narcolepsy type 1)***; or***
        ii. Hypocretin-1 (orexin A) deficiency (≤110 pg/mL or <1/3 of mean values of healthy individuals tested using the same standardized assay)***; or***
        iii. Nocturnal sleep polysomnography showing rapid eye movement (REM) sleep latency ≤ 15 minutes, or a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency ≤ 8 minutes and ≥ 2 sleep-onset REM periods (SOREMPs). A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnography may replace one of the SOREMPs on the MSLT***; or***
    b. For idiopathic hypersomnia - excessive daytime sleepiness (EDS) persisting for at least 3 months **AND** a Multiple Sleep Latency Test (MSLT) showing a mean sleep latency of ≤ 8 minutes and fewer than 2 sleep-onset REM periods (SOREMPs), or no SOREMPs if the REM latency on the preceding polysomnogram was ≤ 15 minutes***; AND***
4. The member has tried and failed prior treatments as follows:
    a. For members 18 years of age and older with narcolepsy, the member has tried and failed, or has a contraindication to, **ALL** of the following:
        i. Sunosi (solriamfetol)***; and***
        ii. Lumryz (sodium oxybate)***; and***
        iii. Wakix (pitolisant)***; or***

b. For members 7 to 17 years of age with narcolepsy and excessive daytime sleepiness (EDS), the member has tried and failed, or has a contraindication to, **ALL** of the following:
    i. Wakix (pitolisant)***; and***
    ii. Lumryz (sodium oxybate); ***or***
c. For members 7 to 17 years of age with narcolepsy and cataplexy, **the member has tried and failed, or has a contraindication to, Lumryz (sodium oxybate)**; ***or***
d. For adults with idiopathic hypersomnia, the member is unable to use, or has adequately tried and failed at least **THREE** (3) of the following for at least 30 days duration each:
    i. amphetamine-dextroamphetamine; ***and/or***
    ii. dextroamphetamine; ***and/or***
    iii. methylphenidate; ***and/or***
    iv. armodafinil; ***and/or***
    v. modafinil; ***AND***

5. The member does **NOT** have **ANY** of the following:
    a. Succinic semialdehyde dehydrogenase (SSADH) deficiency***; or***
    b. Documentation indicating concomitant use with, or inability to abstain from, any of the following while taking Xywav:
        i. Alcohol (e.g., beer, wine, whisky)***; or***
        ii. Sedative hypnotics (e.g., alprazolam, diazepam, lorazepam, zolpidem)***; or***
        iii. Xyrem, Lumryz, or other sodium oxybate products***; or***
    c. A condition that better explains the hypersomnolence and/or MSLT findings, such as:
        i. Insufficient sleep***; or***
        ii. Obstructive sleep apnea***; or***
        iii. Delayed sleep phase disorder***; or***
        iv. The effect of medication or substances or their withdrawal***; AND***
6. Xywav is being prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

If the above prior authorization criteria are met, the requested product will be authorized for 12 months.

Medical Necessity Criteria for Reauthorization

Reauthorization for 12 months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating **ALL** of the following criteria:

1. The member has experienced a positive clinical response to Xywav therapy as demonstrated by a reduction in symptoms of cataplexy, EDS, or IH; ***AND***
2. The member continues to abstain from alcohol and sedative hypnotics; ***AND***
3. Xywav will not be used in combination with Xyrem, Lumryz, or other sodium oxybate products; ***AND***
4. Xywav continues to be prescribed at a dose and frequency that is within FDA approved labeling **OR** is supported by compendia or evidence-based published dosing guidelines for the requested indication.

Experimental or Investigational / Not Medically Necessary

Xywav (calcium, magnesium, potassium, and sodium oxybates) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- When used in combination with alcohol, sedative hypnotics, or other medications containing sodium oxybate, gamma-hydroxybutyrate (GHB), or GHB precursors.
- When used in members with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
- For members under 7 years of age, safety and efficacy have not been established in this pediatric population.

