Medical Policy Bulletin
Title:
Natalizumab (Tysabri®) and Related Biosimilars
Policy #:
MA08.029d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

MULTIPLE SCLEROSIS (MS)
Natalizumab (Tysabri®) and related biosimilars are considered medically necessary and, therefore, covered as monotherapy for the treatment of adults with relapsing forms of MS (to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) when **one** of the following criteria is met:

- The individual has documentation of highly active (aggressive) relapsing MS defined as, but not limited to, accumulating disability, multiple new or enlarging of lesions of brain and/or spinal cord that developed in the first year of illness
- The individual has had an inadequate response to, or is unable to tolerate, alternate MS therapies (e.g., interferon beta-1a [Avonex®, Rebif®], interferon beta-1b [Betaseron®, glatiramer acetate [Copaxone®])

CROHN'S DISEASE (CD)
Natalizumab (Tysabri) and related biosimilars are considered medically necessary and, therefore, covered for the treatment of adults with moderately to severely active CD, who have evidence of inflammation, to induce and maintain clinical response and remission when **all** of the following criteria are met:

- The individual has had an inadequate response to, or is unable to tolerate, conventional CD therapies and inhibitors of tumor necrosis factor-alpha (TNF-α)

- Natalizumab (Tysabri) and related biosimilars will not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, methotrexate) or TNF-α inhibitors (e.g., adalimumab, infliximab)

ANTI-JCV ANTIBODY
Measurement of anti-JCV antibodies (John Cunningham Virus) with ELISA (enzyme-linked immunosorbent assay) is considered medically necessary and, therefore, covered when tested prior to initiation of natalizumab (Tysabri) and related biosimilars treatment and every six months thereafter, to assess the risk of developing progressive multifocal leukoencephalopathy (PML).

ANTI-NATALIZUMAB ANTIBODIES
Measurement of anti-natalizumab antibodies is considered medically necessary and, therefore, covered in an individual receiving treatment with natalizumab (Tysabri) and related biosimilars when persistent anti-natalizumab antibodies are suspected to have caused a documented hypersensitivity or when there has been an extended dose interruption of natalizumab (Tysabri) and related biosimilars therapy. This test should be repeated three months after an initial positive result is detected to confirm that the antibodies are persistent.

EXPERIMENTAL/INVESTIGATIONAL

All other uses of natalizumab (Tysabri) and related biosimilars, including nonrelapsing secondary progressive MS, are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

There is no Medicare coverage determination addressing natalizumab (Tysabri); therefore, the Company policy is applicable.

BLACK BOX WARNINGS

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Natalizumab (Tysabri) was approved by the US Food and Drug Administration (FDA) with a risk evaluation and mitigation strategy (REMS) called the TOUCH® Prescribing Program. Natalizumab-sztn (Tyruko®) was approved by the FDA with a REMS called Tyruko REMS. The goal is to ensure that the benefits of the drug outweigh the risks of developing progressive multifocal leukoencephalopathy (PML) through a restricted distribution program.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, natalizumab (Tysabri) and related biosimilars are covered under the medical benefits of the Company’s Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when natalizumab (Tysabri) is covered under a member's medical benefit (Part B benefit). It does not address instances when natalizumab (Tysabri) is covered under a member’s pharmacy benefit (Part D benefit).

INDICATION AND USAGE IN MULTIPLE SCLEROSIS

The safety and effectiveness of treatment with natalizumab (Tysabri) and related biosimilars in individuals with primary progressive multiple sclerosis (PPMS) have not been demonstrated.

A gadolinium-enhanced magnetic resonance imaging (MRI) scan should be obtained prior to initiating therapy with natalizumab (Tysabri) and related biosimilars. The MRI scan may be helpful in differentiating subsequent MS symptoms from progressive multifocal leukoencephalopathy (PML).

INDICATION AND USAGE IN CROHN'S DISEASE

Natalizumab (Tysabri) and related biosimilars should not be used in combination with immunosuppressants (eg, 6-mercaptopurine, azathioprine, cyclosporine, methotrexate) or inhibitors of TNF-α. Aminosalicylates may be continued during treatment with natalizumab (Tysabri) and related biosimilars.

If the individual with Crohn's disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue natalizumab (Tysabri) and related biosimilars.

