Medical Drug Clinical Criteria

Subject:	Natalizumab Agents (Tysabri, Tyruko)		
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Overview

This document addresses the use of natalizumab, 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. 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 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 natalizumab 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.

Clinical Criteria

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.

Natalizumab Agents (Tysabri, Tyruko)

Requests for Tysabri (natalizumab) 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) and is using Tysabri/Tyruko for induction and maintenance of clinical response and remission; **AND**
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.

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

I. Individual is using to treat primary progressive multiple sclerosis; **OR**
II. Individual is using to treat non-active secondary progressive multiple sclerosis; **OR**
III. Individual is currently responsive to and tolerating another treatment for multiple sclerosis or Crohn's disease; **OR**
IV. Individual has a current or prior history of progressive multifocal leukoencephalopathy (PML); **OR**
V. Individual has a medical condition which significantly compromises the immune system including HIV infection or AIDS, leukemia, lymphoma or organ transplantation; **OR**
VI. Use in combination with chronic antineoplastics, immunosuppressants (for example, azathioprine) or TNF-α inhibitors; **OR**
VII. Use in combination with other MS disease modifying agents (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**
VIII. May not be approved when the above criteria are not met and for all other indications.

Step Therapy

Note: When natalizumab agents (Tysabri, Tyruko) are deemed approvable based on the clinical criteria referenced above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Natalizumab Agents (Tysabri, Tyruko) Step Therapy

A list of the preferred products is available here.

Requests for Tysabri (natalizumab) or Tyruko (natalizumab-sztn) for Multiple Sclerosis may be approved when the following criteria are met:

I. Documentation is provided that individual has been on the natalizumab agent (Tysabri/Tyruko);

OR
II. Documentation has been provided that individual has had a trial and inadequate response (including but not limited to clinical relapse, new or enlarged lesions on MRI or confirmed disability progression) or intolerance to a preferred agent;

OR
III. Documentation is provided that individual has high disease activity despite treatment with fingolimod (Gilenya, Tascenso ODT) defined as the following (AAN 2018, Devonshire 2012):
A. At least one relapse in the previous year while on therapy; **AND**
B. At least 9 T_2-hyperintense lesions in cranial MRI;

OR
C. At least one Gadolinium-enhancing lesion.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Quantity Limits

Natalizumab Agents Quantity Limit

Drug	Limit
Tysabri (natalizumab) 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

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

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

ICD-10 Diagnosis

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

Document History

Revised: 11/15/2024
Document History:

- 07/23/2025 – Step therapy table updates.
- 11/15/2024 – Annual Review: Add Ocrevus Zunovo to exclusion for concurrent use with other disease modifying therapy criteria. Coding Reviewed: No changes.
- 03/01/2024 – Administrative update to add documentation.
- 11/17/2023 – Annual Review: Add Briumvi and Tascenso ODT to exclusion for concurrent use with other disease modifying therapy criteria. Coding Reviewed: No changes. Effective 04/01/24 Added HCPCS Q5134. Removed HCPCS J3490, J3590.
- 9/11/2023 – Select Review: Add Tyruko into natalizumab clinical criteria; add quantity limit. Align Crohn's disease wording with criteria for other Crohn's disease agents. Coding Reviewed: Added HCPCS J3490, J3590.
- 03/27/2023 – Step therapy table updates.
- 01/25/2023 – Step therapy language update.
- 8/19/2022 – Annual Review: Wording and formatting changes. Coding reviewed: No changes.
- 8/20/2021 – Annual Review: Remove exclusion for positive test for JCV antibodies; replace with criteria requiring JCV antibody testing. Update drug list in exclusion for concurrent use with other disease modifying therapy. Coding reviewed: Added ICD-10-CM Z01.84.
- 06/21/2021 – Quantity limits added; Step therapy section and tables added.
- 11/20/2020 – Select Review: Remove trial of one alternative treatment from multiple sclerosis criteria.
- 08/21/2020 – Annual Review: Update drug list in exclusion for concurrent use with other disease modifying therapy. Coding reviewed: No changes.
- 08/16/2019 – Annual Review: Update MS criteria to align with updated labeled indication. Clarify prior trial requirements in MS criteria. Wording and formatting changes. Coding Reviewed: No changes.
  08/17/2018 – Annual Review: Initial review of ING-CC-0020 Tysabri (natalizumab). Removed age criteria from Crohn's disease indication for consistency with criteria for MS. Updated concurrent use exclusion criteria with the addition of TNF-α inhibitors. Updated combination MS therapy exclusion criteria wording to align with criteria for other MS agents.

References

1. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 23, 2024.
2. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
3. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
4. Olek MJ, Howard J. Clinical presentation, course and prognosis of multiple sclerosis in adults. Last updated: April 26, 2024. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: October 27, 2024.
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: October 27, 2024.

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.

CC-0020 Tysabri

Commercial

Effective Date	Preferred Agents	Non-Preferred Agents
10/01/2021	Fumaric acid derivative: generic dimethyl fumarate	Tysabri
05/01/2024	Fumaric acid derivative: generic dimethyl fumarate	Tysabri Tyruko

Medicaid

Effective Date	Preferred Agents	Non-Preferred Agents
10/01/2021: GA, MD, NV, NJ, NY, WNY, SC 04/01/2023: DC	Fumaric acid derivative: generic dimethyl fumarate	Tysabri
08/1/2025: DC, GA, MD, NJ, NV, NY, SC, WNY	Generic dimethyl fumarate Glatiramer Glatopa Teriflunomide	Tysabri

Medicare

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A