References

1. Aurora RN, Lamm CI, Zak RS, Kristo DA, Bista SR, Rowley JA, Casey KR. Practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing for children. Sleep. 2012 Nov 1;35(11):1467-73. doi: 10.5665/sleep.2190. PMID: 23115395; PMCID: PMC3466793.
2. Howell M, Avidan AY, Foldvary-Schaefer N, Malkani RG, During EH, Roland JP, McCarter SJ, Zak RS, Carandang G, Kazmi U, Ramar K. Management of REM sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2023 Apr 1;19(4):759-768. doi: 10.5664/jcsm.10424. PMID: 36515157; PMCID: PMC10071384.
3. Maski K, Trotti LM, Kotagal S, Robert Auger R, Rowley JA, Hashmi SD, Watson NF. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021 Sep 1;17(9):1881-1893. doi: 10.5664/jcsm.9328. PMID: 34743789; PMCID: PMC8636351.

4. Xywav (calcium, magnesium, potassium, and sodium oxybates) [prescribing information]. Palo Alto, CA: Jazz Pharmaceuticals Inc; April 2023.

Clinical Guideline Revision / History Information

Original Date: 09/18/2024
Reviewed/Revised: 07/01/2025

Oscar Clinical Guideline: Zepbound (tirzepatide) for the Treatment of Obstructive Sleep Apnea (PG255, Ver. 2)

Zepbound (tirzepatide) for the Treatment of Obstructive Sleep Apnea

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Obstructive sleep apnea (OSA) is a common sleep disorder characterized by repetitive episodes of complete or partial upper airway obstruction during sleep, leading to reduced or absent breathing and sleep fragmentation. OSA is associated with significant morbidity, including excessive daytime sleepiness, impaired cognitive function, and increased risk of cardiovascular disease, metabolic disorders, and accidents.

Obesity is a major risk factor for OSA, and weight loss is an important component of OSA management. However, achieving and maintaining significant weight loss through lifestyle modifications alone can be challenging for many patients.

Zepbound (tirzepatide) is a novel once-weekly injectable medication that acts as a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist.

Initially approved for the treatment of type 2 diabetes and chronic weight management, tirzepatide has shown promising results in reducing body weight and improving metabolic parameters.

- Recent clinical trials have demonstrated that tirzepatide can significantly reduce the severity of OSA in adults with obesity, as measured by the apnea-hypopnea index (AHI) and other sleep-related parameters. Tirzepatide treatment was associated with improvements in OSA-related symptoms, quality of life, and cardiovascular risk factors.

NOTE: This clinical guideline addresses the use of Zepbound (tirzepatide) for the treatment of moderate-to-severe obstructive sleep apnea in adults with obesity. It does not apply to the use of Zepbound (tirzepatide) for other indications, such as type 2 diabetes management or chronic weight management in patients without OSA. Coverage of Zepbound (tirzepatide) for weight management may vary depending on a member's benefit policy; please refer to the applicable plan documents or contact the Plan to confirm coverage details.

- Please refer to the Plan's Weight Loss Agents (PG070) Clinical Guideline for specific coverage criteria related to the use of Zepbound (tirzepatide) and other GLP-1 receptor agonists for weight management in members without OSA. The Plan's Weight Loss Agents (PG070) Clinical Guideline only applies to members whose Plan covers prescription drugs prescribed for the treatment of obesity or for use in any weight reduction, weight loss, or dietary control.

Definitions

"**Apnea-hypopnea index (AHI)**" is the number of apneas and hypopneas per hour of sleep, used to assess the severity of OSA.

"**Body mass index (BMI)**" is a measure of body fat based on height and weight that applies to adult men and women.

"Habitual snoring" is snoring every night or almost every night.

"**Moderate obstructive sleep apnea**" is defined as an AHI of 15 to 30 events per hour.

"**Obesity**" is defined as a BMI of 30 kg/m² or greater.

"**Obstructive sleep apnea (OSA)**" is a sleep disorder characterized by repetitive episodes of complete or partial upper airway obstruction during sleep.

"**Severe obstructive sleep apnea**" is defined as an AHI greater than 30 events per hour.

