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Current Effective Date: 05/30/2026
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Next Review Due By: 04/2027
Policy Number: C10276-A

Tysabri (natalizumab) and Biosimilars

PRODUCTS AFFECTED

Tysabri (natalizumab), Tyruko (natalizumab-sztn)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Relapsing form of multiple sclerosis, Moderately to severely active Crohn’s disease

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. This clinical policy will be reviewed along with state and federal requirements, the benefit being administered, and formulary preferencing. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available. The Pharmacy and Therapeutics Committee has determined that biosimilars may be preferred.

A. FOR ALL INDICATIONS:
   1. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA

labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to natalizumab include: Patients who have or have had PML, Patients who have had a hypersensitivity reaction to natalizumab]
AND

2. (a) IF THIS IS A PHARMACY BENEFIT REQUEST FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or serious side effects to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Documentation of medication(s) tried, dates of trial(s) and reason for treatment failure(s) is required.
   AND
   (b) If request is for a NON-PREFERRED/NON-FORMULARY reference product with a biosimilar available for initial or continuation of therapy requests: Documentation of a trial and failure, serious side effects or contraindication to a majority (not more than 3) biosimilar product(s) is required (unless otherwise specified per applicable state regulations and/or there is data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs).
   [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]
   MOLINA REVIEWER NOTE: For Illinois Marketplace, please see Appendix.
   OR
3. FOR INITIAL OR CONTINUATION OF THERAPY REQUESTS OF A PHYSICIAN ADMINISTERED MEDICATION: BIOSIMILAR DRUGS are preferred when requested as a physician administered drug per applicable state regulations and/or there is a lack of data demonstrating clinical superiority of reference drugs over the FDA approved biosimilar drugs. A NON-PREFERRED/NON-FORMULARY reference medication is approved under the following conditions:
   a. Treatment with at least two associated biosimilar drug(s) has been ineffective, resulted in serious side effects, or is contraindicated (i.e., an allergic reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR an adverse reaction to a specific inactive ingredient in the preferred biologic product or biosimilar OR therapeutic success while taking a non-preferred biologic product or biosimilar and therapeutic failure while taking the preferred biologic product or biosimilar documented by patient diary or medical charted notes)

   [DOCUMENTATION REQUIRED: Document when the preferred biologic product or biosimilar was tried and the length of the trial period. Provide specific clinical documentation of therapeutic failure on the preferred biologic product or biosimilar whenever possible. Describe the medical problem caused by the preferred referenced biologic. Vague and non-descriptive symptoms are not adequate rationale (e.g., stomachache).]

B. MODERATE TO SEVERE ACTIVE CROHN'S DISEASE:

1. Documentation of a diagnosis of Crohn's Disease
   AND
2. Member has one or more high risk feature:
   a. Diagnosis at a younger age (<30 years old)
   b. History of active or recent tobacco use
   c. Elevated C-reactive protein and/or fecal calprotectin levels
   d. Deep ulcers on colonoscopy
   e. Long segments of small and/or large bowel involvement
   f. Perianal disease
   g. Extra-intestinal manifestations

h. History of bowel resections

AND

3. (a) Documentation of treatment failure, serious side effects or clinical contraindication to an adequate trial (> 3 months) of ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine, methotrexate) up to maximally indicated doses
   OR
   (b) Prescriber provides documented medical justification that supports the inability to use immunomodulators
   i. Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
   ii. High risk factors for intestinal complications may include: Initial extensive ileal, ileocolonic, or proximal GI involvement, Initial extensive perianal/severe rectal disease, Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas), Deep ulcerations, Penetrating, stricturing or stenosis disease and/or phenotype, Intestinal obstruction or abscess
   iii. High risk factors for postoperative recurrence may include: Less than 10 years duration between time of diagnosis and surgery, Disease location in the ileum and colon, Perianal fistula, Prior history of surgical resection, Use of corticosteroids prior to surgery
   AND
4. Documented treatment failure, serious side effects or clinical contraindication to an adequate trial of one TNF-inhibitor
   AND
5. Documentation by prescriber of baseline disease activity evaluation and goals for treatment to be used to evaluate efficacy of therapy at renewal [DOCUMENTATION REQUIRED]