For individuals with Crohn's disease who start natalizumab (Tysabri) and related biosimilars while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of natalizumab (Tysabri) and related biosimilars has occurred. If the individual with Crohn's disease cannot be tapered off oral corticosteroids within six months of starting natalizumab (Tysabri) and related biosimilars, discontinue natalizumab (Tysabri) and related biosimilars.

Other than the initial six-month taper, prescribers should consider discontinuing natalizumab (Tysabri) and related biosimilars for individuals who require additional steroid use that exceeds three months in a calendar year to control their Crohn's disease.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

Natalizumab (Tysabri) was initially approved by the FDA in November 2004 but was withdrawn by the manufacturer in February 2005 after three individuals in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious and rare viral infection of the brain. On June 5, 2006, the FDA approved an application for resumed marketing of natalizumab (Tysabri), subject to a special restricted distribution program. Natalizumab (Tysabri) is indicated as monotherapy for the treatment of individuals with relapsing forms of multiple sclerosis. Supplemental approval for use in Crohn's disease was issued on January 14, 2008.

Natalizumab-sztn (Tyruko) was approved by the FDA in August 2023 as a biosimilar to natalizumab (Tysabri). Natalizumab-sztn (Tyruko) is indicated as monotherapy for the treatment of individuals with relapsing forms of multiple sclerosis and individuals with Crohn’s disease.

PEDIATRIC USE
Natalizumab (Tysabri) and related biosimilars are not indicated for use in individuals less than 18 years of age.

Description

Natalizumab (Tysabri) and related biosimilars are a recombinant humanized monoclonal antibody administered by intravenous infusion. They are approved by the US Food and Drug Administration (FDA) for use in adults with relapsing forms of multiple sclerosis (MS) (to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease) as monotherapy and in adults with Crohn's disease (CD). The specific mechanism(s) by which natalizumab (Tysabri) and related biosimilars exerts their effects in relapsing forms of MS and CD have not been fully defined.

MULTIPLE SCLEROSIS (MS), RELAPSING FORMS

In relapsing forms of MS, natalizumab (Tysabri) and related biosimilars delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. They are generally recommended for adults who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

In MS, lesions are believed to occur when activated inflammatory cells, including T lymphocytes (a type of white

blood cell that develops in the thymus gland), cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors that are present on the endothelial cells of the vessel wall. The clinical effect of natalizumab (Tysabri) and related biosimilars in MS may be secondary to blockade of the molecular interaction of the alpha 4 beta 1 (α4ß1) integrin that is expressed by inflammatory cells with vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells and with connecting segment-1 (CS-1) and/or osteopontin expressed by parenchymal cells in the brain. Data from an experimental autoimmune encephalitis animal model of MS demonstrate the reduction of leukocyte migration into the brain parenchyma and the reduction of plaque formation detected by magnetic resonance imaging following repeated administration of natalizumab (Tysabri) and related biosimilars. The clinical significance of these animal data is unknown.

PEER-REVIEWED LITERATURE
Summary

Natalizumab (Tysabri) was evaluated in two randomized, double-blind, placebo-controlled trials with over 2,000 study participants who had relapsing forms of MS, at least one clinical relapse during the past year, and a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0. In Study one, 942 individuals who had not received any interferon-beta or glatiramer acetate for at least the previous six months were randomized to receive natalizumab (Tysabri) (n=627) or placebo (n=315) every four weeks for up to 28 months. In Study two, 1171 individuals who had experienced one or more relapses while on interferon beta-1a during the year prior to study entry, were randomized to receive natalizumab (Tysabri) (n=589) or placebo (n=582) every four weeks for up to 28 months. Interferon beta-1a treatment was continued during the study. In both studies, the time to onset of sustained increase in disability (defined as at least one-point increase on the EDSS from baseline EDSS 1.0 or greater that was sustained for 12 weeks or at least 1.5-point increase on the EDSS from baseline EDSS=0 sustained for 12 weeks) was longer in the natalizumab (Tysabri) group than the placebo group. The proportion of individuals with increased disability and the annualized relapse rates were lower in the natalizumab (Tysabri) group than the placebo group.

CROHN'S DISEASE (CD)

Natalizumab (Tysabri) and related biosimilars may also be used to induce and maintain clinical response and remission in adults with moderately to severely active CD with evidence of inflammation, who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of tumor necrosis factor-alpha (TNF-α). For individuals with CD, natalizumab (Tysabri) and related biosimilars should not be used in combination with immunosuppressants (eg, 6-mercaptopurine, azathioprine, cyclosporine, methotrexate) or TNF-α inhibitors.

In CD, the interaction of the α4β7 integrin with the endothelial receptor mucosal addressin cell adhesion molecule-1 (MAdCAM-1) has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. MAdCAM-1 expression has been found to be increased at active sites of inflammation in individuals with CD, which suggests that it may play a role in the recruitment of leukocytes to the mucosa and contribute to the inflammatory response characteristic of CD. The clinical effect of natalizumab (Tysabri) and related biosimilars in CD may, therefore, be secondary to blockade of the molecular interaction of the α4ß7-integrin receptor with MAdCAM-1 expressed on the venular endothelium at inflammatory foci. VCAM-1 expression has been found to be upregulated on colonic endothelial cells in a mouse model of inflammatory bowel disease (IBD) and appears to play a role in leukocyte recruitment to sites of inflammation. The role of VCAM-1 in CD, however, is not clear.

PEER-REVIEWED LITERATURE
Summary

The safety and effectiveness of natalizumab (Tysabri) were evaluated in three randomized, double-blind, placebo-controlled clinical trials in 1,414 adults with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] greater than or equal to 220 and less than or equal to 450). Concomitant inhibitors of TNF-α were not permitted. Combination therapy with immunosuppressants (eg, 6-mercaptopurine, azathioprine, methotrexate) is not recommended, although it was allowed in the clinical trials. Induction of clinical response (defined as greater than or equal to a 70-point decrease in CDAI from baseline) was evaluated in two studies, and maintenance therapy was evaluated in the third study (n=331).

In Study one, 896 individuals were randomized to receive three monthly infusions or either natalizumab (Tysabri) or placebo. At week 10 the clinical results were not significant. In a post hoc analysis of a subset of 653 individuals with elevated baseline C-reactive protein (CRP), the natalizumab (Tysabri) group (57 percent) had statistically more

subjects in response than the placebo group (45 percent). In Study two, 509 individuals with elevated serum CRP were randomized to receive natalizumab (Tysabri) or placebo in three monthly infusions. Clinical response and clinical remission (defined as CDAI score greater than 150) were measured at Week eight and Week 12. The natalizumab (Tysabri) group had a statistically better clinical response and clinical remission than the placebo group.

Maintenance therapy was evaluated in 331 individuals from Study one that had a clinical response to natalizumab (Tysabri) at both Weeks 10 and 12. They were randomized to either continue treatment with natalizumab (Tysabri) or placebo. Maintenance of response was assessed at Month nine and Month 15. At Month nine, the natalizumab (Tysabri) group had a statistically significant better clinical response and clinical remission than the placebo group.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) AND THE RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAMS

Natalizumab (Tysabri) was initially approved by the FDA in November 2004 but was withdrawn by the manufacturer in February 2005 after three individuals in the drug's clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious and rare viral infection of the brain caused by a common virus known as the John Cunningham Virus (JC virus or JCV). This virus stays dormant in most individuals, but may become active in immunocompromised individuals. Among other factors, including a longer duration of treatment (especially greater than two years) and prior treatment with immunosuppressants (mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil), the presence of anti-JCV antibodies (anti-JCV antibody positive) increases the risk of developing PML. (Note: According to peer-reviewed literature, there is no threshold level for anti-JCV antibodies. The presence of anti-JCV antibodies put an individual at risk for developing PML). Due to this increased risk, consideration should be made to test for anti-JCV antibody status prior to treatment, or during treatment if antibody status is unknown. Those who are anti-JCV antibody negative are still at risk for developing PML, due to the potential for a new JCV infection or a false negative test result. Therefore, individuals with a negative anti-JCV antibody test result may need to be retested every six months.

For individuals who test positive for anti-JCV antibodies, a decision must be made between the individual and the healthcare provider to assess the perceived risks and benefits of continuing therapy, taking into account the total number of risk factors the individual has. Those who choose to continue therapy should do so cautiously with more frequent monitoring (eg, office visits, magnetic resonance imaging [MRIs]).

An early diagnosis of PML has been documented in asymptomatic individuals during periodic MRI monitoring for radiographic signs consistent with PML. Consider monitoring patients at high risk for PML more frequently.

