

**Tysabri® (Natalizumab)
(Intravenous)**

Effective Date: 01/01/2020

Review Date: 9/12/2018, 12/13/2019, 1/22/2020, 6/10/2021, 1/20/2022, 7/13/2023, 12/07/2023, 01/10/2024, 01/22/2025, 6/4/2025

Scope: Medicaid, Commercial, Medicare

I. Length of Authorization

Crohn's Disease:

- Coverage is eligible for renewal
 - Initial coverage will be provided for 12 weeks
 - Renewal coverage will be provided for 12 months

Multiple Sclerosis:

- Initial coverage will be provided for 6 months
- Renewal coverage will be provided for 12 months

II. Dosing Limits

Max Units (per dose and over time) [HCPCS Unit]:

- 300 billable units every 28 days

III. Summary of Evidence

Tysabri (natalizumab) is an integrin receptor antagonist used to treat multiple sclerosis (MS) and Crohn's disease. Clinical trials evaluating its efficacy and safety have demonstrated significant benefits in reducing the frequency of relapses and slowing disease progression in patients with MS. Tysabri has shown superior efficacy compared to placebo and other disease-modifying therapies in reducing the risk of disability progression. The AFFIRM trial showed that Tysabri reduced the annualized relapse rate by 68% compared to placebo in patients with relapsing-remitting MS. Additionally, the SENTINEL trial demonstrated that Tysabri reduced the risk of disability progression by 42% compared to placebo. The most common adverse reactions (incidence $\geq 10\%$) were headache and fatigue in both the multiple sclerosis (MS) and Crohn's disease (CD) studies. There is a black box warning for risk of progressive multifocal leukoencephalopathy (PML).

IV. Initial Approval Criteria ^{1,2}

- Patient is at least 18 years of age; **AND**

Universal Criteria ^{1,2,14}

- Prescriber and patient must be enrolled in and meet the conditions of the TOUCH (*applicable to Tysabri*) or REMS (*applicable to Tyrukto*) programs; **AND**
- Documented negative JCV antibody ELISA test within the past 6 months§; **AND**
- Not used in combination with antineoplastic, immunosuppressant, or immunomodulating agents; **AND**
- Patient must not have a systemic medical condition resulting in significantly compromised immune system function; **AND**
- Medicare members who have previously received this medication within the past 365 days are not subject to Step Therapy Requirements

Multiple Sclerosis (MS) † ^{1,2,7,16}

- Patient has a diagnosis of a relapsing form of multiple sclerosis [i.e. relapsing-remitting disease (RRMS)*, active secondary progressive disease (SPMS)**, or clinically isolated syndrome (CIS)***]; **AND**
- Must be prescribed by or in consultation with a neurologist; **AND**
- Patient must have a confirmed diagnosis of MS as documented by laboratory report (i.e. MRI); **AND**
- Used as single agent therapy

Crohn's Disease (CD) † ^{1,2,14,28,29}

- Patient has moderate to severe active disease; **AND**
- Tysabri is prescribed by or in consultation with a gastroenterologist; **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool; **AND**
- Patient has had failure, intolerance, or contraindication to infliximab IV or adalimumab therapy for at least 3 months at maximum tolerated doses; **AND**
- Patient has had failure, intolerance, or contraindication to ustekinumab for at least 6 months at maximum tolerated doses; **AND**
- Used as single agent therapy [Not used concurrently with another biologic drug, targeted synthetic therapy (e.g., upadacitinib, etc.), or immunosuppressant (e.g., 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, etc.) used for Crohn's Disease]

***Definitive diagnosis of MS with a relapsing-remitting course is based upon BOTH dissemination in time and space. Unless contraindicated, MRI should be obtained (even if criteria are met).¹⁶**

