STATE OF IOWA DEPARTMENT OF
Health AND Human
SERVICES

Tysabri (natalizumab)
PAM–014

Iowa Medicaid Program:	Prior Authorization	**Effective Date:**	01/01/2008
Revision Number:	7	**Last Rev Date:**	04/21/2023
Reviewed By:	Medicaid Medical Director	**Next Rev Date:**	04/19/2024
Approved By:	Medicaid Clinical Advisory Committee	**Approved Date:**	04/13/2020

Overview

Medication:[1]	natalizumab
Brand Name:	Tysabri®
Pharmacologic Category:	Integrin receptor antagonist.
FDA-Approved Indication(s):	**Multiple Sclerosis (MS):** Indicated as monotherapy for the treatment of relapsing forms of MS in adults, to include: • Clinically isolated syndrome (CIS); • Relapsing-remitting disease (RRMS); • Active secondary progressive disease (SPMS). **Crohn's Disease (CD):** Indicated for inducing and maintaining clinical response and remission in adult patients 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 TNF-α.
How Supplied:	Single-dose vial: 300 mg/15 mL (20 mg/mL)
Dosage and Administration:	IV infusion: 300 mg every 4 weeks
Benefit Category:	Medical

Black Box Warning

Tysabri® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for the development of PML include the presence of anti-JCV (John Cunningham virus) antibodies, duration of therapy, and prior use of immuno-suppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment:

- Healthcare professionals should monitor patients on Tysabri® for any new sign or symptom that may be suggestive of PML. Tysabri® dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA is recommended.
- Because of the risk of PML, Tysabri® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the TOUCH® Prescribing Program.

Descriptive Narrative

Multiple sclerosis (MS) affects more than 400,000 people in the United States, and more than 2.3 million people have multiple sclerosis worldwide. It is the most common immune-mediated inflammatory demyelinating disease of the central nervous system and is a leading cause of disability in young adults. The core phenotypes of multiple sclerosis are relapsing-remitting and progressive disease. The pattern and course of MS is further categorized into the following clinical subtypes:

1. Clinically isolated syndrome (CIS).
2. Relapsing-remitting multiple sclerosis (RRMS).
3. Secondary progressive multiple sclerosis (SPMS).
4. Primary progressive multiple sclerosis (PPMS).

Clinically isolated syndrome (CIS) is the first clinical episode that is consistent with a demyelinating etiology and suggestive of multiple sclerosis (MS). Symptoms usually develop over the course of hours to days, and then gradually remit over the ensuing weeks to months, although remission may not be complete. CIS is considered as a precursor to MS in most patients. The long-term (i.e., 10- to 20-year) likelihood of developing MS ranges from 60 to 80 percent. In patients with a CIS who have a normal baseline MRI, limited data suggests that the long-term prevalence of MS is approximately 20 percent.

Relapsing-remitting multiple sclerosis (RRMS) accounts for 85 to 90 percent of cases at onset. It is characterized by clearly defined attacks (also known as relapses, flares, or exacerbations) with full or incomplete recovery. Symptoms and signs associated with a relapse usually reach a peak in days to weeks, followed by a remission during which the symptoms and signs resolve to a variable extent.

Secondary progressive multiple sclerosis (SPMS) begins as relapsing-remitting disease, but over time the disease enters a stage of steady deterioration in function. There are no established criteria to determine when RRMS converts to SPMS; the diagnosis of SPMS is made retrospectively. SPMS ultimately develops in up to 90 percent of patients with RRMS after 25 years and causes the greatest amount of neurologic disability attributable to MS.

Primary progressive multiple sclerosis (PPMS) is characterized by progressive accumulation of disability from disease onset with occasional plateaus, temporary minor improvements, or acute relapses still consistent with the definition. A diagnosis of PPMS is made exclusively on patient history, and there are no imaging or exam findings that distinguish PPMS from RRMS. PPMS represents about 10 percent of adult MS cases at disease onset.[2]

Crohn's disease (CD) is one of two major disorders that comprise inflammatory bowel disease (IBD), the other being ulcerative colitis (UC). While UC affects only the colon and is characterized by inflammation of the mucosal layer, CD is characterized by transmural inflammation and may involve any portion of luminal gastrointestinal (GI) tract, from the oral cavity to the perianal area. Patterns of disease distribution include:

- Approximately 80 percent of patients have small bowel involvement, usually in the distal ileum, with one-third of patients having ileitis exclusively.
- Approximately 50 percent of patients have ileocolitis, which refers to involvement of both the ileum and colon.

