Tzield (teplizumab-mzwv)

Summary

Diabetes, or diabetes mellitus (DM), 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. Inadequate glycemic control can lead to serious complications including cardiovascular disease, nephropathy, retinopathy, and

neuropathy. The goal of diabetes management is to maintain blood glucose levels as close to the normal range as possible to prevent or delay complications.

Diabetes is commonly classified into four categories:

1. Type 1 diabetes (T1D) - the pancreas makes little or no insulin.
2. Type 2 diabetes - the body's cells do not respond to insulin the way they should (insulin resistance); sometimes the pancreas does not make enough insulin.
3. Gestational diabetes - occurs during pregnancy, placing the individual at a higher risk of developing type 2 diabetes in the future.
4. Specific types of diabetes due to other causes (e.g., drug or chemical-induced diabetes)

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 type 1 diabetes, the primary treatment is insulin, however management of insulin takes extensive training and education.

Tzield (teplizumab-mzwv) is FDA-approved as treatment to delay the onset of Stage 3 type 1 diabetes in adults and pediatric individuals 8 years of age and older with Stage 2 type 1 diabetes. Tzield is an intravenously (IV) administered anti-CD3-directed antibody designed to bind to certain immune system cells and delay progression to stage 3 T1D. Tzield is administered by intravenous infusion once daily for 14 consecutive days. In the pivotal trial, Tzield (teplizumab-mzwv) resulted in the delay of diagnosis of type 1 diabetes by about 24 months (median time to diagnosis of type 1 diabetes 48.4 months in the Tzield [teplizumab] group and 24.4 months in the placebo group, HR 0.41 [95% CI, 0.22-0.78]).

While the exact cause of both type 1 and type 2 diabetes are not known, potential risk factors are known. For type 1 diabetes, these include but are not limited to factors such as having a family member with T1D, having a gene that makes it more likely to develop T1D, certain conditions where the body's immune system attacks itself (e.g., autoimmune disease), and various other genetic and environmental factors. People may develop T1D at any age, but it is more commonly diagnosed in younger children, teens and young adults. The American Diabetes Association (ADA) has identified three distinct stages of type 1 diabetes with accompanying characteristics and diagnostic criteria (see "stage 1 type 1 diabetes," "stage 2 type 1 diabetes," and "stage 3 type 1 diabetes" in the Definitions below) .

Definitions

"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).

"Documentation" refers to written information, including but not limited to:

- Up-to-date chart notes, relevant test results, and/or relevant imaging reports to support diagnoses; or

- Prescription claims records, and/or prescription receipts to support prior trials of formulary alternatives.

"Fasting blood glucose (FG) test" is taken by blood sample after 8 hours of fasting (not eating).

"Hemoglobin A1c (HbA1c or A1C)" 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.

"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.

"No evidence of" indicates that the reviewer has not identified any records of the specified item or condition within the submitted materials or claims history. In the absence of such evidence, the member is considered eligible. If any evidence of the item or condition is present upon review of the request, the member does not qualify.

"Oral glucose tolerance test (OGTT)" is a recommended test for diabetes screening performed using glucose load containing the equivalent of 1.75g/kg body weight to a maximum of 75 g of anhydrous glucose dissolved in water. The test measures blood glucose at baseline (e.g., after overnight fasting) and two hours after consuming the glucose-containing drink.

"Polyuria" refers to an increased output of urine (or increased urination) commonly associated with hyperglycemia and diabetes diagnoses.

"Polydipsia"refers to an increase in thirst commonly associated with hyperglycemia and diabetes diagnoses.

"[s]" indicates state mandates may apply.

"Stage 1 type 1 diabetes" refers to the presence of two or more pancreatic islet autoantibodies but the blood sugar (glucose) remains within a normal range.

"Stage 2 type 1 diabetes" refers to the presence of two or more pancreatic islet autoantibodies and dysglycemia without overt hyperglycemia, as demonstrated by oral glucose tolerance testing or other appropriate methods.

"Stage 3 type 1 diabetes" is defined as clinical type 1 diabetes with symptoms of hyperglycemia, including polyuria, polydipsia, weight loss, and/or diabetic ketoacidosis.

"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

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Stage 2 Type 1 Diabetes Mellitus

The Plan considers Tzield (teplizumab-mzwv) medically necessary when ALL of the following criteria are met:

1. Prescribed by or in consultation with an endocrinologist, pediatric endocrinologist, or physician specializing in diabetes care*; AND*
2. The member is between 8 to 65 years of age*; AND*
3. Tzield (teplizumab-zwv) is being given to delay the onset of Stage 3 type 1 diabetes*; AND*
4. The member has a documented diagnosis of Stage 2 type 1 diabetes, defined as having BOTH:
    a. TWO (2) or more of the following pancreatic islet autoantibodies:
        i. Glutamic acid decarboxylase 65 (GAD) autoantibodies (anti-GAD65)*; and/or*
        ii. Insulin autoantibody (IAA)*; and/or*
        iii. Insulinoma-associated antigen 2 autoantibody (IA-2A)*; and/or*
        iv. Zinc transporter 8 autoantibody (ZnT8A)*; and/or*
        v. Islet cell autoantibody (ICA) or anti-ICA512*; and*

b. Abnormal glucose tolerance, evidenced by ONE (1) of the following within the past 90 days:
    i. Fasting plasma glucose ≥ 110 mg/dL (6.1 mmol/L), and <126 mg/dL (6.9 mmol/L)*; or*
    ii. 2-hour plasma glucose measurement ≥140 mg/dL (7.8 mmol/L), and <200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)*; or*
    iii. 30, 60, 90 minute value of ≥ 200 mg/dl on OGTT; *or*
    iv. A1C ≥5.7% (39 mmol/mol), and <6.5% (48 mmol/mol)*; AND*

5. The member meets ALL of the following criteria:
    a. No evidence of a clinical history suggesting type 2 diabetes*; or*
    b. No evidence of current pregnancy*; or*
    c. No evidence of a previous diagnosis of diabetes (i.e., "stage 3 type 1 diabetes" or "type 1 diabetes") or clear clinical diagnosis of diabetes, as evidenced by:
        i. Fasting plasma glucose level ≥ 126 mg/dL (7 mmol/L)*; or*
        ii. 2-hour plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during oral glucose tolerance test*; or*
        iii. Hemoglobin A1C ≥ 6.5%*; or*
        iv. Classic symptoms of hyperglycemia (polyuria, polydipsia, unexplained weight loss) with random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)*; or*
        v. Hyperglycemic crisis*; or*
    d. No evidence of ANY of the following laboratory findings:
        i. Lymphocyte count less than 1,000 lymphocytes/mcL*; or*
        ii. Hemoglobin less than 10 g/dL*; or*
        iii. Platelet count less than 150,000 platelets/mcL*; or*
        iv. Absolute neutrophil count less than 1,500 neutrophils/mcL*; or*
        v. Elevated ALT or AST greater than 2 times the upper limit of normal (ULN) or bilirubin greater than 1.5 times ULN*; or*
    e. No evidence of an active serious infection, including:
        i. Acute infection with Epstein-Barr virus (EBV) or cytomegalovirus (CMV)*; or*
        ii. Any chronic active infection other than localized skin infections*; AND*
6. The member does not have a history of prior treatment with Tzield (teplizumab-mzwv)*; AND*
7. Will be administered at the FDA-approved and recommended dosage once daily for 14 consecutive days.

<u>If the above prior authorization criteria are met, the requested product will be authorized for a one-time 14-day treatment course.</u>[5]

Experimental or Investigational / Not Medically Necessary[s]

Tzield (teplizumab-mzwv) 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:

- Treatment of established type 1 diabetes (Stage 3). While studies are undergoing in this subpopulation, there have not been enough high-quality studies to support the safety and efficacy of Tzield (teplizumab-mzwv) in those with stage 3 type 1 diabetes.
- Treatment of type 2 diabetes. Tzeild (teplizumab-mzwv) is not intended for use in those with type 2 diabetes.
- Use in members under 8 years of age. Tzield (teplizumab-mzwv) has not been studied in those 8 years of age and under and safety and efficacy has not yet been established in this age group.
- Repeat treatment courses beyond the initial 14-day regimen. Thus far, Tzield (teplizumab-mzwv) has only been studied as a one-time administration.
- Use in combination with other immunomodulatory therapies for type 1 diabetes prevention. Tzield (teplizumab-mzwv) has only been studied on its own, and those with a history of monoclonal antibody administration in the last year were excluded from the pivotal trial.
- Treatment of other autoimmune disorders not related to type 1 diabetes. Tzield (teplizumab-mzwv) has only been studied in those with type 1 diabetes. Two studies submitted to clinicaltrials.gov have attempted to study Tzield (teplizumab-mzwv) in those with psoriasis (NCT00954915) and psoriatic arthritis (NCT00239720) but both have been terminated without results.

Applicable Billing Codes

Table 1	
CPT/HCPCS Codes for stage 2 type 1 diabetes mellitus considered medically necessary if criteria are met:	
Code	*Description*
J9381	Injection, teplizumab-mzwv, 5 mcg
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour

Table 2
ICD-10 diagnosis codes considered medically necessary for stage 2 type 1 diabetes mellitus with Table 1 (CPT/HCPCS) codes if criteria are met:

Code	*Description*
E10.A2	Type 1 diabetes mellitus, presymptomatic, Stage 2
E10.8	Type 1 diabetes mellitus with unspecified complications
E10.9	Type 1 diabetes mellitus with unspecified complications

Table 3	
CPT/HCPCS Codes for stage 2 type 1 diabetes mellitus but may be subject to medical-necessity review:	
Code	*Description*
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

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