<u>Dissemination in time</u> <i>(Development/appearance of new CNS lesions over time)</i>	<u>Dissemination in space</u> <i>(Development of lesions in distinct anatomical locations within the CNS; multifocal)</i>
• ≥ 2 clinical attacks; OR • 1 clinical attack AND one of the following: ○ MRI indicating simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to baseline scan ○ CSF-specific oligoclonal bands	• ≥ 2 lesions; OR • 1 lesion AND one of the following: ○ Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location ○ MRI indicating ≥ 1 T2-hyperintense lesions characteristic of MS in ≥ 2 of 4 areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord)

****Active secondary progressive MS (SPMS) is defined as the following:^{8,16-18,27}**

- Expanded Disability Status Scale (EDSS) score ≥ 3.0 ; **AND**
- Disease is progressive ≥ 3 months following an initial relapsing-remitting course (i.e., EDSS score increase by 1.0 in patients with EDSS ≤ 5.5 or increase by 0.5 in patients with EDSS ≥ 6); **AND**
 - ≥ 1 relapse within the previous 2 years; **OR**
 - Patient has gadolinium-enhancing activity OR new or unequivocally enlarging T2 contrast-enhancing lesions as evidenced by MRI

*****Definitive diagnosis of CIS is based upon ALL of the following:** ¹⁶

- A monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the CNS
- Neurologic symptom duration of at least 24 hours, with or without recovery
- Absence of fever or infection
- Patient is not known to have multiple sclerosis

§ Risk factors for the development of Progressive Multifocal Leukoencephalopathy (PML) ^{1,2,14,15}

- Presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil)
- Longer treatment duration, especially beyond 2 years
- Elevated levels of anti-JCV antibody response index (i.e., index > 0.9).
 - In those using natalizumab for 25-36 months with no prior use of immunosuppressants, the PML risk is 0.2 per 1,000 in those with an index of 0.9 or less, 0.3 per 1,000 in those with an index of 0.9-1.5, and 3 per 1,000 in those with an index greater than 1.5.

Anti-JCV Antibody Negative	Natalizumab Exposure (months)	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1/10,000	1-24	<1/1,000	1/1,000
	25-48	2/1,000	6/1,000
	49-72	4/1,000	7/1,000
	73-96	2/1,000	6/1,000

Note: Requirements for JCV negativity are based upon recommendations from current guidelines^{14,15}. Use in patients who are anti-JCV antibody positive will be reviewed on a case-by-case basis.

V. Renewal Criteria ^{1,2}

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria identified in

section IV; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: hypersensitivity reactions/antibody formation, hepatotoxicity, signs or symptoms of progressive multifocal leukoencephalopathy (PML), herpes infections (including herpes encephalitis and meningitis and acute retinal necrosis), immunosuppression, infections (including pneumonias, pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, urinary tract infections, gastroenteritis, vaginal infections, tooth infections, tonsillitis, etc.), thrombocytopenia, etc.; **AND**

Multiple Sclerosis (MS) ^{15,22}

- Continuous monitoring of response to therapy indicates a beneficial response* [manifestations of increased MS disease activity include, but are not limited to, an increase in annualized relapse rate (ARR), development of new/worsening T2 hyperintensities or enhancing lesions on brain/spinal MRI, and progression of sustained impairment as evidenced by expanded disability status scale (EDSS), timed 25-foot walk (T25-FW), 9-hole peg test (9-HPT)]

***Note:**

- Inadequate response, in those who have been adherent and receiving therapy for sufficient time to realize the full treatment effect, is defined as ≥ 1 relapse, ≥ 2 unequivocally new MRI-detected lesions, or increased disability on examination over a one-year period
- Infusion reactions or breakthrough disease activity may indicate neutralizing natalizumab antibodies. Therapy should be discontinued in patients who have persistent neutralizing antibodies to natalizumab.

