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

Document Number: EOCCO-0133

Last Review Date: 10/03/2023

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

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 6 months

Multiple Sclerosis:

- Coverage will be provided for 6 months and is eligible for renewal.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Tysabri 300 mg/15 mL single-dose vial for injection: 1 vial per 28 days
- Tyruko 300 mg/15 mL single-dose vial for injection: 1 vial per 28 days

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

- 300 billable units every 28 days

III. 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 Tyruko*) programs; **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**

Multiple Sclerosis † [1,2,7,16]

- Patient has been diagnosed with a relapsing form of multiple sclerosis [i.e. relapsing-remitting disease (RRMS)*, active secondary progressive disease (SPMS)**, or clinically isolated syndrome (CIS)***]; **AND**
- Confirmed diagnosis of MS as documented by laboratory report (i.e. MRI); **AND**
- Used as single agent therapy

Crohn's Disease † [1,2,14]

- Patient 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; **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 or immunosuppressant (e.g., 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, etc.) used for Crohn's Disease]

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

***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]**

Dissemination in time *(Development/appearance of new CNS lesions over time)*	**Dissemination in space** *(Development of lesions in distinct anatomical locations within the CNS; multifocal)*

• ≥ 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

IV. 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 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.), thrombocytopenia, etc.; **AND**

Multiple Sclerosis [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 [1,2,14,20]

- 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 Tysabri; **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 compared to IBW, hematocrit, presence of extra intestinal complications, tapering or discontinuation of corticosteroid therapy, use of anti-diarrheal drugs, and/or an improvement on a disease activity scoring tool [e.g. an improvement on the Crohn's Disease Activity Index (CDAI) score or the Harvey-Bradshaw Index score.]

- 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 compared to IBW, hematocrit, presence of extra intestinal complications, tapering or discontinuation of corticosteroid therapy, use of anti-diarrheal drugs, and/or an improvement on a disease activity scoring tool [e.g. an improvement on the Crohn's Disease Activity Index (CDAI) score or the Harvey-Bradshaw Index score.]

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:

- J2323 – Injection, natalizumab, 1 mg; 1 billable unit = 1mg *(Tysabri Only)*
- J3590 – Unclassified biologics *(Tyruko Only)*

NDC:

- 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.; April 2023. Accessed September 2023.
2. Tyruko [package Insert]. Princeton, NJ; Sandoz, Inc.; August 2023. Accessed September 2023.

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.
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 September 2023.
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.0000000000012323. Epub 2021 Jun 4.

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
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)

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 Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered 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)
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, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
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