Medical Necessity Criteria for Initial Authorization

The Plan considers **Zepbound (tirzepatide)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a sleep specialist, pulmonologist, or physician who regularly treats sleep disorders; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member has a diagnosis of moderate-to-severe obstructive sleep apnea (AHI ≥ 15 events per hour) confirmed by polysomnography or home sleep apnea testing; ***AND***
4. The member has a body mass index (BMI) ≥ 30 kg/m²; ***AND***
5. The member is unable to use, or has tried and failed, or has a contraindication or intolerance to, at least 3 months of continuous positive airway pressure (CPAP) therapy or other appropriate noninvasive ventilation (e.g., bi-level positive airway pressure [BiPAP], automatic positive airway pressure [APAP], adaptive servo ventilation [ASV]); ***AND***
6. The member does **NOT** have:
    a. History of type 1 diabetes (T1DM) or type 2 diabetes mellitus (T2DM); ***and/or***
    b. Personal history of multiple endocrine neoplasia type 2 (MEN2); ***and/or***
    c. Personal or family history of medullary thyroid carcinoma; ***and/or***
    d. History of pancreatitis; ***and/or***
    e. Pregnancy (negative pregnancy test required for females of reproductive potential); ***AND***
7. Will be used in combination with:
    a. Lifestyle modifications including reduced calorie diet and increased physical activity; ***and***
    b. Standard OSA treatments as appropriate (e.g., CPAP, oral appliances); ***AND***
8. Zepbound (tirzepatide) will not be used concurrently with other tirzepatide-containing products or any other GLP-1 receptor agonists; ***AND***
9. The prescribed dose does not exceed 15 mg once weekly.

If the above prior authorization criteria are met, the requested product will be authorized for 6-months.

Medical Necessity Criteria for Reauthorization

Zepbound (tirzepatide) may be reauthorized for an additional 12-months if the member meets **ALL** of the following:

1. The member has demonstrated clinical response as demonstrated by at least **ONE** of the following:
    a. a clinically significant reduction in AHI (e.g., ≥ 50% reduction from baseline or AHI < 15 events per hour) as compared to baseline (i.e., pre-treatment); ***or***
    b. improvement in OSA-related symptoms (e.g., daytime sleepiness, habitual snoring, morning headaches); ***AND***
2. The member continues to adhere to lifestyle modifications; ***AND***
3. If the member has achieved remission or non-symptomatic OSA, the prescriber provides rationale for continuing therapy (e.g., at risk for returning symptoms); ***AND***
4. The member has not developed any contraindications to continued Zepbound (tirzepatide) therapy.

Experimental or Investigational / Not Medically Necessary

Zepbound (tirzepatide) is considered experimental, investigational, or not medically necessary for all other indications, including but not limited to[ℓ], the following:

- Treatment of mild OSA (AHI < 15 events per hour).
- Treatment of OSA in non-obese individuals (BMI < 30 kg/m²).
- Treatment of central sleep apnea.
- Treatment of obesity without concurrent OSA.
- Treatment of type 2 diabetes without concurrent OSA.

[ℓ]*The above list of experimental and investigational uses is not exhaustive. The fact that an indication is not listed above does not imply that Zepbound (tirzepatide) is medically necessary for that use. All requests for Zepbound (tirzepatide) for non-FDA approved indications will be reviewed on an individual basis in accordance with the member's benefit policy and applicable Clinical Guidelines.*

NOTE: While the clinical evidence supports the medical necessity of Zepbound (tirzepatide) for weight management in obese and some overweight individuals with or without OSA, as outlined in Pharmacy Guideline - Weight Loss Agents (PG070), coverage depends on the specific terms of the member's benefit plan. Members should refer to their specific plan documents or contact the Plan to confirm coverage details for weight loss medications.

Appendix

In the SURMOUNT-OSA trials [ClinicalTrials.gov Identifier: NCT05412004], tirzepatide demonstrated significant reductions in AHI and improvements in OSA-related outcomes in adults with obesity and moderate-to-severe OSA. Key findings include:

- Mean reduction in AHI of up to 29.3 events per hour (58.7% change from baseline) with tirzepatide compared to 5.5 events per hour with placebo.
- Up to 51.5% of participants treated with tirzepatide achieved disease resolution (defined as AHI < 5 events/hour or AHI 5-14 events/hour with Epworth Sleepiness Scale score ≤ 10).
- Significant improvements in hypoxic burden, sleep-related quality of life measures, and cardiovascular risk factors (e.g., blood pressure, hsCRP).
- Mean weight loss of 17.7% to 19.6% with tirzepatide compared to 1.6% to 2.3% with placebo
- Most common adverse events were gastrointestinal and generally mild to moderate in severity.