- Approximately 20 percent have disease limited to the colon. In contrast to rectal involvement in patients with UC, one-half of CD patients with colitis have sparing of the rectum.
- Approximately one-third of patients have perianal disease.
- Approximately 5 to 15 percent have involvement of the mouth or gastroduodenal area, while fewer patients have involvement of the esophagus and proximal small bowel.

Patients with CD may have symptoms for many years prior to diagnosis, or they may present acutely. The cardinal GI symptoms of CD include abdominal pain and diarrhea (with or without bleeding), as well as systemic symptoms such as fatigue and weight loss.[3]

Tysabri® (natalizumab) is a humanized monoclonal antibody against the cell adhesion molecule α4-integrin. The drug is believed to work by reducing the ability of inflammatory immune cells to attach to and pass through the cell layers lining the intestines and blood-brain barrier.

Guidelines

Multiple Sclerosis (MS)

The American Academy of Neurology (AAN) published practice guidelines in 2018 regarding disease-modifying therapies (DMTs) for adults with multiple sclerosis (MS).[4] Recommendations regarding starting, switching, and stopping DMT were reviewed and assigned one of three recommendation designations: A, B, or C. Each designation denotes the level of recommendation strength.

Level	Helping Verb	Description
A	MUST	Level A is the strongest recommendation level. These recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk.
B	SHOULD	These recommendations are more common, as the requirements are less stringent but still based on the evidence and benefit-risk profile.
C	MAY	Level C represents the lowest allowable recommendation level the AAN considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Starting DMT: Level A ("must") Recommendation Statements	
2a	Clinicians must ascertain and incorporate/review preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common adverse effects, and tolerability in the choice of DMT in people with MS being considered for DMT.
2b	Clinicians must engage in an ongoing dialogue regarding treatment decisions throughout the disease course with people with MS.
3b	Clinicians must counsel people with MS on DMTs to notify the clinicians of new or worsening symptoms.
Switching DMT: Level A ("must") Recommendation Statements	
9a	Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation.
Discontinuing DMT: Level A ("must") Recommendation Statements	
	There are not any Level A recommendations regarding discontinuing DMT.

Crohn's Disease (CD)

Guidelines published by the American College of Gastroenterology (ACG) in 2018 and were developed to review Crohn's disease clinical features and natural history, diagnostics, and therapeutic interventions. [5]

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to evaluate the level of evidence and strength of recommendations.

Recommendations Statements	Level of Evidence
Strong: the desirable effects of an intervention clearly outweigh the undesirable effects. **Conditional:** there is uncertainty about the trade-offs.	**High:** further research is unlikely to change the authors' confidence in the estimate of the effect. **Moderate:** further research would be likely to have an impact on the confidence in the estimate of effect. **Low:** further research would be expected to have an important impact on the confidence in the estimate of the effect and would be likely to change the estimate. **Very Low:** any estimate of effect is very uncertain.

Recommendations related to Tysabri® which have a **strong** grade are as follows:

Medical Therapy – *Moderate-to-severe disease/moderate-to-high-risk disease*	
17	Oral corticosteroids are effective and can be used for short-term use in alleviating signs and symptoms of moderate to severely active CD (strong recommendation, moderate level of evidence).
19	Azathioprine (at doses of 1.5–2.5 mg/kg/day) and 6-mercaptopurine (at doses of 0.75–1.5 mg/kg day) are not more effective than placebo to induce short-term symptomatic remission and should not be used in this manner (strong recommendation, low level of evidence).
20	Thiopurines (azathioprine, 6-mercaptopurine) are effective and should be considered for use for steroid sparing in CD (strong recommendation, low level of evidence).
21	Azathioprine and 6-mercaptourine are effective therapies and should be considered for treatment of patients with CD for maintenance of remission (strong recommendation, moderate level of evidence).
22	Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with CD (strong recommendation, low level of evidence).
24	Anti-TNF agents (infliximab, adalimumab, certolizumab pegol) should be used to treat CD that is resistant to treatment with corticosteroids (strong recommendation, moderate level of evidence).
25	Anti-TNF agents should be given for CD refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence).
28	Natalizumab is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active CD (strong recommendation, high level of evidence).
29	Natalizumab should be used for maintenance of natalizumab-induced remission of CD only if serum antibody to JCV is negative. Testing for anti-JCV antibody should be repeated every 6 months and treatment stopped if the result is positive (strong recommendation, moderate level of evidence).
31	Cyclosporine, mycophenolate mofetil, and tacrolimus should not be used for CD (strong recommendation, moderate level of evidence).