C. MULTIPLE SCLEROSIS:

1. Documentation of a diagnosis of a relapsing form of multiple sclerosis (relapsing- remitting MS, secondary-progressive MS with relapses, or clinically isolated syndrome)
   AND
2. (a) Documentation of **inadequate response (trial of 3 months) to ONE of the following: ONE of Interferon therapy (Avonex, Rebif, Extavia, Betaseron, Plegridy) OR Glatiramer OR formulary oral disease modifying therapy [e.g., Aubagio (teriflunomide), Tecfidera (dimethyl fumarate), Gilenya (fingolimod), etc.]
   **Inadequate response is defined as meeting at least TWO of the following three criteria during treatment: 1) Clinical relapses (at least two relapses within the past 12 months), 2) CNS lesion progression as measured by MRI, OR 3) Worsening disability (e.g., sustained worsening of EDSS score or neurological exam findings; worsening disability including, but not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or EDSS > 3.5)
   OR
   (b) Documentation member has indicators of a highly active course of multiple sclerosis: (i) age of MS onset > 40 years of age, (ii) male gender, (iii) African American, (iv) motor, sphincter, brainstem-cerebellar symptoms, (v) MRI lesions in brainstem or spina cord, OR
   (vi) ≥ 2 acute relapses in first 2 years of onset with significant sustained disability following relapse

CONTINUATION OF THERAPY:

A. FOR ALL INDICATIONS:

1. For continuation of therapy requests at 24 months or beyond: Member and/or caregiver has been informed about the risks of natalizumab, including that the risk of PML increases with longer treatment duration, and re-instruction on the early signs and symptoms of PML

AND

2. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity [e.g., hypersensitivity reactions, hepatotoxicity, signs or symptoms of PML, development of severe infections (including pneumonias, pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellular, bronchopulmonary aspergillosis, herpes, urinary tract infections, gastroenteritis, vaginitis, tonsillitis, meningitis)]

B. CROHN'S DISEASE:
1. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms [DOCUMENTATION REQUIRED]
AND
2. Documentation natalizumab is prescribed for use as monotherapy only (not prescribed for combination use with immunosuppressants or inhibitors of TNF-α)

C. MULTIPLE SCLEROSIS:
1. Documentation of positive clinical response or stable disease based on ONE of the following:
(a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
OR
(b) Documentation of lack of progression or sustained disability
OR
(c) Recent (within the last 6 months) MRI shows lack of development of new asymptomatic lesions

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of Therapy: 12 months
MOLINA REVIEWER NOTE: For Connecticut Marketplace, please see Appendix.

PRESCRIBER REQUIREMENTS:
Multiple Sclerosis: Prescribed by or in consultation with aboard certified neurologist or Multiple sclerosis specialist
Crohn's Disease: Prescribed by or in consultation with a board certified gastroenterologist or colorectal surgeon
[If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
300 mg every 4 weeks

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for natalizumab. For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous Infusion

DRUG CLASS:
Multiple Sclerosis Agents - Monoclonal Antibodies

FDA-APPROVED USES:
Tysabri and Tyruko are indicated for treatment of:
Multiple sclerosis (MS): Indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Natalizumab products increases the risk of PML. When initiating and continuing treatment with natalizumab, physicians should consider whether the expected benefit of natalizumab is sufficient to offset this risk.
Crohn's disease (CD): Indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. *Important limitations: In CD, natalizumab should not be used in combination with immunosuppressants or inhibitors of TNF alpha.*