Table 1: SURMOUNT-OSA Trials - Key Details, Results, and Insights

Aspect	Details
Trial name	SURMOUNT-OSA (Trial 1 and Trial 2) [ClinicalTrials.gov Identifier: NCT05412004]
Intervention	Tirzepatide (maximum tolerated dose of 10 mg or 15 mg) vs placebo, once weekly for 52 weeks.
Study population • **Inclusion criteria**	469 adults with moderate-to-severe obstructive sleep apnea (OSA) and obesity (Trial 1: 234; Trial 2: 235) • Age ≥18 years • AHI ≥15 events/hour • Obesity (BMI ≥30) or overweight (BMI ≥27 in Japan) • Trial 1: Unable/unwilling to use PAP therapy • Trial 2: Using PAP therapy for ≥3 months
Exclusion criteria	• Type 1 or 2 diabetes • Weight change >5 kg in 3 months before screening • Planned surgery for sleep apnea or obesity • Central or mixed sleep apnea • Major craniofacial abnormalities
Study design	Two phase 3, multicenter, parallel-group, double-blind, randomized, controlled trials.
Number of sites	60 sites across 9 countries
Primary endpoint	Change in AHI from baseline to week 52

Key secondary endpoints	• Percent change in AHI • Proportion with ≥50% reduction in AHI • Proportion with AHI <5 or AHI 5-14 with ESS ≤10 • Percent change in body weight • Change in hsCRP, hypoxic burden, PROMIS scores, systolic blood pressure

Primary endpoint results	• Trial 1: -20.0 events/hour difference (95% CI -25.8 to -14.2), p<0.001
	  ○ Tirzepatide, -25.3 events/hr vs Placebo, -5.3 events
	• Trial 2: -23.8 events/hour difference (95% CI -29.6 to -17.9), p<0.001
	  ○ Tirzepatide, -29.3 events/hr vs Placebo, -5.5 events/hr

Key secondary endpoint results	Significant improvements in all key secondary endpoints with tirzepatide vs placebo • Weight loss: 17.7% vs 1.6% (Trial 1), 19.6% vs 2.3% (Trial 2) • Significant reductions in hypoxic burden and hsCRP • Improved sleep-related patient-reported outcomes
Adverse events	• Most common adverse events were gastrointestinal (mild to moderate) • Serious AEs were similar between groups. No deaths reported • Two cases of acute pancreatitis in tirzepatide group (Trial 2)
Conclusions	Tirzepatide significantly reduced AHI, body weight, hypoxic burden, hsCRP, blood pressure, and improved sleep-related patient-reported outcomes in adults with moderate-to-severe OSA and obesity. *Note: The results from both trials demonstrated consistent efficacy regardless of baseline PAP therapy status, suggesting potential benefit for patients both with and without concurrent PAP use.*

AHI = apnea-hypopnea index, BMI = body mass index, PAP = positive airway pressure, ESS = Epworth Sleepiness Scale, hsCRP = high-sensitivity C-reactive protein, PROMIS = Patient-Reported Outcomes Measurement Information System, CI = confidence interval, AEs = adverse events

References

1. Lilly's tirzepatide reduced obstructive sleep apnea (OSA) severity, with up to 51.5% of participants meeting the criteria for disease resolution. Eli Lilly and Company. June 21, 2024.
2. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009 Jun 15;5(3):263-76.
3. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, Harrod CG. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017 Mar 15;13(3):479-504. doi: 10.5664/jcsm.6506. PMID: 28162150; PMCID: PMC5337595.

