Natalizumab Agents (Tysabri, Tyruko)

Tysabri® (natalizumab)
Tyruko® (natalizumab-sztn)
PAM – 077

Iowa Medicaid Program	Prior Authorization	**Effective Date**	04/01/2024
Revision Number	2	**Last Reviewed**	04/18/2025
Reviewed By	Medicaid Medical Director	**Next Review**	04/17/2026
Approved By	Medicaid Clinical Advisory Committee	**Approved Date**	04/19/2024

Overview

Medication:	natalizumab[1]	natalizumab-sztn[2]
Brand Name:	Tysabri®	Tyruko® (biosimilar)
Pharmacologic Category:	Integrin receptor antagonist	
FDA-Approved Indication(s):	**Tysabri (natalizumab) and Tyruko (natalizumab-sztn)** are both indicated for the treatment of multiple sclerosis (MS) and Crohn's disease (CD): 1. Indicated as monotherapy for the treatment of relapsing forms of MS in adults, to include: a. Clinically isolated syndrome (CIS); b. Relapsing-remitting disease (RRMS); c. Active secondary progressive disease (SPMS). 2. 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:	• Multiple Sclerosis: 300 mg intravenous infusion once every 4 weeks • Crohn's Disease: 300 mg intravenous infusion once every 4 weeks	
Benefit Category:	Medical	

BOXED WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Natalizumab products increase 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 antibodies, duration of therapy, and prior use of immunosuppressants. These factors should be considered in the context of expected benefit when initiating and continuing treatment with a natalizumab agent (Tysabri® or Tyruko®).

- Healthcare professionals should monitor patients on a natalizumab agent (Tysabri® or Tyruko®) for any new sign or symptom that may be suggestive of PML. Natalizumab dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

BOXED WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

• Because of the risk of PML:
  ○ Tyruko® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Tyruko® REMS Program.
  ○ 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

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), often representing the first attack of MS;
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.[3]

Crohn's Disease

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 with CD have small bowel involvement, usually in the distal ileum, with one-third of patients having ileitis exclusively.
- Approximately 50 percent of patients with CD have ileocolitis, which refers to involvement of both the ileum and colon.
- Approximately 20 percent of patients with CD 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 with CD have perianal disease.
- Approximately 5 to 15 percent of patients with CD 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.

Transmural bowel inflammation can lead to complications such as bowel obstruction or perforation. Additionally, it is associated with sinus tracts that may penetrate and lead to:

- fistulas (tracts or communications that connect two epithelial-lined organs);
- phlegmon (a walled-off inflammatory mass without bacterial infection);
- abscess (localized collection of pus, often develops in the abdomen, pelvis, or anal area);
- perianal disease (perianal fistula or abscess).[4]

Guidelines

Multiple Sclerosis

The American Academy of Neurology (AAN) published practice guidelines in 2018 regarding disease-modifying therapies (DMTs) for adults with multiple sclerosis. Recommendations regarding starting, switching, and stopping DMT were reviewed and assigned one of three designations: A, B, or C. Each designation denotes the level of recommendation strength. These guidelines were reaffirmed on October 19, 2024.[5]

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 disease-modifying therapy (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

Guidelines published by the American College of Gastroenterology in 2018 were developed to review Crohn's disease clinical features and natural history, diagnostics, and therapeutic interventions. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to evaluate the level of evidence and strength of recommendations.[6]

Recommendation Statements	Level of Evidence
Strong: the desirable effects of an intervention clearly outweigh the undesirable effects. **Conditional:** uncertainty exists 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 natalizumab which have a **strong** grade include the following:

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).

* Number in left column references the recommendation number within the original article. Only recommendations with a strong grade are included in this summary; reference source for complete list of all recommendations.

Criteria

Prior authorization is required.

Multiple Sclerosis

Natalizumab (as either Tysabri® or Tyruko®) is considered medically necessary when **ALL** of the following are met:

1. Confirmed diagnosis of one of the following subtypes of multiple sclerosis (MS) (a, b, or c):
   a. Clinically isolated syndrome (CIS); **OR**
   b. Relapsing-remitting MS (RRMS); **OR**
   c. Active secondary progressive MS (SPMS); **AND**
2. Member is 18 years of age or older; **AND**
3. Natalizumab is not prescribed or administered concurrently with other disease-modifying therapies (DMTs) for MS (with the exception of dalfampridine*, which may be used concurrently with natalizumab); **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. Request meets one of the following (a or b):
   a. Regimen prescribed does not exceed 300 mg every 4 weeks; or
   b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Natalizumab (as either Tysabri® or Tyruko®) 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. Natalizumab is not prescribed or administered concurrently with other disease-modifying therapies (DMTs) for multiple sclerosis (with the exception of dalfampridine*, which may be used concurrently with natalizumab); **AND**
4. Prescribed by, or in consultation with, a neurologist; **AND**
5. Request meets one of the following (a or b):
   a. Regimen prescribed does not exceed 300 mg every 4 weeks; or
   b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