Criteria

Prior authorization is required.

Multiple Sclerosis (MS)

Tysabri® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of one of the following clinical subtypes of multiple sclerosis (MS) (a, b, or c):
    a. Clinically isolated syndrome (CIS); **OR**
    b. Relapsing-remitting multiple sclerosis (RRMS); **OR**
    c. Active secondary progressive multiple sclerosis (SPMS); **AND**
2. Member is 18 years of age or older; **AND**
3. Tysabri® is not prescribed or administered concurrently with other disease-modifying therapies (DMTs) for MS (with the exception of dalfampridine*, which may be used in combination with Tysabri®); **AND**
4. Member has had an anti-JCV antibody level drawn prior to initiation of therapy, and the results, as well as risks and benefits of therapy, have been discussed and understood; **AND**
5. Prescribed by, or in consultation with, a neurologist; **AND**
6. The regimen prescribed is within the FDA-approved labeling: 300 mg every 4 weeks as an intravenous infusion.

Tysabri® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit or has previously met initial approval criteria; **AND**
2. Documentation of positive clinical response to therapy; **AND**
3. Tysabri® is not prescribed or administered concurrently with other disease-modifying therapies (DMTs) for multiple sclerosis (MS) (with the exception of dalfampridine*, which may be used in combination with Tysabri®); **AND**
4. Prescribed by, or in consultation with, a neurologist; **AND**
5. The regimen prescribed is within the FDA-approved labeling: 300 mg every 4 weeks as an intravenous infusion.

* Dalfampridine may require a separate pharmacy prior authorization (see Iowa Medicaid preferred drug list for more information).

Crohn's Disease (CD)

Tysabri® is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of moderate to severe Crohn's disease (CD); **AND**
2. Member is 18 years of age or older; **AND**
3. Documentation of failure after a minimum consecutive 90-day trial of at least one immunomodulator (e.g., azathioprine, 6-mercaptopurine [6-MP], methotrexate [MTX]) at up to maximally indicated doses, unless clinically adverse effects are experienced or all are contraindicated; **AND**
4. Documentation of failure after a minimum consecutive 90-day trial of at least one TNF- α inhibitor therapy (adalimumab [Humira® or biosimilar], certolizumab [Cimzia®], infliximab [Remicade® or biosimilar]), unless clinically adverse effects are experienced or all are contraindicated; **AND**
5. Tysabri® is not prescribed concurrently with other immunosuppressants (e.g., azathioprine, 6-MP, MTX) or TNF-α inhibitors; **AND**
6. Prescribed by, or in consultation with, a gastroenterologist; **AND**
7. The regimen prescribed is within the FDA-approved labeling: 300 mg every 4 weeks as an intravenous infusion.

Tysabri® is considered medically necessary for continuation of therapy when **ALL** of the following are met:

1. Member is currently receiving medication through the Iowa Medicaid benefit and/or has previously met initial approval criteria; **AND**
2. Documentation of positive clinical response to therapy; **AND**
3. Tysabri® is not prescribed concurrently with other immunosuppressants (e.g., azathioprine, 6-mercaptopurine [6-MP], methotrexate [MTX]) or TNF-α inhibitors (adalimumab [Humira® or biosimilar], certolizumab [Cimzia®], infliximab [Remicade® or biosimilar]); **AND**
4. Prescribed by, or in consultation with, a gastroenterologist; **AND**
5. The regimen prescribed is within the FDA-approved labeling: 300 mg every 4 weeks as an intravenous infusion.