Crohn's Disease (CD) ^{1,2,20,30,31}

- Initial renewal only:
 - Clinical response and remission of disease is seen by 12 weeks
- Second renewal only:
 - Patient has been tapered off of oral corticosteroids within 6 months of starting Natalizumab;
AND
 - Disease response as indicated by improvement in signs and symptoms compared to baseline such as endoscopic activity, number of liquid stools, presence and severity of abdominal pain, presence of abdominal mass, body weight regain, hematocrit, presence of extra intestinal complications, tapering or discontinuation of corticosteroid therapy, use of anti-diarrheal drugs, improvement in biomarker levels [i.e., fecal calprotectin or serum C-reactive protein (CRP)], and/or an

improvement on a disease activity scoring tool [e.g. an improvement on the Harvey-Bradshaw Index score, etc.]

- All subsequent renewals:

- Patient does not require additional steroid use that exceeds 3 months in a calendar year to control their Crohn's disease; **AND**
- Disease response as indicated by improvement in signs and symptoms compared to baseline such as endoscopic activity, number of liquid stools, presence and severity of abdominal pain, presence of abdominal mass, body weight regain, hematocrit, presence of extra intestinal complications, tapering or discontinuation of corticosteroid therapy, use of anti-diarrheal drugs, improvement in biomarker levels [i.e., fecal calprotectin or serum C-reactive protein (CRP)], and/or an improvement on a disease activity scoring tool [e.g. an improvement on the Harvey-Bradshaw Index score, etc.]

VI. Dosage/Administration ^{1,2}

Indication	Dose
All Indications	Administer 300 mg intravenously over one hour every four weeks

VII. Billing Code/Availability Information

HCPCS Code(s):

- J2323 – Injection, natalizumab, 1 mg; 1 billable unit = 1mg

NDC(s):

- Tysabri 300 mg/15 mL single-dose vial: 64406-0008-xx

VIII. References

1. Tysabri [package Insert]. Cambridge, MA; Biogen, Inc.; October 2023. Accessed October 2024.
2. Tyruko [package Insert]. Princeton, NJ; Sandoz, Inc.; August 2023. Accessed October 2024.
3. Goodin DS, Cohen BA, O'Connor P, et al. Assessment: the use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2008; 71:766.
4. Gawronski KM, Rainka MM, Patel MJ, Gengo FM. Treatment Options for Multiple Sclerosis:

- Current and Emerging Therapies. *Pharmacotherapy*. 2010;30(9):916-927.
5. Goodin DS, Frohman EM, Garmany GP Jr, et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002 Jan 22;58(2):169-78.
 6. Freedman MS, Selchen D, Arnold DL, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. *Can J Neurol Sci*. 2013 May;40(3):307-23.
 7. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Ann Neurol*. 2011 Feb; 69(2): 292–302. doi: 10.1002/ana.22366.
 8. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014 Jul 15;83(3):278-86. doi: 10.1212/WNL.0000000000000560.
 9. Lichtenstein GR, Hanauer SB, Sandborn WJ, Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009;104(2):465.
 10. Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF- α biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology*. 2013 Dec;145(6):1459-63. doi: 10.1053/j.gastro.2013.10.047.
 11. Best WR, Beckett JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70(3): 439-444.
 12. Gomollón F, Dignass A, Annese V, et al. EUROPEAN Evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis*. 2016 Sep 22. pii: jjw168.
 13. National Institute for Health and Care Excellence. NICE 2012. Crohn's Disease: Management. Published 10 October 2012. Clinical Guideline [CG152].
<https://www.nice.org.uk/guidance/cg152/resources/crohns-disease-management-pdf-35109627942085>.
 14. Lichtenstein GR, Loftus EV, Isaacs KI, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. *Am J Gastroenterol* 2018; 113:481–517; doi: 10.1038/ajg.2018.27
 15. Rae-Grant A, Day GS, Marrie RA, 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;90:777-788.
 16. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018 Feb;17(2):162-173. doi: 10.1016/S1474-4422(17)30470- 2.

17. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263. Epub 2018 Mar 23.
18. Lorscheider J, Buzzard K, Jokubaitis V, et al, on behalf of the MSBase Study Group. Defining secondary progressive multiple sclerosis. *Brain*, Volume 139, Issue 9, September 2016, Pages 2395–2405, <https://doi.org/10.1093/brain/aww173>.
19. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263. Epub 2018 Mar 23.
20. National Institute for Health and Care Excellence. NICE 2019. Crohn's Disease: management. Published 3 May 2019. Clinical Guideline [NG129]. <https://www.nice.org.uk/guidance/ng129/resources/crohns-disease-management-pdf-66141667282885>. Accessed October 2024.
21. Sandborn WJ, Colombel JF, Enns R, et al; International Efficacy of Natalizumab as Active Crohn's Therapy (ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy (ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2005 Nov 3;353(18):1912-25. doi: 10.1056/NEJMoa043335. Erratum in: *N Engl J Med*. 2015 May 21;372(21):2074.
22. Freedman MS, Devonshire V, Duquette P, et al. Treatment Optimization in Multiple Sclerosis: Canadian MS Working Group Recommendations. *Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques*, 47(4), 437-455. doi:10.1017/cjn.2020.66.
23. Polman CH, O'Connor PW, Havrdova E, et al; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006 Mar 2;354(9):899-910. doi: 10.1056/NEJMoa044397.
24. Rudick RA, Stuart WH, Calabresi PA, et al; SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med*. 2006 Mar 2;354(9):911-23. doi: 10.1056/NEJMoa044396.
25. Hemmer B, Wiendl H, Roth K, et al. Efficacy and safety of proposed biosimilar natalizumab (PB006) in patients with relapsing-remitting multiple sclerosis: the Antelope phase 3 randomized clinical trial. *JAMA Neurol*. Published online January 23, 2023. doi:10.1001/jamaneurol.2022.5007.
26. Torres J, Bonovas S, Doherty G, et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. *J Crohn's Colitis*. 2020 Jan 1;14(1):4-22. doi: 10.1093/ecco-jcc/jjz180. PMID: 31711158.
27. Cree BAC, Arnold DL, Chataway J, et al. Secondary Progressive Multiple Sclerosis: New Insights.

- Neurology. 2021 Aug 24;97(8):378-388. doi: 10.1212/WNL.00000000000012323. Epub 2021 Jun 4.
28. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021 Jun;160(7):2496-2508. doi: 10.1053/j.gastro.2021.04.022. PMID: 34051983; PMCID: PMC8988893.
29. Gordon H, Minozzi S, Kopylov U et al. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment, Journal of Crohn's and Colitis, 2024; jjae09. <https://doi.org/10.1093/ecco-jcc/jjae091>.
30. Ranasinghe IR, Tian C, Hsu R. Crohn Disease. [Updated 2024 Feb 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK436021/>.
31. Ananthakrishnan AN, Alder J, Chachu KA, et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Crohn's Disease. Gastroenterology. 2023 Dec;165(6):1367- 1399. doi: 10.1053/j.gastro.2023.09.029. PMID: 37981354.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
G35	Multiple Sclerosis
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding

ICD-10	ICD-10 Description
K50.112	Crohn's disease of large intestine with intestinal obstruction

K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents: <https://www.cms.gov/medicare-coverage-database/search.aspx>. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions

Jurisdiction	Applicable State/US Territory	Contractor
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
Jurisdiction	Applicable State/US Territory	Contractor
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Policy Rationale:

Tysabri was reviewed by the Neighborhood Health Plan of Rhode Island Pharmacy & Therapeutics (P&T) Committee. Neighborhood adopted the following clinical coverage criteria to ensure that its members use Tysabri according to Food and Drug Administration (FDA) approved labeling and/or relevant clinical literature. Neighborhood worked with network prescribers and pharmacists to draft these criteria. These criteria will help ensure its members are using this drug for a medically accepted indication, while minimizing the risk for adverse effects and ensuring more cost-effective options are used first, if applicable and appropriate. For Medicare members, these coverage criteria will only apply in the absence of National Coverage Determination (NCD) or Local Coverage Determination (LCD) criteria. Neighborhood will give individual consideration to each request it reviews based on the information submitted by the prescriber and other information available to the plan.