4. Malhotra A, Grunstein RR, Fietze I, Weaver TE, Redline S, Azarbarzin A, Sands SA, Schwab RJ, Dunn JP, Chakladar S, Bunck MC, Bednarik J; SURMOUNT-OSA Investigators. Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. N Engl J Med. 2024 Oct 3;391(13):1193-1205. doi: 10.1056/NEJMoa2404881. Epub 2024 Jun 21. Erratum in: N Engl J Med. 2024 Oct 17;391(15):1464. doi: 10.1056/NEJMx240005. PMID: 38912654; PMCID: PMC11598664.
5. Marc-André Cornier, M. D. A Review of Current Guidelines for the Treatment of Obesity. Dec. 2022. www.ajmc.com, https://www.ajmc.com/view/review-of-current-guidelines-for-the-treatment-of-obesity.
6. Mysliwiec V, Martin JL, Ulmer CS, Chowdhuri S, Brock MS, Spevak C, Sall J. The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guidelines. Ann Intern Med. 2020 Mar 3;172(5):325-336. doi: 10.7326/M19-3575. Epub 2020 Feb 18. Erratum in: Ann Intern Med. 2021 Apr;174(4):584. doi: 10.7326/L20-1419. PMID: 32066145.
7. Nicolini A, Banfi P, Grecchi B, Lax A, Walterspacher S, Barlascini C, Robert D. Non-invasive ventilation in the treatment of sleep-related breathing disorders: A review and update. Rev Port Pneumol. 2014 Nov-Dec;20(6):324-35.
8. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019 Feb 15;15(2):335-343. doi: 10.5664/jcsm.7640. PMID: 30736887; PMCID: PMC6374094.
9. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015 Jul 15;11(7):773-827. doi: 10.5664/jcsm.4858. PMID: 26094920; PMCID: PMC4481062.
10. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014 Nov;146(5):1387-1394. doi: 10.1378/chest.14-0970. PMID: 25367475.
11. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993 Apr 29;328(17):1230-5. Zepbound (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; October 2024.
12. Zepbound (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; December 2024.

Clinical Guideline Revision / History Information

Original Date: 01/30/2025
Reviewed/Revised: 07/01/2025

Oscar Clinical Guideline: Spravato (esketamine) (PG257, Ver. 1)

Spravato (esketamine)

Disclaimer

Clinical guidelines are developed and adopted to establish evidence-based clinical criteria for utilization management decisions. Clinical guidelines are applicable according to policy and plan type. The Plan may delegate utilization management decisions of certain services to third parties who may develop and adopt their own clinical criteria.

Coverage of services is subject to the terms, conditions, and limitations of a member's policy, as well as applicable state and federal law. Clinical guidelines are also subject to in-force criteria such as the Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD) or local coverage determination (LCD) for Medicare Advantage plans. Please refer to the member's policy documents (e.g., Certificate/Evidence of Coverage, Schedule of Benefits, Plan Formulary) or contact the Plan to confirm coverage.

Summary

Major depressive disorder is a mental health disorder that causes symptoms of sadness, hopelessness, and loss of interest in things. It can disrupt relationships and everyday activities, such as work, school, and activities that are usually pleasant. There are many medications from several classes that are available to treat major depressive disorder including selective serotonin-reuptake inhibitors (SSRIs), serotonin- and norepinephrine-reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase (MAO) inhibitors, and other antidepressants (e.g., bupropion, mirtazapine, trazodone).

Treatment resistant depression (TRD) refers to individuals who may improve partially but do not remit symptomatically nor regain full functional status. Partial response is the presence of residual symptoms.

In studies, TRD generally refers to major depressive episodes that do not respond satisfactorily after two (2) trials of antidepressant monotherapy. Response is generally classified by the amount of improvement from baseline on a depression rating scale:

- No response: improvement <25%
- Partial response: improvement 25% to 49%
- Response: improvement ≥50% but less than the threshold for remission
- Remission: depression rating scale score less than or equal to a specific cutoff that defines the normal range.

It is estimated that at least 30% of individuals with depression have TRD. However, a notable percentage of individuals with TRD are pseudo-resistant (e.g., due to inadequacy of treatment trials or non-adherence to treatment).

Spravato (esketamine) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated for the treatment of:

1. Treatment-resistant depression (TRD) in adults, as monotherapy or in conjunction with an oral antidepressant; or
2. Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant.