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

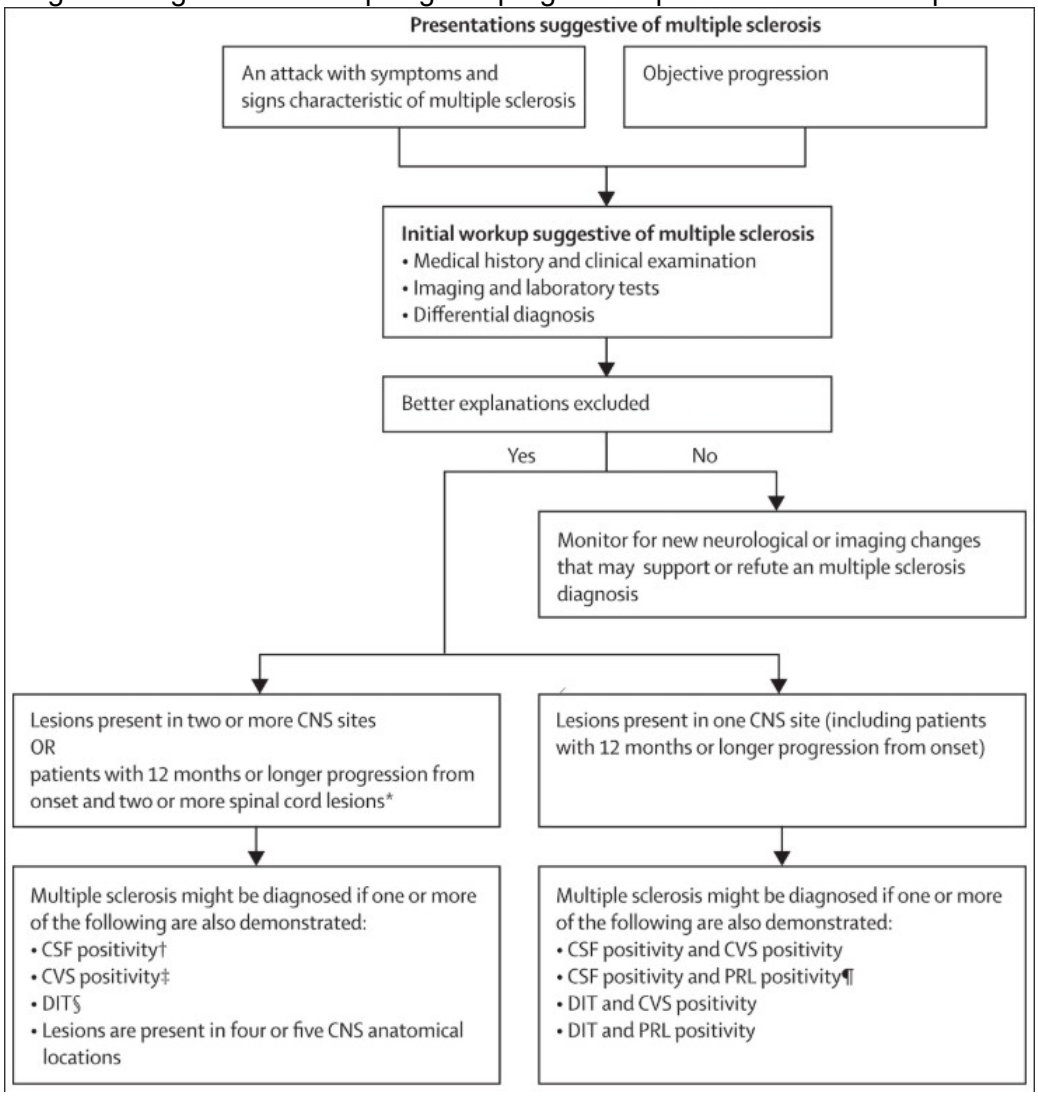
APPENDIX:
Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Connecticut (Source: State of Connecticut)
"Sec. 38a-591o. Restrictions applicable to prospective or concurrent review of certain recurring prescription drugs. Exceptions…. (b) No health carrier shall require a prospective or concurrent review of a *recurring prescription drug to directly treat any autoimmune disorder, multiple sclerosis or cancer after such health carrier has certified such prescription drug through utilization review*. Nothing in this section shall require a health carrier to cover: (1) Any prescription drug to treat any autoimmune disorder, multiple sclerosis or cancer if the terms of coverage completely exclude such prescription drug from the policy's covered benefits; (2) a brand name drug when an equivalent generic drug is available; (3) a prescription drug that was certified through prospective or concurrent review (A) by such covered person's previous health carrier, or (B) under a previous employer's fully insured health plan administered by a third-party administrator that provided coverage to such covered person."

