Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of *Natalizumab (Tysabri®), and Natalizumab-sztn (Tyruko®),* approved by the Food and Drug Administration (FDA) as an infused monotherapy for adults with relapsing forms of multiple sclerosis, including clinically isolated syndrome, relapsing-remitting disease or active secondary progressive disease. Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment, physicians should consider whether the expected benefit is sufficient to offset the risk. Natalizumab is also approved to induce and maintain clinical response and remission in adults with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to conventional Crohn's disease therapies and TNF-α inhibitors.

Background Information

Natalizumab binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils and inhibits the α4-mediated adhesion of leukocytes to their 17 counter-receptor(s). The receptors for the α4 family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressing cell adhesion molecule-1 (MAdCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. In vitro, anti-α4-integrin antibodies also block α4- mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). In vivo, natalizumab may further act to inhibit the interaction of α4-expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells. The specific mechanism(s) by which TYSABRI exerts its effects in multiple sclerosis and Crohn's disease have not been fully defined. In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counterreceptors present on endothelial cells of the vessel wall. In Crohn's disease, the interaction of the α4β7 integrin with the endothelial receptor MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. Tysabri (natalizumab) is the reference natalizumab agent; Tyruko (natalizumab-sztn) is biosimilar to Tysabri.

Multiple sclerosis is an autoimmune inflammatory demyelinating disease of the central nervous system. Common symptoms of the disease include fatigue, numbness, coordination and balance problems, bowel and bladder dysfunction, emotional and cognitive changes, spasticity, vision problems, dizziness, sexual dysfunction

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

and pain. Multiple sclerosis can be subdivided into four phenotypes: clinically isolated syndrome (CIS), relapsing remitting (RRMS), primary progressive (PPMS) and secondary progressive (SPMS). Relapsing multiple sclerosis (RMS) is a general term for all relapsing forms of multiple sclerosis including CIS, RRMS and active SPMS.

The treatment goal for multiple sclerosis is to prevent relapses and progressive worsening of the disease. Currently available disease modifying therapies (DMT) are most effective for the relapsing-remitting form of multiple sclerosis and less effective for secondary progressive decline. DMT include injectable agents, infusion therapies and oral agents.

The American Academy of Neurology (AAN) guidelines suggest starting disease-modifying therapy in individuals with relapsing forms of multiple sclerosis with recent clinical relapses or MRI activity. The guidelines also suggest DMT for individuals who have experienced a single clinical demyelinating event and two or more brain lesions consistent with multiple sclerosis if the individual wishes to start therapy after a risks and benefits discussion. The guidelines do not recommend one DMT over another. However, some DMTs were recommended for certain multiple sclerosis subpopulations, including a recommendation for natalizumab for highly active disease.

Crohn's disease is a chronic, relapsing inflammatory bowel disease affecting the gastrointestinal mucosa. Fistula formation, fissuring, discontinuous intestinal and transmural involvement with bowel-wall thickening and extraintestinal manifestations including arthritis, skin and eye manifestations, metabolic deficiencies, hypercoagulation and hepatobiliary disease are frequent complications. Treatment options include 5-ASA products, glucocorticoids, antibiotics, immunosuppressive drugs, methotrexate and targeted immune modulator agents.

Natalizumab has a black box warning for progressive multifocal leukoencephalopathy (PML). Natalizumab increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include duration of therapy, prior use of immunosuppressants and presence of anti-JCV antibodies. Monitor patients and withhold Tysabri immediately at the first sign or symptom suggestive of PML. Because of this safety concern, natalizumab has been generally reserved for individuals who have had an inadequate response or are unable to tolerate alternate therapies for multiple sclerosis or Crohn's disease. Natalizumab is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH Prescribing Program

Approved Indications (FDA Label indications)

A. Multiple Sclerosis (MS)

B. Crohn's Disease (CD)

Other Uses (off-label uses, example: NCCN)

i. N/A

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J2323	Injection, natalizumab, 1 mg [Tysabri]
Q5134	Injection, natalizumab-sztn (Tyruko), biosimilar, 1 mg

ICD-10 Diagnosis	Description
G35	Multiple sclerosis
K50.00-K50.919	Crohn's disease [regional enteritis]
Z01.84	Encounter for antibody response examination

Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Clinical Criteria

Natalizumab agents (Tysabri®, Tyruko®)

A. Criteria for Initial Approval

Initial requests for Natalizumab agents (Tysabri, Tyruko) may be approved if the following criteria are met:

i. Individual has a diagnosis of relapsing multiple sclerosis (RMS) (including clinically isolated syndrome, relapsing-remitting disease or active secondary progressive disease); **AND**
ii. Individual is enrolled in and meeting all conditions of the MS Touch Prescribing Program; **OR**
iii. Individual has a diagnosis of moderate to severe Crohn's disease (CD) with evidence of inflammation and is using Tysabri for induction and maintenance of clinical response and remission; **AND**

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

iv. Individual has had an inadequate response to or is unable to tolerate conventional Crohn's disease therapies and TNF-α inhibitors; **AND**

v. Individual is enrolled in and meeting all conditions of the CD Touch Prescribing Program; **AND**

vi. Individual has had a John Cunningham virus (JCV) antibody test and the results as well as risks and benefits have been discussed and understood.

B. Criteria for Continuation of Therapy

Continuation requests for natalizumab agents may be approved if the following criteria are met:

i. Progress notes or clinical documentation from the prescriber confirms that the patient requires continued treatment and has demonstrated stabilization and/or improvement in disease activity; **AND**

ii. There is no evidence of treatment-limiting adverse effects associated with natalizumab.

C. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Natalizumab (Tysabri) or natalizumab-sztn (Tyruko)may not be approved for the following:

A. Individual is using to treat primary progressive multiple sclerosis; **OR**
B. Individual is using to treat non-active secondary progressive multiple sclerosis; **OR**
C. Individual is currently responsive to and tolerating another treatment for multiple sclerosis or Crohn's disease; **OR**
D. Individual has a current or prior history of progressive multifocal leukoencephalopathy (PML); **OR**
E. Individual has a medical condition which significantly compromises the immune system including HIV infection or AIDS, leukemia, lymphoma or organ transplantation; **OR**
F. Use in combination with chronic antineoplastics, immunosuppressants (for example, azathioprine) or TNF-α inhibitors; **OR**
G. Use in combination with other MS disease modifying agents s (including Aubagio, Avonex, Bafiertam, Betaseron, Briumvi, Copaxone/Glatiramer/Glatopa, Extavia, Gilenya, Kesimpta, Lemtrada, Mavenclad, Mayzent, Ocrevus, Ocrevus Zunovo, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity and Zeposia); **OR**
H. May not be approved when the above criteria are not met and for all other indications.

D. Authorization Duration

i. Initial Approval Duration: Up to 12 months

ii. Reauthorization Approval Duration: Up to 12 months

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Natalizumab Agents Quantity Limit

Drug	Limit
Natalizumab (Tysabri) 300 mg/15 mL single-use vial	1 vial per 28 days
Tyruko (natalizumab-sztn) 300 mg/15 mL single-dose vial	1 vial per 28 days

Reference Information

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 7, 2022.
2. Devonshire V, Havrdova E, Radue EW, et al. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. Lancet Neurol. 2012; 11:420-28. DOI: http://dx.doi.org/10.1016/S1474-4422(12)70056-X.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
5. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90: 777-788. Available from: https://www.aan.com/Guidelines/home/GuidelineDetail/898. Accessed: January 4, 2023

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Natalizumab agents (Tysabri®, Tyruko®)	MP-RX-FP-97-23	☒ MMM MA ☒ MMM Multihealth

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Annual Review 9/2/2025	Minimal changes; word formatting. Add Ocrevus Zunovo to exclusion for concurrent use with other disease modifying therapy criteria. Coding Reviewed: No changes.	9/5/2025	9/16/2025
Annual Review 9/27/2024	Add sections: approved indications, other uses, criteria for continuation therapy, approval duration, therapeutic alternatives. Add Briumvi and Tascenso ODT to exclusion for concurrent use with other disease modifying therapy criteria. Add Tyruko into natalizumab clinical criteria; add quantity limit. Align Crohn's disease wording with criteria for other Crohn's disease agents. Added HCPCS Q5134. Removed HCPCS J3490, J3590.	3/14/2025	4/2/2025
Policy Inception 9/27/2023	Elevance Health's Medical Policy adoption.	N/A	11/30/2023