Due to the risk for sedation, dissociation, respiratory depression, abuse and misuse, Spravato (esketamine) is only available through a Risk Evaluation and Mitigation Strategy (REMS) Program. Spravato (esketamine) can only be administered at healthcare settings certified in the Spravato REMS Program. Patients treated in outpatient healthcare settings (e.g., medical offices and clinics) must be enrolled in the program.

Definitions

"Major depressive disorder", also known as **(MDD)**, is a psychiatric condition characterized by persistent low mood, low energy, or loss of interest in enjoyable activities causing substantial impairment in daily life. MDD is thought to be caused by a combination of genetic, environmental and psychological 2 factors. Risk factors include family history, major life changes, certain medications, chronic health problems, and substance use disorders.

"Depression assessment instruments" are used to screen and track treatment outcomes. These instruments may include interview and/or self-reported measures. Examples of validated and reliable

instruments include Beck Depression Inventory-II [BDI-II], Hamilton Rating Scale for Depression [HAM-D], Inventory of Depressive Symptomatology–Clinician Rating [IDS-C], Montgomery-Asberg Depression Rating Scale [MADRS], Patient Health Questionnaire-9 [PHQ-9], and Quick Inventory of Depressive Symptomatology [QIDS-C16].

"Risk Evaluation and Mitigation Strategy", also known as **(REMS),** is a drug safety program that the Food and Drug Administration (FDA) requires for certain medications to ensure the benefits of the medication outweigh its risks.

Clinical Indications

General Medical Necessity Criteria for Authorization

The Plan considers **Spravato (esketamine)** medically necessary when **ALL** of the following criteria are met:

1. The medication is prescribed by or in consultation with a psychiatrist; ***AND***
2. The member is 18 years of age or older; ***AND***
3. The member does **NOT** have documentation of **ANY** of the following:
    a. Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation; ***and***
    b. History of intracerebral hemorrhage; ***and***
    c. Hypersensitivity to esketamine, ketamine, or any of the excipients; ***AND***
4. **Spravato (esketamine)** is being prescribed at a dose and frequency that is within FDA approved labeling.

Treatment Resistant Depression (TRD)

Medical Necessity Criteria for Initial Authorization

The Plan considers **Spravato (esketamine)** medically necessary when **ALL** of the following criteria are met:

5. The member meets the above General Medical Necessity Criteria for Authorization; ***AND***
6. The member has a diagnosis of TRD; ***AND***
7. The member has a diagnosis of major depressive disorder (MDD) that is treatment resistant defined as nonresponse to an adequate trial (dosage, duration, and adherence) of at least two (2) antidepressants in an episode; ***AND***
8. There is documentation of baseline scoring by a validated rating scale prior to starting therapy (e.g., BDI-II, HAM-D, IDS-C, MADRS, PHQ-9, QIDS-C16); ***AND***

9. The member is unable to use all, or has tried and failed **TWO (2)** antidepressants from at least **TWO (2)** different classes for at least six (6) weeks each at an adequate dose:
    a. Aminoketones (e.g., bupropion); ***and/or***
    b. Monoamine oxidase inhibitors (e.g., selegiline, tranylcypromine); ***and/or***
    c. Noradrenaline and serotonergic antidepressants (e.g., mirtazapine); ***and/or***
    d. Selective serotonin reuptake inhibitors (e.g., citalopram, fluoxetine, paroxetine, sertraline); ***and/or***
    e. Serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine, desvenlafaxine); ***and/or***
    f. Tricyclic antidepressants (e.g., amitriptyline, nortriptyline); ***and/or***
    g. Serotonin modulators (e.g., nefazodone, trazodone, vilazodone); ***and/or***
    h. Augmentation with lithium, thyroid hormone (e.g., liothyronine), atypical antipsychotics, or anticonvulsants.

If the above prior authorization criteria are met, the requested product will be authorized for up to 6 months.

Major Depressive Disorder (MDD) with Acute Suicidal Ideation or Behavior

Medical Necessity Criteria for Authorization

The Plan considers **Spravato (esketamine)** medically necessary when **ALL** of the following criteria are met:

5. The member meets the above General Medical Necessity Criteria for Authorization; ***AND***
6. The member has a diagnosis of major depressive disorder (MDD); ***AND***
7. The member has current suicidal ideation or behavior with intent; ***AND***
8. Spravato (esketamine) will be used in conjunction with an oral antidepressant (e.g. venlafaxine, escitalopram, duloxetine, sertraline, quetiapine).