Illinois (Source: Illinois General Assembly)
"(215 ILCS 134/45.1) Sec. 45.1. Medical exceptions procedures required. (c) An off-formulary exception request shall not be denied if: (1) the formulary prescription drug is contraindicated; (2) the patient has tried the formulary prescription drug while under the patient's current or previous health insurance or health benefit plan and the prescribing provider submits evidence of failure or intolerance; or (3) the patient is stable on a prescription drug selected by his or her health care provider for the medical condition under consideration while on a current or previous health insurance or health benefit plan. (d) Upon the granting of an exception request, the insurer, health plan, utilization review organization, or other entity shall authorize the coverage for the drug prescribed by the enrollee's treating health care provider, to the extent the prescribed drug is a covered drug under the policy or contract up to the quantity covered. (e) Any approval of a medical exception request made pursuant to this Section shall be honored for 12 months following the date of the approval or until renewal of the plan."

Appendix 1: Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria

Diagnostic algorithm for relapsing and progressive presentations of multiple sclerosis



CSF=cerebrospinal fluid. CVS=central vein sign. DIT=dissemination in time. PRL=paramagnetic rim lesion. *In patients presenting with 12 months or longer disease progression from symptom onset, the presence of two or more spinal cord lesions is considered evidence of dissemination in space and meets criteria for the presence of lesions in two CNS locations. †CSF positivity is demonstrated by presence of oligoclonal bands or kappa free-light chains. ‡CVS positivity is demonstrated by the presence of six or more lesions with CVS; if fewer than ten white matter lesions are seen on MRI, the number of CVS positive lesions should outnumber the CVS negative lesions. §DIT is demonstrated by the presence of one or more new T2 lesions or one or more gadolinium-positive lesions or a clinical attack. ¶PRL positivity is demonstrated by the presence of one or more PRL.

Criteria	Definition
Dissemination in space (DIS)	1 or more hyperintense T2 lesions on MRI that are characteristic of MS in at least 2 of 5 MS-typical topographies: • Optic nerve • Periventricular • Cortical/juxtacortical • Infratentorial • Spinal cord Or

	An additional clinical attack implicating a different CNS site
Dissemination in time (DIT)	A new hyperintense T2 and/or gadolinium-enhancing lesion(s) of follow-up MRI Or An additional clinical attach characteristic of MS
Central vein sign (CVS)	A thin linear hypointense line or dot representing a small venule on susceptibility-weighted MRI, positioned centrally within a demyelinating MS white matter lesion
CVS positivity	Need 1 of the following for adults: • 6 or more MRI lesions have a CVS • If MRI has < 6 lesions, the majority of lesions have a CVS For children age < 18: • 50% or more of MRI lesions have a CVS
Paramagnetic rim lesion (PRL)	MRI lesion characterized by a hyperintense core on T2-weighted MRI surrounded by a hypointense rim on susceptibility weighted MRI
PRL positivity	1 or more PRLs on MRI
Cerebrospinal fluid (CSF) positivity	1 of the following: • CSF restricted oligoclonal bands • Kappa free light chains (kFLCs)