The FDA allowed a clinical trial of natalizumab (Tysabri) to resume in February 2006, after confirming that there were no additional cases of PML. On June 5, 2006, the FDA approved an application for resumed marketing of natalizumab (Tysabri), subject to a special risk evaluation and mitigation strategy (REMS) called the Tysabri Outreach Unified Commitment to Health (TOUCH®) Prescribing Program. Natalizumab-sztn (Tyruko) has its own REMS called Tyruko REMS.

Due to the risk of PML, natalizumab (Tysabri) and related biosimilars are available only through these programs and can only be administered to individuals who are enrolled in and meet all of the conditions of the programs. Under the TOUCH® Prescribing Program/Tyruko REMS, only prescribers, infusion centers, and pharmacies associated with infusion centers that are registered with the programs can prescribe, distribute, or infuse the drug.

ANTI-NATALIZUMAB ANTIBODIES

Anti-natalizumab antibodies may form at any time during natalizumab (Tysabri) and related biosimilars therapy. These antibodies may cause a substandard clinical response. In addition, there may be an increased risk of serious hypersensitivity reactions after an extended dose interruption compared to individuals who received regularly scheduled treatment. Consideration should be given to testing for the presence of antibodies in individuals who wish to recommence therapy following a dose interruption. (Note: According to peer-reviewed literature, there is no threshold level for anti-natalizumab antibodies.)

If the presence of persistent antibodies is suspected due to a substandard clinical response or if the individual is resuming treatment after a dose interruption, antibody testing should be performed. Once an initial positive result is detected, repeat testing three months later is recommended to confirm that antibodies are persistent. Providers should consider the overall benefits and risks of natalizumab (Tysabri) and related biosimilars in persons with persistent antibodies.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of professional clinical guidelines.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

MEASUREMENT OF ANTI-NATALIZUMAB ANTIBODY
83516, 83518

MEASUREMENT OF ANTI-JCV ANTIBODY
86711

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

G35.A Relapsing-remitting multiple sclerosis
G35.C1 Active secondary progressive multiple sclerosis
G35.D Multiple sclerosis, unspecified
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
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

HCPCS Level II Code Number(s)

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

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.029d:

12/15/2025	This version of the policy will become effective 12/15/2025. Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time. The following ICD-10 codes have been added to this policy: G35.A Relapsing-remitting multiple sclerosis G35.C1 Active secondary progressive multiple sclerosis G35.D Multiple sclerosis, unspecified The following ICD-10 code has been removed from this policy: G35 Multiple sclerosis

Revisions From MA08.029c:

03/28/2025	The policy has been reviewed and reissued to communicate the Company's continuing position on natalizumab (Tysabri).
05/07/2024	This version of the policy will become effective 05/07/2024. The following has been **added** to this policy: Information regarding the biosimilar natalizumab-sztn (Tyruko) and its risk evaluation and mitigation strategy (REMS) program. The following HCPCS code has been **added** to this policy: Q5134 Injection, natalizumab-sztn (Tyruko), biosimilar, 1 mg

Revisions From MA08.029b:

09/05/2023	The policy has been reviewed and reissued to communicate the Company's continuing position on natalizumab (Tysabri).
06/01/2022	The policy has been reviewed and reissued to communicate the Company's continuing position on natalizumab (Tysabri).
11/17/2021	The policy has been reviewed and reissued to communicate the Company's continuing position on natalizumab (Tysabri).
11/18/2020	The policy has been reviewed and reissued to communicate the Company's continuing position on natalizumab (Tysabri).
10/21/2019	This policy has undergone a routine review and the medical necessity criteria have been revised to reflect the updated FDA labeling for relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. Additional coverage criteria were added for the treatment of highly active relapsing MS. Experimental/Investigational coverage position has been expanded for nonrelapsing secondary progressive MS.

Revisions From MA08.029a:

04/25/2018	This policy has undergone a routine review, and no revision have been made.
11/22/2017	This policy has been reissued in accordance with the Company's annual review process.
05/04/2016	This version of the policy will become effective 05/04/2016. This policy has been updated to be consistent with the US Food and Drug Administration (FDA) labeling: • The description section was updated to include additional information about the clinical studies. • Glatiramer acetate (Copaxone®) was added as an example of an alternate MS therapy The following code was added to the policy: 83518.

Revisions From MA08.029:

01/21/2015	The policy has been reviewed and reissued to communicate the Company's continuing position on Natalizumab (Tysabri®).
01/01/2015	This is a new policy.

Version Effective Date:
12/15/2025
Version Issued Date:
12/15/2025
Version Reissued Date:
N/A