Clinical Policy: Natalizumab (Tysabri)

Reference Number: CP.PHAR.259
Effective Date: 07/16
Last Review Date: 07/17

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for natalizumab (Tysabri®).

Policy/Criteria
It is the policy of health plans affiliated with Centene Corporation® that Tysabri is **medically necessary** for the following indications:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of relapsing-remitting multiple sclerosis (MS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Failure of one of the following (a or b) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced:
   a. Tecfidera or Gilenya and any of the following: an interferon-beta agent *(Avonex and Plegridy are preferred agents)*, or glatiramer *(Glatopa 20 mg and Copaxone 40 mg are preferred agents)*;
   b. Tecfidera and Gilenya;
5. Member will not use other disease modifying therapies for MS concurrently;
6. Dose does not exceed 300 mg every 4 weeks (1 vial every 4 weeks).

Approval duration: 6 months

B. Crohn's Disease (must meet all):

1. Diagnosis of Crohn's disease (CD) and (a or b):
   a. Member is identified as moderate/high risk based on one of the following:
      i. Age at initial diagnosis < 30 years;
      ii. Extensive anatomic involvement (e.g., ileocecal disease, continuous ileocolonic disease, small bowel disease);
      iii. Perianal and/or severe rectal disease;
      iv. Deep ulcers;
      v. Prior surgical resection;
      vi. Stricturing and/or penetrating behavior;
   b. Failure of an immunomodulator (e.g., azathioprine, 6-mercaptopurine (6MP), methotrexate (MTX)], used for ≥ 3 months unless contraindicated or clinically significant adverse effects are experienced;

2. Failure of adalimumab (*Humira is preferred)* AND one other tumor-necrosis factor (TNF) α inhibitor (i.e., infliximab, Cimzia) each used for ≥ 3 consecutive months, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab and all TNFα inhibitors*
3. Prescribed by or in consultation with a gastroenterologist;
4. Age ≥ 18 years;
5. Immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors will not be administered concurrently – aminosalicylates may be continued;
6. Prescribed dose does not exceed 300 mg every 4 weeks.

Approval duration: 6 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy

II. Continued Approval

A. Multiple Sclerosis (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member is responding positively to therapy (e.g., improved or maintained disease control evidenced by decreased or stabilized Expanded Disability Status Scale score or reduction in relapses or magnetic resonance imaging lesions);
3. Member is not using other disease modifying therapies for MS concurrently;
4. If request is for a dose increase, new dose does not exceed 300 mg every 4 weeks (1 vial every 4 weeks).

Approval duration: 12 months

B. Crohn's Disease (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Responding positively to therapy;
3. Immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors will not be administered concurrently – aminosalicylates may be continued;
4. Prescribed regimen does not exceed 300 mg every 4 weeks.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy;

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

Tysabri is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. It binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). The specific mechanism(s) by which Tysabri exerts its effects in multiple sclerosis and Crohn's disease have not been fully defined.

- In multiple sclerosis, the clinical effect of natalizumab may be secondary to blockade of the molecular interaction of α4β1-integrin expressed by inflammatory cells with vascular cell adhesion molecule-1 on vascular endothelial cells, and with connecting segment-1 and/or osteopontin expressed by parenchymal cells in the brain.
- In Crohn's disease, the clinical effect of natalizumab may be secondary to blockade of the molecular interaction of the α4ß7-integrin receptor with mucosal addressin cell adhesion molecule-1 expressed on the venular endothelium at inflammatory foci. The interaction of the α4β7 integrin with the endothelial receptor mucosal addressin cell adhesion molecule-has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease.

Formulations:
Tysabri is supplied as 300 mg natalizumab in 15 mL in a sterile, single-use vial free of preservatives.

FDA Approved Indication(s):
Tysabri is an integrin receptor antagonist/intravenous infusion indicated for:

- Treatment of patients with relapsing forms of multiple sclerosis.
- Inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of (TNF-α).

Limitations of use:

- Tysabri increases the risk of progressive multifocal leukoencephalopathy . When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk.
- In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF-α.

Appendices

Appendix A: Abbreviation Key

6-MP: 6-mercaptopurine
CD: Crohn's disease
FDA: Food and Drug Administration
MS: multiple sclerosis
MTX: methotrexate
RRMS: relapsing-remitting multiple sclerosis
TNF-α: tumor-necrosis factor-α

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J2323	Injection, natalizumab, 1 mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.18 MS Treatments and CP.PHAR.87.IBD Treatment_4_. MS criteria: added max dosing, clarified monotherapy restriction, removed re-authorization requirement for documented adherence, updated contraindications and reasons to discontinue, modified efficacy criteria from "No increase in neurologic dysfunction/disability as a result of relapses or progressive disease, including a change in diagnostic status from RRMS to SPMS" to "Responding positively to therapy". CD criteria: added poor prognostic indicators; removed criteria related to concurrent administration of live vaccines; added dosing requirement; added requirement for trial and failure of PDL Humira as one of the two required TNF inhibitors, unless contraindicated. Modified trial/failure of immunomodulator, aminosalicylate or corticosteroid to failure of "corticosteroid, with or without immunomodulator" per 2014 AGA Clinical decision tool. Re-auth: added criteria related to dosing per PI and reasons to discontinue. Modified approval duration to 6 months for initial and 12 months for renewal.	06/16	07/16
Removed trial and failure of corticosteroid as an option for moderate to severe CD, per 2014 AGA Clinical decision tool- corticosteroids are appropriate for low-risk patients.	11/16	
All indications: Removed both contraindications and reasons to discontinue. MS: Requirement for MRI removed as this is not a specific diagnostic test and involvement of specialist in the care is required. Added age requirement as safety and efficacy have not been established in pediatric populations. Updated preferencing to require at least one of the highly effective disease-modifying therapy on formulary (Tecfidera or Gilenya). CD: modified poor prognostic indicator list to match AGA guidelines.	06/17	07/17
CD: Reclassified "failure of an immunomodulator…" as one of the options to meet criteria point 1 (along with other poor prognostic indicators), instead of as an alternative to failing Humira and another TNF inhibitor in criteria point 2.	08/17	

References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; May 2016. Available at http://www.tysabri.com. Accessed June 14, 2017.
2. Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis, principles and current evidence – a consensus paper by the Multiple Sclerosis Coalition. July 2016. Accessed June 13, 2017.

3. Olek MJ. Disease-modifying treatment of relapsing-remitting multiple sclerosis. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2017. Available at www.UpToDate.com. Accessed June 13, 2017.
4. Olek MJ. Diagnosis of multiple sclerosis in adults. In: UpToDate, Waltham, MA: Walters Kluwer Health; 2017. Available at www.UpToDate.com. Accessed June 13, 2017.
5. Lichtenstein GR, Hanauer SB, Sandborn WJ, and the Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol. 2009;104(2):465-483.
6. Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology 2014; 147: 702-705.
7. Bernell O, Lapidus A, Hellers G. Risk Factors for Surgery and Postoperative Recurrence in Crohn's Disease. Annals of Surgery. 2000; 231(1): 38-45.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.