Appendix 2:
Molina Healthcare, Inc National Pharmacy and Therapeutics Committee will create and maintain a biosimilar position statement: A biosimilar is a highly similar version of a brand name biological drug that meets strict controls for structural, pharmaceutical, and clinical consistency. A biosimilar manufacturer must demonstrate that there are no meaningful clinical differences (i.e., safety and efficacy) between the biosimilar and the reference product. Clinical performance is demonstrated through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, an assessment of clinical immunogenicity, and, if needed, additional clinical studies.[1]
As costs for biological specialty drugs continue to rise, the growing biosimilar market will benefit providers and patients by broadening biological treatment options and expanding access to these medications at lower costs. Molina Healthcare, Inc. continues to be committed to continually reevaluating preferred strategies and applying innovative cost-controls to ensure patients receive safe, effective, and quality healthcare. This commitment includes potentially creating a preference for biosimilars when value can be added without compromising patient satisfaction and safety.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Multiple Sclerosis (MS) is a chronic autoimmune disease that degrades the protective myelin sheath that covers nerve cells in the central nervous system, specifically in the areas of the brain, spinal cord, and optic nerves. For most Americans, the risk of developing MS is approximately 0.1% but the risk is increased for individuals with a first-degree relative with MS. MS occurs at least two to three times more commonly in women than in men. Most patients are diagnosed between the ages of 20 to 50 years. Relapsing remitting MS (RRMS) is the most common type of MS affecting approximately 85% of the patients initially diagnosed with MS. Complications of MS include fatigue, loss of coordination, visual problems, cognitive and sexual dysfunction, depression, spasticity, and pain.
Clinically, MS presents with four relatively distinguishable patterns based on the course of disease. Of the four clinical subtypes of MS (primary progressive, progressive relapsing, RRMS and secondary progressive), RRMS is the most common and is characterized by acute relapses followed by partial or full recovery.

1. Relapsing–remitting MS: the most common form, affecting about 85% of MS patients. It is marked by flare-ups (relapses or exacerbations) of symptoms followed by periods of

remission when symptoms improve or disappear.

2. Secondary progressive MS: may develop in some patients with relapsing–remitting disease. For many patients, treatment with disease-modifying agents helps delay such progression. The disease course continues to worsen with or without periods of remission or leveling off of symptom severity (plateaus).
3. Primary progressive MS affects approximately 10% of MS patients. Symptoms continue to worsen gradually from the beginning. There are no relapses or remissions, but there may be occasional plateaus. This form of MS is more resistant to the drugs typically used to treat the disease.
4. Progressive-relapsing MS: PRMS affects about 5% of patients. It is characterized by continuous neurologic decline from the time of diagnosis, accompanied by distinct attacks. Itis progressive from the start, with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission.

Crohn's disease (CD) is a chronic, inflammatory, multisystem disorder of unknown etiology with genetic, immunologic, and environmental influences. CD involves any area of the gastrointestinal tract (GIT) from the oral cavity to the anus, but it is limited primarily to the colon with or without small- intestine disease. Moreover, the inflammation in CD is often described as transmural, damaging each mucosal layer of the GIT, and noncontinuous. Therapy for CD includes medical therapy with pharmacologic agents consisting of 5-aminosalicylates (5-ASA), antibiotics, corticosteroids, immunomodulators, and biologics. Surgery is reserved for patients who are refractory to medical therapy. The key symptoms of CD include abdominal pain, diarrhea, and fatigue. Weight loss, fever, growth failure, anemia, recurrent fistulas, or extraintestinal manifestations (e.g., arthritis, iritis) can also occur. There is no single laboratory test that can make an unequivocal diagnosis of CD. The anti-tumor necrosis factor (anti-TNF) agents (infliximab, adalimumab, and certolizumab pegol) are effective for treatment of patients with CD who respond inadequately to treatment with corticosteroids, thiopurines, and methotrexate. Other monoclonal antibodies approved for CD are the integrin inhibitors. Natalizumab, an α4 integrin inhibitor, is approved for use in CD. These drugs are reserved for patients nonresponsive to conventional therapies, including TNF inhibitors, and carry a risk of PML. Natalizumab is a monoclonal antibody against the alpha-4 subunit of integrin molecules. These molecules are important to adhesion and migration of cells from the vasculature into inflamed tissue. Natalizumab blocks integrin association with vascular receptors, limiting adhesion and transmigration of leukocytes. Efficacy in specific disorders may be related to reduction in specific inflammatory cell populations in target tissues. In multiple sclerosis, efficacy may be related to blockade of T-lymphocyte migration into the central nervous system; treatment results in a decreased frequency of relapse. In Crohn disease, natalizumab decreases inflammation by binding to alpha-4 integrin, blocking adhesion and migration of leukocytes in the gut.

