Natalizumab: (Tyruko®; Tysabri®) (Intravenous)

Document Number: IC-0133

Last Review Date: 05/05/2026
Date of Origin: 11/28/2011
Dates Reviewed: 12/2011, 08/2012, 02/2013, 06/2013, 06/2013, 09/2013, 12/2013, 03/2014, 06/2014, 09/2014, 01/2015, 02/2015, 06/2015, 09/2015, 12/2015, 03/2016, 06/2016, 09/2016, 12/2016, 03/2017, 06/2017, 09/2017, 12/2017, 03/2018, 06/2018, 10/2018, 09/2019, 04/2020, 10/2020, 10/2021, 10/2022, 09/2023, 10/2023, 12/2024, 12/2025, 05/2026

I. Length of Authorization

Crohn's Disease:

- Initial: Prior authorization validity will be provided initially for 12 weeks.
- Renewal: Prior authorization validity may be renewed every 6 months (180 days) thereafter.

Multiple Sclerosis:

- Initial: Prior authorization validity will be provided initially for 12 (365 days) months.
- Renewal: Prior authorization validity may be renewed every 12 months (365 days) thereafter.

II. Dosing Limits

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

- 300 billable units every 28 days

III. Initial Approval Criteria [1,2]

Prior authorization validity is provided in the following conditions:

- Patient must have a contraindication, intolerance, or failure to ONE generic disease-modifying agent prior to the consideration of a natalizumab product; **AND**
- Member is at least 18 years of age; **AND**

Universal Criteria [1,2,32]

- Documented JCV antibody ELISA test within the past 6 months**§**; **AND**
- Not used in combination with antineoplastic, immunosuppressant, or immunomodulating agents; **AND**
- Member must not have a systemic medical condition resulting in significantly compromised immune system function; **AND**

Multiple Sclerosis (MS) † [1,2,7,16,31]

- Member must have a confirmed diagnosis of MS as documented by laboratory report (i.e., MRI); **AND**
- Member 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**
- Used as single agent therapy

Crohn's Disease (CD) † [1,2,14,27,28,32]

- Member has moderate to severe active disease; **AND**
- Physician has assessed baseline disease severity utilizing an objective measure/tool; **AND**
  - Documented trial and failure on ONE oral immunosuppressive therapy for at least 3 months, unless use is contraindicated, such as corticosteroids, methotrexate, azathioprine, and/or 6-mercaptopurine; **OR**
  - Member is already established on biologic or targeted synthetic therapy for the treatment of CD; **AND**
- Documented trial and failure on ONE TNF-Inhibitor therapy for at least 3 months, unless contraindicated, such as infliximab, certolizumab, or adalimumab; **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]

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

§ Risk factors for the development of Progressive Multifocal Leukoencephalopathy (PML) [1,2,15,32]
• The 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.

IV. Renewal Criteria [1,2]

Prior authorization validity may be renewed based upon the following criteria:

- Member continues to meet the universal and other indication-specific relevant criteria identified in section III; **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.), hematological abnormalities (including thrombocytopenia), etc.; **AND**

Multiple Sclerosis (MS) [15,21]

- Continuous monitoring of response to therapy indicates a beneficial response* [manifestations of 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 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) [1,2,19,29,30]

- Initial renewal only:
  - Clinical response and remission of disease is seen by 12 weeks
- Second renewal only:
  - Member 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:
  - Member 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.]

V. Dosage/Administration [1,2]

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

VI. Billing Code/Availability Information

HCPCS Code(s):

- J2323 – Injection, natalizumab, 1 mg; 1 billable unit = 1mg *(Tysabri Only)*
- Q5134 – Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg; 1 billable unit = 1 mg *(Tyruko Only)*

NDC(s):

- Tysabri 300 mg/15 mL single-dose vial: 64406-0008-xx
- Tyruko 300 mg/15 mL single-dose vial: 61314-0543-xx

VII. References

1. Tysabri [package Insert]. Cambridge, MA; Biogen, Inc.; March 2025. Accessed April 2026.
2. Tyruko [package Insert]. Princeton, NJ; Sandoz, Inc.; October 2025. Accessed April 2026.
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, Becktel 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. Reaffirmed: 2024 Oct 19.
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. 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 November 2025.
20. 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.
21. 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. 2020;47(4): 437-455. doi:10.1017/cjn.2020.66.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.0000000000012323. Epub 2021 Jun 4.
27. 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.
28. 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.
29. 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/.
30. 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.
31. Montalban X, Lebrun-Frénay C, Oh J, et al. Diagnosis of multiple sclerosis: 2024 revisions of the McDonald criteria. Lancet Neurol. 2025 Oct;24(10):850-865. doi: 10.1016/S1474-4422(25)00270-4.
32. Lichtenstein GR, Loftus EV, Afzali, A, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2025; 120:1225–1264; doi: 10.14309/ajg.0000000000003465.
33. Scott FI, Ananthakrishnan AN, Click B, et al. AGA Living Clinical Practice Guideline on the Pharmacologic Management of Moderate-to-Severe Crohn's Disease. Gastroenterology. 2025 Dec;169(7):1397-1448. doi:10.1053/j.gastro.2025.06.091.

Appendix A – Non-Quantitative Treatment Limitations (NQTL) Factor Checklist

Non-quantitative treatment limitations (NQTLs) refer to the methods, guidelines, standards of evidence, or other conditions that can restrict how long or to what extent benefits are provided under a health plan. These may include things like utilization review or prior authorization. The utilization management NQTL applies comparably, and not more stringently, to mental health/substance use disorder (MH/SUD) Medical Benefit Prescription Drugs and medical/surgical (M/S) Medical Benefit Prescription Drugs. The table below lists the factors that were considered in designing and applying prior authorization to this drug/drug group, and a summary of the conclusions that Prime's assessment led to for each.

Factor	Conclusion
Indication	Yes: Consider for PA
Safety and efficacy	Yes: Consider for PA
Potential for misuse/abuse	No: PA not a priority
Cost of drug	Yes: Consider for PA

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
G35.A	Relapsing-remitting multiple sclerosis
G35.B0	Primary progressive multiple sclerosis, unspecified
G35.B1	Active primary progressive multiple sclerosis
G35.B2	Non-active primary progressive multiple sclerosis
G35.C0	Secondary progressive multiple sclerosis, unspecified
G35.C1	Active secondary progressive multiple sclerosis
G35.C2	Non-active secondary progressive multiple sclerosis
G35.D	Multiple sclerosis, unspecified
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
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

ICD-10	ICD-10 Description
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
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)

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
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