If the above prior authorization criteria are met, the requested product will be authorized for up to 1 month.

Medical Necessity Criteria for Reauthorization

Treatment Resistant Depression (TRD)

Reauthorization for up to 12 months for **Spravato (esketamine)** will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating ALL of the following criteria:

5. The member meets the above applicable General Medical Necessity Criteria for Authorization; ***AND***
6. The member has experienced a documented improvement compared to baseline by a validated rating scale (e.g., BDI-II, HAM-D, IDS-C, MADRS, PHQ-9, QIDS-C16); ***AND***
7. There is no recorded evidence of unacceptable toxicity or adverse reactions to Spravato (esketamine).

Experimental or Investigational / Not Medically Necessary

Spravato (esketamine) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, the following:

- Anesthetic agent
- Acute pain
- Chronic pain
- Migraine headaches

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
G2082	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation
G2083	Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care professional and provision of greater than 56 mg esketamine nasal self-administration, includes 2 hours post-administration observation
S0013	Esketamine, nasal spray, 1 mg
ICD-10 codes considered medically necessary if criteria are met:	

Code	*Description*
F06.31	Mood disorder due to known physiological condition with depressive features
F06.32	Mood disorder due to known physiological condition with major depressive-like episode
F32.1	Major depressive disorder, single episode, moderate
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.5	Major depressive disorder, single episode, in full remission
F32.89	Other specified depressive episodes
F32.9	Major depressive disorder, single episode, unspecified
F32.A	Depression, unspecified
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.8	Other recurrent depressive disorders
F33.9	Major depressive disorder, recurrent, unspecified

References

1. Spravato (esketamine hydrochloride solution) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; January 2025.
2. Popova V, Daly EJ, Trivedi M, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry. 2019 Jun 1;176(6):428-438.
3. Daly EJ, Trivedi MH, Janik A, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019 Sep 1;76(9):893-903.

4. Fu DJ, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). J Clin Psychiatry. 2020 May 12;81(3):19m13191.
5. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients With Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). Int J Neuropsychopharmacol. 2021 Jan 20;24(1):22-31.
6. ClinicalTrials.gov. A Study of Esketamine Nasal Spray, Administered as Monotherapy, in Adult Participants With Treatment-resistant Depression. https://clinicaltrials.gov/study/NCT04599855. Accessed February 17, 2025.
7. Guideline Development Panel for the Treatment of Depressive Disorders. APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts. Am Psychol. 2019.
8. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399.
9. NP Psych Navigator. Understanding the Montgomery-Åsberg Depression Rating Scale (MADRS) Video. Available at: https://www.nppsychnavigator.com/NP_Perspectives/Clinical-Insights/Understanding-the-MADRS. Accessed February 17, 2025.
10. McIntyre RS, Alsuwaidan M, Baune BT, et al. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023 Oct;22(3):394-412.
11. UptoDate. Unipolar treatment-resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis. Available at: https://www.uptodate.com/contents/unipolar-treatment-resistant-depression-in-adults-epidemiology-risk-factors-assessment-and-prognosis. Accessed February 17, 2025.
12. American Family Physician. Common Questions About the Pharmacologic Management of Depression in Adults. Available at: https://www.aafp.org/pubs/afp/issues/2015/0715/p94.html#afp20150715p94-b51. Accessed February 17, 2025.
13. World Health Organization. Duration of antidepressant treatment. Available at: https://www.who.int/teams/mental-health-and-substance-use/treatment-care/mental-health-gap-action-programme/evidence-centre/depression/duration-of-antidepressant-treatment. Accessed February 17, 2025.
14. U.S. Food & Drug Administration. Risk Evaluation and Mitigation Strategies REMS. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems. Accessed February 17, 2025.
15. APA. Depression Assessment Instruments. Available at: https://www.apa.org/depression-guideline/assessment. Accessed February 18, 2025.

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