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

Crohn's Disease

Natalizumab (as either Tysabri® or Tyruko®) is considered medically necessary when **ALL** of the following are met:

1. Diagnosis of moderate-to-severe Crohn's disease; **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 (e.g., adalimumab [Humira® or biosimilar], certolizumab [Cimzia®], infliximab [Remicade® or biosimilar]), unless clinically adverse effects are experienced or all are contraindicated; **AND**
5. Natalizumab is not prescribed concurrently with other immunosuppressants (e.g., 6-MP, azathioprine, MTX) or TNF-α inhibitors (e.g., adalimumab [Humira® or biosimilar], certolizumab [Cimzia®], infliximab [Remicade® or biosimilar]); **AND**
6. Prescribed by, or in consultation with, a gastroenterologist; **AND**
7. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 300 mg every 4 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

Natalizumab (as either Tysabri® or Tyruko®) 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. Natalizumab is not prescribed concurrently with other immunosuppressants (e.g., 6-MP, azathioprine, MTX) or TNF-α inhibitors (e.g., adalimumab [Humira® or biosimilar], certolizumab [Cimzia®], infliximab [Remicade® or biosimilar]); **AND**
4. Prescribed by, or in consultation with, a gastroenterologist; **AND**
5. Request meets one of the following (a or b):
    a. Regimen prescribed does not exceed 300 mg every 4 weeks; or
    b. Regimen is supported by clinical practice guidelines. Supporting clinical documentation must be provided with any request for which regimen prescribed does not align with FDA-approved labeling.

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 labels for natalizumab agents, if a patient with Crohn's disease (CD) has not experienced therapeutic benefit by 12 weeks of induction therapy, treatment with natalizumab should be discontinued.

‡ For patients with CD who start natalizumab therapy while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of natalizumab therapy has occurred; if the patient with CD cannot be tapered off of oral corticosteroids within 6 months of starting natalizumab therapy, discontinue natalizumab therapy.

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.

Brand	HCPCS	Description
Tysabri®	J2323	Injection, natalizumab, 1 mg
Tyruko®	Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg

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

Brand	NDC (Strength)	Labeler	Dosage	Pkg Size	Pkg Qty	Units /Pkg
Tysabri®	64406-0008-01 (300 mg/15 mL)	Biogen Inc. (64406)	1 mg	1	EA	300
Tyruko®	61314-0543-94 (300 mg/15 mL)	Sandoz Inc. (61314)	1 mg	1	EA	300

Compliance

1. Should conflict exist between the 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 (10/2023). Biogen Inc.: Cambridge, MA. Available online at: www.tysabrihcp.com. Accessed March 4, 2025.

[2] Tyruko® prescribing information (08/2023). Sandoz Inc.: Princeton, NJ. Available online at: www.tyruko.com. Accessed March 4, 2025.

[3] 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 March 4, 2025.

[4] 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 March 4, 2025.

[5] Rae-Grant A, 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. Reaffirmed on October 19, 2024.

[6] Lichtenstein GR, Loftus EV, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018 Apr;113(4):481-517. Epub 2018 Mar 27. Erratum in: Am J Gastroenterol. 2018 Jul;113(7):1101. PMID: 29610508.

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
[mm/dd/yyyy]	CAC		
Signature			

Change Date	Changed By	Description of Change	Version
[mm/dd/yyyy]	CAC		
Signature			

Change Date	Changed By	Description of Change	Version
04/18/2025	CAC	Annual review. Added notation in Guidelines section for multiple sclerosis: the 2018 AAN Guidelines were reaffirmed on October 19, 2024.	2
Signature William (Bill) Jagiello, DO			

Change Date	Changed By	Description of Change	Version
04/19/2024	CAC	Criteria implementation. Criteria same as previous single-drug policy “PAM-014: Tysabri (natalizumab)”, which will be archived. New policy “Natalizumab Agents” includes Tysabri and any biosimilars (currently Tyruko is the only FDA-approved biosimilar).	1
Signature William (Bill) Jagiello, DO			

CAC = Medicaid Clinical Advisory Committee