Tysabri was evaluated in multiple sclerosis in two randomized, double-blind, placebo-controlled trials. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0. Median time on study drug was 120 weeks in each study. Study MS1 enrolled patients who had not received any interferon-beta or glatiramer acetate for at least the previous 6 months; approximately 94% had never been treated with these agents. Patients were randomized in a 2:1 ratio to receive Tysabri 300 mg intravenous infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions). Study MS2 enrolled patients who had experienced one or more relapses while on treatment with Avonex® (Interferon beta-1a) 30 mcg intramuscularly (IM) once weekly during the year prior to study entry. Patients were evenly randomized to receive Tysabri 300 mg (n=589) or placebo (n=582) every 4 weeks for up to 28 months (30 infusions). All patients continued to receive Avonex 30 mcg IM once weekly. The efficacy of Tysabri alone was not compared with the efficacy of Tysabri plus Avonex. The primary endpoint at 2 years was time to onset of sustained increase in disability, defined as an increase of at least 1 point on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 12 weeks. Time to onset of sustained increase in disability was longer in Tysabri-treated patients than in placebo-treated patients in Studies MS1 (Figure 1) and MS2. The proportion of patients with increased disability and the annualized relapse rate were also lower in Tysabri treated patients than in placebo-treated patients in Studies MS1 and MS2.

Drug and Biologic Coverage Criteria

The safety and efficacy of Tysabri in Crohn's Disease were evaluated in three randomized, double-blind, placebo controlled clinical trials in 1414 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥220 and ≤450). Concomitant inhibitors of TNF-α were not permitted. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercatopurine, azathioprine, or methotrexate) were permitted, and 89% of patients continued to receive at least one of these medications. Although permitted in the clinical trials, combination therapy with immunosuppressants is not recommended. Overall, approximately two-thirds of patients were not taking concomitant immunosuppressants, and approximately one-third of patients were taking neither concomitant immunosuppressants nor concomitant corticosteroids. Induction of clinical response (defined as ≥70-point decrease in CDAI from baseline) was evaluated in two studies. In Study CD1, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg TYSABRI or placebo. At Week 10, 56% of the 717 patients receiving Tysabri were in response compared to 49% of the 179 patients receiving placebo (treatment effect: 7%; 95% confidence interval (CI): [-1%, 16%]; p=0.067). In a post hoc analysis of the subset of 653 patients with elevated baseline C-reactive protein (CRP), indicative of active inflammation, 57% of TYSABRI patients were in response compared to 45% of those receiving placebo (treatment effect: 12%; 95% CI: [3%, 22%]; nominal p=0.01). Proportion with Sustained Increase in Disability In the second induction trial, Study CD2, only patients with elevated serum C-reactive Protein (CRP) were studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. In Study CD2, in contrast to Study CD1, clinical response and clinical remission (defined as CDAI score <150) were required to be met at both Weeks 8 and 12, rather than at a single time-point. In studies CD1 and CD2, for subgroups defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF-α appeared to have lower clinical response and lower clinical remission in both the treatment and placebo groups. For patients in Study CD2 with an inadequate response to prior treatment with inhibitors of TNF-α, clinical response at both Weeks 8 and 12 was seen in 38% of those randomized to Tysabri, and clinical remission at both Weeks 8 and 12 was seen in 17%. Maintenance therapy was evaluated in Study CD3. In this study, 331 patients from Study CD1 that had had a clinical response to Tysabri at both Weeks 10 and 12 were re-randomized 1:1 to treatment with continuing monthly infusions of either 300 mg TYSABRI or placebo. Maintenance of response was assessed by the proportion of patients who did not lose clinical response at any study visit for an additional 6 and 12 months of treatment. For subgroups in study CD3 defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF-α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF-α appeared to have lower maintenance of clinical response and lower maintenance of clinical remission in both the treatment and placebo groups. For patients in study CD3 with an inadequate response to prior treatment with inhibitors of TNF-α, maintenance of clinical response through Month 9 was seen in 52% of those randomized to Tysabri, and maintenance of clinical remission through Month 9 was seen in 30%. Given the requirement to discontinue chronic steroids it is important to note that in the subgroup of patients (n=65) who were receiving corticosteroid medication at baseline, responded to Tysabri in Study CD1, and were re-randomized to Tysabri in Study CD3, approximately two thirds were able to discontinue steroids within 10 weeks of initiating a steroid taper.

