Effective Date **3/1/2024**
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Coverage Policy Number **IP0215**

Natalizumab

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INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for natalizumab (**Tysabri®**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Natalizumab (Tysabri) is considered medically necessary when ONE of the following is met:

1. **Crohn's Disease.** Individual meets **ALL** of the following criteria:
   A. 18 years of age or older
   B. Diagnosis of moderate to severe Crohn's disease
   C. Documentation of failure, contraindication or intolerance to **ONE** anti-tumor necrosis factor biologic

D. Medication is being prescribed by, or in consultation with, a gastroenterologist or a prescriber who specializes in Crohn's disease

Dosing in Crohn's Disease. The recommended dose of natalizumab (Tysabri) is up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

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2. **Multiple Sclerosis when the individual meets ALL of the following criteria:**
   A. 18 years of age or older
   B. Documented diagnosis of **ONE** of the following relapsing forms of Multiple Sclerosis:
      i. Active Secondary Progressive Multiple Sclerosis (SPMS) (for example, SPMS with a documented relapse)
      ii. Clinically Isolated Syndrome (CIS)
      iii. Relapsing-Remitting Multiple Sclerosis (RRMS)
   C. **ONE** of the following:
      i. Documentation of failure or intolerance to **ONE** of the following:
         a. dimethyl fumarate delayed-release capsules (generic for Tecfidera) [may require prior authorization]
         b. fingolimod (generic for Gilenya) [may require prior authorization]
      ii. Documented contraindication to **BOTH** of the following:
         a. dimethyl fumarate delayed-release capsules (generic for Tecfidera) [may require prior authorization]
         b. fingolimod (generic for Gilenya) [may require prior authorization
      iii. Treatment of highly-active or aggressive multiple sclerosis documented by **ONE** of the following:
         a. Demonstration of rapidly-advancing deterioration(s) in physical functioning (for example, loss of mobility / or lower levels of ambulation, severe changes in strength or coordination)
         b. Documentation of disabling relapse(s) with suboptimal response to systemic corticosteroids
         c. Magnetic resonance imaging (MRI) findings suggest highly-active or aggressive multiple sclerosis (for example, new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions)
         d. Documentation of cognitive impairment related to multiple sclerosis (for example, deficits in short-term or long-term memory, visual spatial ability deficits)
      iv. Currently receiving Tysabri
   D. Medication is being prescribed by, or in consultation with, a neurologist or a physician who specializes in the treatment of multiple sclerosis

      Dosing in Multiple Sclerosis. The recommended dose of natalizumab (Tysabri) is up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of natalizumab (Tysabri) is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration is up to 12 months.
Reauthorization approval duration is up to 12 months.

Conditions Not Covered

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

1. **Concurrent Use with an Immunosuppressant Agent (for example, 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab IV product, Zymfentra [infliximab-dyyb subcutaneous injection], an adalimumab product, Cimzia, Entyvio IV, Skyrizi [risankizumab-rzaa intravenous infusion and subcutaneous injection on-body injector], Stelara, and Rinvoq [upadacitinib extended-release tablets]) in Patients with Crohn's Disease.**
   Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.[1]

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).**
   These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **Non-Relapsing Forms of Multiple Sclerosis.** The safety and efficacy of Tysabri have not been established in patients with primary progressive multiple sclerosis.

4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.[10]

Coding / Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J2323	Injection, natalizumab, 1 mg

Background

OVERVIEW
Tysabri, an integrin receptor antagonist, is indicated for the treatment of:[1]

- Relapsing forms of **multiple sclerosis (MS)** include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy.
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML).[1] When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri should not be used in combination with immunosuppressants (e.g.,

azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. The safety and effectiveness in patients with MS or Crohn's disease < 18 years of age have not been established.

Disease Overview

Multiple Sclerosis

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria.

Crohn's Disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[8] The prevalence has been increasing worldwide.[9] Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, and recurrent fistulas. Adults with Crohn's disease may be at risk of bone fractures, as well as thromboembolism. Other extraintestinal manifestations may occur (e.g., primary sclerosing cholangitis). Younger patients may experience growth failure.[8,9] The chronic intestinal inflammation over time leads to intestinal complications such as strictures, fistulas, and abscesses. Only 20% to 30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, it is appropriate to identify therapies that will achieve adequate control for the patient. Many different therapies are available including corticosteroids, immunomodulators (e.g., azathioprine, 6-mercaptopurine), and anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol subcutaneous injection]).

Guidelines

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Tysabri for patients with MS who have highly active disease.[7]

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various drug classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

The American College of Gastroenterology has guidelines on management of Crohn's disease in adults (2018).[9] Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids, thiopurines, or methotrexate. For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with Entyvio® [vedolizumab intravenous infusion]) with or without an immunomodulator is more effective than placebo and should be considered for use for induction of symptomatic remission in patients with Crohn's disease. Tysabri is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation; high level of evidence). Tysabri should be used for maintenance of Tysabri-induced remission of Crohn's disease only if serum antibody to John Cunningham virus is negative. Stelara® (ustekinumab subcutaneous injection or intravenous infusion) should be given for moderate to severe Crohn's disease patients who failed treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF agents or who have had no prior exposure to anti-TNF agents.

Safety
Tysabri has a Boxed Warning regarding the risk of PML.[1] Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called the TOUCH® Prescribing Program.

Appendix

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Briumvi™ (ublituximab-xiiy intravenous infusion)	Intravenous infusion
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory™ (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tascenso ODT™ (fingolimod orally disintegrating tablets)	Oral
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tyruko® (natalizumab intravenous infusion)	Intravenous infusion
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral

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