Medical Policy:

Tysabri (natalizumab) Intravenous

POLICY NUMBER	LAST REVIEW	ORIGIN DATE
MG.MM.PH.108	February 10, 2025	January 1, 2020

Definitions

Tysabri, an integrin receptor antagonist, is indicated for the treatment of:

- Relapsing forms of **multiple sclerosis** (MS) include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy.
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)-α.

Length of Authorization

Crohn's Disease:

- 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

Dosing Limits [Medical Benefit]

A. Max Units (per dose and over time):

300 billable units every 28 days

Guideline

I. INITIAL APPROVAL CRITERIA

- Patient is at least 18 years old; **AND**
- Prescriber and patient must be enrolled in and meet the conditions of the TOUCH program; **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**

1. **Multiple Sclerosis.** †

A. Patient has a relapsing form of multiple sclerosis; **AND**

Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

A. Patient has confirmed diagnosis of MS as documented by a laboratory report (i.e. MRI): **AND**

B. Used as single agent therapy

2. **Crohn's Disease.** †

A. Patient has moderately to severely active Crohn's disease; **AND**

B. Physician has assessed baseline disease severity utilizing an objective measure/tool; **AND**

C. 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**

D. Documented trial and failure on **ONE** TNF-Inhibitor therapy for at least 3 months, unless contraindicated, such as infliximab, certolizumab, or adalimumab; **AND**

E. 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)

***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).**	
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)

B. RENEWAL CRITERIA

Authorizations can be renewed based on the following criteria:

- Patient continues to meet the criteria identified above; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: hypersensitivity reactions, hepatotoxicity, signs or symptoms of progressive multifocal leukoencephalopathy (PML), development of severe infections (including pneumonias, pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, herpes, urinary tract infections, gastroenteritis, vaginitis, tonsillitis, meningitis), etc.

Multiple Sclerosis

- Continuous monitoring of response to therapy [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 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

- 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 six 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 three 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.]

Dosage/Administration

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

Limitations/Exclusions

Tysabri® (natalizumab) is not considered medically necessary for indications other than those listed above due to insufficient evidence of therapeutic value.

Applicable Procedure Codes

Code	Description
J2323	Injection, natalizumab, 1 mg
Q5134	Injection, natalizumab-sztn (tyruko), biosimilar, 1 mg

Applicable NDCs

Code	Description
64406-0008-01	Tysabri 300 mg/15 mL single-use vial
61314-0543-94	Tyruko (natalizumab-sztn) injection, 300 mg/15 mL (20 mg/mL) single-dose vial per carton

ICD-10 Diagnoses

Code	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

Revision History

Company(ies)	DATE	REVISION
EmblemHealth & ConnectiCare	2/10/2025	Annual Review: Initial Criteria: Multiple Sclerosis: Removed: "Patient meets one of the following (a or b):According to the prescriber the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis; OR *Note: See Appendix for examples.*According to the prescriber the patient has highly active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]: Patient has demonstrated rapidly advancing deterioration(s) in physical functioning; OR *Note: Examples include loss of mobility/or lower levels of ambulation, severe changes in strength or coordination.* Disabling relapse(s) with suboptimal response to systemic corticosteroids; OR Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis; OR *Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions*. Manifestations of multiple sclerosis-related cognitive impairment; AND Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis" Replaced with: "Patient has confirmed diagnosis of MS as documented by a laboratory report (i.e. MRI): AND Used as single agent therapy" Crohn's Disease. † Removed: "Patient has tried at least two biologics for Crohn's disease; AND*Note: Examples include an adalimumab product (Humira, biosimilars), Cimzia (certolizumab pegol subcutaneous injection), an infliximab product (Remicade, biosimilars), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), Stelara (ustekinzumab subcutaneous injection or intravenous infusion). A previous trial of the requested biologic (or a biosimilar of the requested biologic) does not count.* Medication is prescribed by or in consultation with a gastroenterologist" "replaced with: "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]"
EmblemHealth & ConnectiCare	1/2/2024	Annual Review: Initial Criteria: MS- removed documentation required, updated length of authorization for both indications.
EmblemHealth & ConnectiCare	5/16/2023	Removed "Documented negative JCV antibody ELISA test within the past 6 months" from initial criteria and renewal criteria

EmblemHealth & ConnectiCare	4/13/2023	Annual Review: Added Definition; Multiple Sclerosis- Removed: A. Confirmed diagnosis* of MS as documented by laboratory report (i.e. MRI); AND B. Must be used as single agent therapy Added: iii. Patient meets one of the following (a or b): a. According to the prescriber the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis; OR Note: See Appendix for examples. b. According to the prescriber the patient has highly active or aggressive multiple sclerosis by meeting one of the following [(1), (2), (3), or (4)]: (1) Patient has demonstrated rapidly advancing deterioration(s) in physical functioning [documentation required]; OR Note: Examples include loss of mobility/or lower levels of ambulation, severe changes in strength or coordination. (2) Disabling relapse(s) with suboptimal response to systemic corticosteroids [documentation required]; OR (3) Magnetic resonance imaging [MRI] findings suggest highly active or aggressive multiple sclerosis [documentation required]; OR Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions. (4) Manifestations of multiple sclerosis-related cognitive impairment [documentation required]; AND iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR Crohns Disease Criteria: Removed: A. Physician has assessed baseline disease severity utilizing an objective measure/tool; AND B. 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 C. Documented trial and failure on ONE TNF-Inhibitor therapy for at least 3 months, unless contraindicated, such as infliximab, certolizumab, or adalimumab; AND D. 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] Added: iii. Patient has tried at least two biologics for Crohn's disease; AND Note: Examples include an adalimumab product (Humira, biosimilars), Cimzia (certolizumab pegol subcutaneous injection), an infliximab product (Remicade, biosimilars), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), Stelara (ustekinzumab subcutaneous injection or intravenous infusion). A previous trial of the requested biologic (or a biosimilar of the requested biologic) does not count. iv. Medication is prescribed by or in consultation with a gastroenterologist
EmblemHealth & ConnectiCare	1/17/2023	Transfer to New Template

EmblemHealth & ConnectiCare	1/1/2020	New Policy

References

1. Tysabri [package Insert]. Cambridge, MA; Biogen Idec, Inc.; August 2019. Accessed December 2019.
2. 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.
3. Gawronski KM, Rainka MM, Patel MJ, Gengo FM. Treatment Options for Multiple Sclerosis: Current and Emerging Therapies. Pharmacotherapy. 2010;30(9):916-927.
4. 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.
5. 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.
6. 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
7. 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
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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
14. 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.
15. 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.
16. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Drugs and Biologics (Non-chemotherapy) (L34741). Centers for Medicare & Medicaid Services, Inc. Updated on 5/242018 with effective date 6/01/2018. Accessed August 2018.

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral