Oscar Clinical Guideline: Natalizumab and Natalizumab Biosimilars (Tysabri, Tyruko) (PG195, Ver. 6)

Tysabri (natalizumab) and Natalizumab Biosimilars

- Tysabri (natalizumab)
- Tyruko (natalizumab-sztn)

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

Multiple sclerosis (MS) and Crohn's disease are both chronic inflammatory diseases, although they affect different areas of the body. MS is a neurological condition that affects the central nervous system (brain and spinal cord), whereas Crohn's disease is a type of inflammatory bowel disease that primarily affects the digestive tract. In both MS and Crohn's disease, the body's immune system mistakenly attacks healthy cells, leading to inflammation and damage. The symptoms and severity of these diseases can vary widely among individuals.

Treatment for both conditions often involves medications to reduce inflammation and modulate the immune response. Natalizumab (Tysabri, Tyruko) is one such treatment option. It is a monoclonal antibody that works by inhibiting the movement of immune cells into the brain and spinal cord in MS, and into the digestive tract in Crohn's disease, thereby reducing inflammation and damage.

Natalizumab (Tysabri, Tyruko) is indicated for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Relapsing-remitting phenotype of MS occurs in about 85% of those with MS, progressive disease occurs in ~15% of patients with MS; progression of disease is highly variable. Natalizumab (Tysabri, Tyruko) is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, or are unable to tolerate, conventional therapies and inhibitors of tumor necrosis factor (TNF)-alpha.

NOTE: Access to Tysabri is managed through a Risk Evaluation and Mitigation Strategy (REMS) program known as the TOUCH® Prescribing Program.

- In order to prescribe or dispense Tysabri, healthcare providers and pharmacies need to be certified with the Tysabri Outreach Unified Commitment to Health (TOUCH) Prescribing Program. Prescribers must be registered in the CD TOUCH® or MS TOUCH® Prescribing Programs to prescribe for CD or MS, respectively.
- The TOUCH® Prescribing Program was created to monitor for the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that can result in severe disability or death. Risk factors include presence of anti-JCV antibodies, duration of therapy, and prior use of immunosuppressants. Concurrent use of immunosuppressants, antineoplastics and immunomodulatory therapies can increase the risk of PML and thus concomitant use is not recommended.
- Members who are prescribed Tysabri must be enrolled in the TOUCH Prescribing Program as well. They can do so by calling 800-456-2255. Depending on their condition, they will be enrolled either in the MS-TOUCH program for multiple sclerosis or the CD-TOUCH program for Crohn's disease.

Tyruko (natalizumab-sztn) was approved in August of 2023 as a biosimilar of Tysabri (natalizumab) for the same indications. However, it has not yet been brought to market.

Definitions

"Anti-JCV antibodies" are markers for exposure to the John Cunningham (JC) virus. If present, anti-JCV antibodies are associated with a higher risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that can result in severe disability or death.

"Clinically isolated syndrome" refers to a first episode of neurologic symptoms lasting at least 24 hours caused by inflammation or demyelination in the central nervous system.

"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. Clinical pharmacology
3. National Comprehensive Cancer Network Drugs and Biologics Compendium
4. Thomson Micromedex DrugDex
5. United States Pharmacopeia-National Formulary (USP-NF)

"Crohn's Disease" is a type of inflammatory bowel disease that can affect any part of the digestive tract, from the mouth to the anus. It causes symptoms such as diarrhea, abdominal pain, weight loss, and fatigue.

"Disease-modifying therapy" is a medication that modifies the course of MS by reducing relapses and slowing disability progression.

"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.

"Monoclonal Antibody" is a type of protein made in the lab that can bind to specific substances in the body. Monoclonal antibodies are used to treat many diseases, including some types of cancer and autoimmune disorders.

"MRI" or "Magnetic Resonance Imaging" refers to a medical imaging technique that creates detailed three-dimensional (3D) images of the organs and tissues in your body. A brain MRI can reveal areas of active MS disease called lesions within the central nervous system.

"Multiple Sclerosis (MS)" refers to a chronic disease that affects the central nervous system (brain and spinal cord), causing symptoms such as fatigue, difficulty walking, numbness or tingling, muscle weakness and spasms, poor balance and coordination, and problems with thinking and memory.

"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.

"Primary progressive MS" refers to worsening neurologic function from the onset of symptoms, without early relapses or remissions.