Tysabri Touch Prescribing Program (REMS)

TYSABRI is available only through a restricted program under a REMS called the TOUCH® Prescribing Program because of the risk of PML.

For prescribers and patients, the TOUCH® Prescribing Program has two components: MS TOUCH® (for patients with multiple sclerosis) and CD TOUCH® (for patients with Crohn's disease).

Selected requirements of the TOUCH® Prescribing Program include the following:

- Prescribers must be certified and comply with the following:
  - Review the TOUCH® Prescribing Program prescriber educational materials, including the

full prescribing information.
- − Educate patients on the benefits and risks of treatment with TYSABRI, ensure that patients receive the Medication Guide, and encourage them to ask questions.
- − Review, complete, and sign the Patient-Prescriber Enrollment Form.
- − Evaluate patients three months after the first infusion, six months after the first infusion, every six months thereafter, and for at least six months after discontinuing TYSABRI.
- − Determine every six months whether patients should continue on treatment and, if so, authorize treatment for another six months.
- − Submit to Biogen the "TYSABRI Patient Status Report and Reauthorization Questionnaire" six months after initiating treatment and every six months thereafter.
- − Complete an "Initial Discontinuation Questionnaire" when TYSABRI is discontinued, and a "6-Month Discontinuation Questionnaire" following discontinuation of TYSABRI.
- − Report cases of PML, hospitalizations due to opportunistic infections, and deaths to Biogen at 1-800-456-2255 as soon as possible.

• Patients must be enrolled in the TOUCH® Prescribing Program, read the Medication Guide, understand the risks associated with TYSABRI, and complete and sign the Patient-Prescriber Enrollment Form.
• Pharmacies and infusion centers must be specially certified to dispense or infuse TYSABRI.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of natalizumab are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to natalizumab include: patients who have or have had PML, patients who have had a hypersensitivity reaction to natalizumab products.

Exclusions/Contraindications:

Patients who are anti-JCV antibody negative have a lower risk of PML than those who are positive. Patients who are anti-JCV antibody negative are still at risk for the development of PML due to the potential for a new JCV infection or a false negative test result. Therefore, patients with a negative anti-JCV antibody test result should be retested periodically. Withhold natalizumab dosing immediately and perform an appropriate diagnostic evaluation at the first sign or symptom suggestive of PML.
Member is NOT receiving any other disease-modifying MS agent, immunosuppressants, or TNF inhibitors (e.g., adalimumab, infliximab).

OTHER SPECIAL CONSIDERATIONS:

(Natalizumab has a **Black Boxed Warning** for Progressive multifocal leukoencephalopathy: Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Monitor patients, and withhold natalizumab immediately at the first sign or symptom suggestive of PML.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all- inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J2323	Injection, natalizumab, 1mg
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg

AVAILABLE DOSAGE FORMS:
Tysabri CONC 300MG/15ML single-dose vial
Tyruko CONC 300MG/15ML single-dose vial

REFERENCES

1. Tysabri (natalizumab) injection, for intravenous use [prescribing information]: Cambridge, MA: Biogen Inc; March 2025.
2. Tyruko (natalizumab-sztn) injection, for intravenous use [prescribing information]. Princeton, NJ: Sandoz Inc.; October 2025.
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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Criteria Name Change Diagnosis Required Medical Information Duration of Approval FDA Approved Uses Appendix Contraindications/Exclusions/Discontinuation Other Special Considerations Coding/Billing Information References	Q2 2026
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation References	Q2 2025

REVISION- Notable revisions: Required Medical Information Continuation of Therapy Appendix Other Special Considerations References	Q2 2024
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Duration of Approval Prescriber Requirements Quantity FDA-Approved Uses Appendix Background Contraindications/Exclusions/Discontinuation Other Special Considerations Available Dosage Forms References	Q2 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file