Approval Duration and Quantity Limits

	Multiple Sclerosis (MS)		Crohn's disease (CD)	
	Initial	Subsequent	Initial	Subsequent
Approval Duration	6 months	12 months	3 months	12 months*
Quantity Limits	300 mg every 4 weeks		300 mg every 4 weeks	

* Per FDA-approved label, if a patient with CD has not experienced therapeutic benefit by 12 weeks of induction therapy, Tysabri® should be discontinued. For patients with CD who start Tysabri® while on chronic oral cortico-steroids, commence steroid tapering as soon as a therapeutic benefit of Tysabri® has occurred; if the patient with CD cannot be tapered off of oral corticosteroids within 6 months of starting Tysabri®, discontinue Tysabri®.

Coding and Product Information

The following list(s) of codes and product information are provided for reference purposes only and may not be all inclusive. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment, nor does the exclusion of a code imply that its association to the HCPCS code is inappropriate.

HCPCS	Description
J2323	Injection, natalizumab, 1 mg

ICD-10	Description
G35	Multiple sclerosis
K50.XX	Crohn's disease [regional enteritis]

NDC	Labeler	Dosage	Pkg Size	Pkg Qty	Units/Pkg
64406-0008-01	Biogen, Inc.	1 mg	1	EA	300

Compliance

1. Should conflict exist between this policy and applicable statute, the applicable statute shall supersede.
2. Federal and State law, as well as contract language, including definitions and specific contract provisions or exclusions, take precedence over medical policy and must be considered first in determining eligibility for coverage.
3. Medical technology is constantly evolving, and Iowa Medicaid reserves the right to review and update medical policy on an annual or as-needed basis.

Medical necessity guidelines have been developed for determining coverage for member benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. Medical necessity guidelines are developed for selected physician-administered medications found to be safe and proven to be effective in a limited, defined population or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. Criteria are revised and updated annually, or more frequently if new evidence becomes available that suggests needed revisions.

References

[1] Tysabri prescribing information (04/2023). Biogen Inc.: Cambridge, MA. Available online at www.tysabrihcp.com. Accessed April 14, 2023.

[2] Olek MJ, Howard J. Clinical presentation, course, and prognosis of multiple sclerosis in adults. Dashe JF, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed April 14, 2023.

[3] Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. Robson KM, ed. UpToDate. Waltham, MA: UpToDate Inc. www.uptodate.com. Accessed April 14, 2023.

[4] Rae-Grant A, Day GS, 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 Apr 24;90(17):777-788. Erratum in: Neurology. 2019 Jan 8;92(2):112. PMID: 29686116.

[5] Lichtenstein, Gary R MD, FACG1; Loftus, Edward V MD, FACG2; Isaacs, Kim L MD, PhD, FACG3; Regueiro, Miguel D MD, FACG4; Gerson, Lauren B MD, MSc, MACG (GRADE Methodologist)5,†; Sands, Bruce E MD, MS, FACG6 ACG Clinical Guideline: Management of Crohn's Disease in Adults, American Journal of Gastroenterology: April 2018 - Volume 113 - Issue 4 - p 481-517.

Development of utilization management criteria may also involve research into other state Medicaid programs, other payer policies, consultation with experts and review by the Medicaid Clinical Advisory Committee (CAC). These sources may not be referenced individually unless they are specifically published and are otherwise applicable to the criteria at issue.

Criteria Change History

Change Date	Changed By	Description of Change	Version
Signature			

Change Date	Changed By	Description of Change	Version
04/21/2023	CAC	Annual review. Added dosing into coverage criteria. Updated references.	7
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
04/15/2022	CAC	Annual review. Rewrite.	6
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
10/16/2019	CAC	Added criterion 1b.	5
Signature William (Bill) Jagiello, DO			
Change Date	**Changed By**	**Description of Change**	**Version**
07/15/2016	Medical Director	Added description above Criteria.	4
Signature Mark E. Randleman, DO			

Criteria Change History continued on next page.

Criteria Change History (cont.)

Change Date	Changed By	Description of Change	Version
07/17/2015	CAC	Added last paragraph in References.	3
Signature			

Change Date	Changed By	Description of Change	Version
07/14/2015	Medical Director	Added prescribing information reference.	2
Signature			

Change Date	Changed By	Description of Change	Version
10/19/2012	CAC	Criterion 1a was removed and 1b was reworded to "member has failed or is unable to tolerate the use…".	1
Signature			

CAC = Medicaid Clinical Advisory Committee