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

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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 thereafter.

Multiple Sclerosis:

- Initial: Prior authorization validity will be provided initially for 12 months.
- Renewal: Prior authorization validity may be renewed every 12 months 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**
- Patient 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**
- Patient must not have a systemic medical condition resulting in significantly compromised immune system function; **AND**

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

- 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**
- 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) † [1,2,14,27,28,32]

- 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; **OR**
  - Patient 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

***Definitive diagnosis of MS with a relapsing-remitting course is based upon [31]:**

- Dissemination in space *(see below)* AND one or more of the following:
  - Positive cerebrospinal fluid (CSF) (e.g., presence of oligoclonal bands or kappa free light chain index)
  - Positive central vein sign (CVS) (e.g., presence of six or more lesions with CVS; if fewer than 6 white matter lesions are seen on MRI, the number of CVS positive lesions should outnumber the CVS negative lesions)
  - Dissemination in time (DIT) *(see below)*
  - Presence of lesions in at least four of five CNS anatomical locations; **OR**
- Lesions present in one CNS site (including patients with 12 months or longer progression from onset) AND one or more of the following:
  - CSF positivity and CVS positivity
  - CSF positivity and paramagnetic rim lesion (PRL) positivity (e.g., presence of one or more PRL)
  - DIT *(see below)* and CVS positivity
  - DIT *(see below)* and PRL positivity

Unless contraindicated, MRI should be obtained (even if criteria are met).	
Dissemination in space (*Development of lesions in distinct anatomical locations within the CNS; multifocal*)	**Dissemination in time** (*Development/appearance of new CNS lesions over time*)
• MRI indicating typical lesions in ≥ 2 of 5 areas of the CNS (optic nerve, intracortical or juxtacortical, periventricular, infratentorial, or spinal cord); **OR** • In patients with progressive disease (patients with 12 months or longer progression from onset), two spinal cord lesions	• ≥2 clinical attacks; **OR** • Simultaneous presence of gadolinium enhancing and non-enhancing lesions at any time; **OR** • A new T2-hyperintense or gadolinium enhancing lesion on follow-up MRI

**Active secondary progressive MS (SPMS) is defined as the following: [8,16-18,26]

• 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) [1,2,15,32]
• 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:

- 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.), hematological abnormalities (including thrombocytopenia), etc.; **AND**

Multiple Sclerosis (MS) [15,21]

- 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 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:
  - 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.]

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

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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
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

ICD-10	ICD-10 Description
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)
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

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