"Relapse" is defined as the appearance of new symptoms or the worsening of existing symptoms lasting at least 24 hours in the absence of fever or infection.

"Relapsing-remitting MS" refers to a disease course characterized by clearly defined attacks of new or increasing neurologic symptoms followed by periods of partial or complete recovery.

"[s]" indicates state mandates may apply.

"Secondary progressive MS" is a disease course following relapsing-remitting MS that is characterized by a progressive worsening of neurologic function over time with or without relapses.

"TNF-alpha inhibitors" are a type of medication that works by blocking the protein, tumor necrosis factor-alpha (TNF-alpha), which plays a role in causing inflammation in the body. These medications are used to treat a variety of conditions, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel diseases like Crohn's disease.

Clinical Indications

Medical Necessity Criteria for Clinical Review

General Medical Necessity Criteria

The Plan considers natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) medically necessary when ONE (1) the following criteria are met for the applicable indication listed below:

1. Authorization may be granted for pediatric members less than 18 years of age with multiple sclerosis when there is documentation that the benefits outweigh the risks*; OR*
   Note: If approved, the requested product will be authorized for up until the member reaches 18 years of age.
2. The member meets ALL of the following:
   a. The member meets ALL of the following:
      i. No evidence of current or history of progressive multifocal leukoencephalopathy (PML); *and*
      ii. No evidence of documentation indicating that the member will use Tysabri (natalizumab) in combination with any of the following:

1. Antineoplastic therapy (e.g., cyclophosphamide, doxorubicin, vincristine); *and*
2. Immunosuppressants (e.g., azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, 6-MP); *and*
3. Immunomodulatory therapy (e.g., ocrelizumab, ofatumumab, TNF-α inhibitors - such as adalimumab, infliximab, etanercept, golimumab, certolizumab pegol); *AND*

b. Natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) 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; *AND*
The requested medication is being used within the Plan's Quantity Limit of:
- *The recommended dose of Tysabri for both MS and Crohn's disease is 300 mg administered by intravenous infusion every 4 weeks (i.e., 1 vial per 28 days). Each single-use vial contains 300 mg natalizumab in 15 mL solution.*
- *Individuals should be observed for one hour post-infusion for the first 12 infusions to assess for the risk of hypersensitivity reactions.*

c. The member meets the applicable Medical Necessity Criteria for Initial Clinical Review or Subsequent Clinical Review listed below.

Medical Necessity Criteria for Initial Clinical Review

Initial Indication-Specific Criteria

Crohn's Disease (CD)

The Plan considers natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) medically necessary when ALL the following criteria are met for the applicable indication listed below:

3. The member meets the above applicable General Medical Necessity Criteria; *AND*
4. Prescribed by or in consultation with a gastroenterologist; *AND*
5. The member has a documented diagnosis of moderately to severely active CD with evidence of inflammation (e.g., elevated C-reactive protein, fecal calprotectin, erythrocyte sedimentation rate, and/or imaging findings such as mucosal ulcerations or strictures); *AND*
6. The member is unable to use, or has tried and failed BOTH of the following:[5]
    a. At least ONE (1) conventional CD therapy (e.g., corticosteroids, immunomodulators); *and*
    b. At least ONE (1) TNF inhibitors (e.g., Humira [adalimumab], Avsola [infliximab]).

Multiple Sclerosis (MS) - Adults

The Plan considers natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) medically necessary when ALL the following criteria are met for the applicable indication listed below:

3. The member meets the above applicable General Medical Necessity Criteria; *AND*
4. Prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; *AND*
5. The member has ONE (1) of the following forms of multiple sclerosis:
    a. Relapsing-remitting (RRMS); *or*
    b. Active secondary progressive (SPMS); *or*
    c. Clinically isolated syndrome (CIS); *AND*
6. The member meets ONE (1) of the following:
    a. Documentation of highly active or aggressive disease, as demonstrated by at least ONE (1) of the following:
        i. Frequent relapses (≥2 in the past year)*; or*
        ii. At least 1 relapse with incomplete recovery and MRI activity*; or*
        iii. Rapidly advancing disability or cognitive impairment*; or*
        iv. Disabling relapse with suboptimal response to corticosteroids*; or*
        v. MRI findings showing high disease activity (e.g., new/enlarging T2 lesions, enhancing lesions)*; or*
    b. The member is unable to use, or has tried and failed at least ONE (1) of the following:[s]
        i. Dimethyl Fumarate (generic Tecfidera)*; and/or*
        ii. Fingolimod (generic Gilenya); *and/or*
        iii. Teriflunomide (generic Aubagio); *AND*
7. Baseline MRI scan will be obtained prior to initiating therapy; *AND*
8. Natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) will be used as monotherapy for multiple sclerosis (i.e., member is not using and will not use other disease-modifying MS therapies while onnatalizumab).

If the above prior authorization criteria are met, the requested product will be authorized for up to 12-months.[s]

Continued Care

Medical Necessity Criteria for Subsequent Clinical Review

Subsequent Indication-Specific Criteria

Crohn's Disease

The Plan considers natalizumab or a natalizumab biosimilar (Tysabri, Tyruko) medically necessary when recent (within the last 6 months) clinical documentation provided indicates the member meets ALL of the following:

1. The member meets the above applicable General Medical Necessity Criteria and Initial Indication-Specific Criteria; *AND*
2. The member has shown a clinical improvement in at least ONE (1) objective measure, such as:
    a. Reduced inflammatory markers (e.g., fecal calprotectin, C-reactive protein [CRP])*; and/or*
    b. Improved endoscopic findings*; and/or*
    c. Reduced corticosteroid dose; *AND*
3. The member has shown improvement in at least ONE (1) symptom, such as:
    a. Decreased pain*; and/or*
    b. Reduced fatigue*; and/or*
    c. Decreased stool frequency*; and/or*
    d. Reduced rectal bleeding.

<u>If the above reauthorization criteria are met, the requested product will be authorized for up to 12-months.</u>[5]

<u>Multiple Sclerosis - Adults</u>

The Plan considers <u>natalizumab or a natalizumab biosimilar (Tysabri, Tyruko)</u> medically necessary when recent (within the last 6 months) clinical documentation provided indicates the member meets ALL of the following:

1. The member meets the above applicable General Medical Necessity Criteria and Initial Indication-Specific Criteria*; AND*
2. The requested medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; *AND*
3. The member has experienced at least ONE (1) of the following:
    a. Improvement in at least ONE (1) objective measure, such as:
        i. Reduced disease activity on MRI*; and/or*
        ii. Improved or stable disability scores*; and/or*
        iii. Reduced relapse rate*; and/or*
        iv. Improved fatigue or walking assessments; *AND/OR*
    b. Member has shown stabilization or improvement in at least ONE (1) MS symptom, such as:
        i. Motor function*; and/or*
        ii. Fatigue*; and/or*
        iii. Vision*; and/or*
        iv. Bowel/bladder function*; and/or*
        v. Spasticity*; and/or*
        vi. Walking/gait*; and/or*
        vii. Pain/numbness/tingling; *AND*

If the above reauthorization criteria are met, the requested product will be authorized for up to 12-months.[5]

Experimental or Investigational / Not Medically Necessary[5]

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

- for use in individuals under 18 years of age for Crohn's disease. The safety and efficacy of natalizumab in pediatric patients have not been established.
- other autoimmune diseases, such as rheumatoid arthritis, lupus, or psoriasis.

Applicable Billing Codes

Table 1	
CPT/HCPCS codes for Multiple Sclerosis or Crohn's Disease 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
J2323	Injection, natalizumab, 1 mg
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg

Table 2	
ICD-10 diagnosis codes considered medically necessary for Crohn's Disease with Table 1 (CPT/HCPCS) codes if criteria are met:	
Code	*Description*
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication

Table 2	
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications

Table 3
ICD-10 diagnosis codes considered medically necessary for Multiple Sclerosis with Table 1 (CPT/HCPCS) codes if criteria are met:

Table 3	
G35	Multiple sclerosis
G35.A	Relapsing-remitting multiple sclerosis
G35.B0	Primary progressive multiple sclerosis, unspecified
G35.B1	Active primary progressive multiple sclerosis
G35.B2	Non-active primary progressive multiple sclerosis
G35.C0	Secondary progressive multiple sclerosis, unspecified
G35.C1	Active secondary progressive multiple sclerosis
G35.C2	Non-active secondary progressive multiple sclerosis
G35.D	Multiple sclerosis, unspecified

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