Clinical Policy: Natalizumab (Tysabri)

Reference Number: PA.CP.PHAR.259
Effective Date: 01/18
Last Review Date: 04/19

Coding Implications
Revision Log

Description
Natalizumab (Tysabri®) is an integrin receptor antagonist.

FDA Approved Indication(s)
Tysabri is indicated:

- As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS)
- For inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of tumor necrosis factor-α (TNF-α)

Limitation(s) 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.

Policy/Criteria
It is the policy of Pennsylvania Health and Wellness® that Tysabri is **medically necessary** for the following indications:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of a relapsing form of multiple sclerosis (MS);
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Failure of Gilenya® at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced, unless the patient is currently stabilized on therapy:
   **Prior authorization is required for Gilenya*
5. Member will not use other disease modifying therapies for MS concurrently;
6. Dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 6 months

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

1. Diagnosis of Crohn's disease (CD)
2. Prescribed by or in consultation with a gastroenterologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):

a. Failure of a ≥ 3 consecutive month trial of at least ONE immunomodulator (e.g., azathioprine, 6-mercaptopurine [6-MP], methotrexate [MTX]) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
b. Medical justification supports inability to use immunomodulators (*see Appendix E*);

5. Failure of adalimumab (*Humira® is preferred)* AND one other TNF-α inhibitor (e.g., infliximab [*Inflectra® and Renflexis™ are preferred*], Cimzia®), each used for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab and all TNF-α inhibitors*
6. Immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors will not be administered concurrently – aminosalicylates may be continued;
7. Prescribed dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 6 months

C. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy;
3. Tysabri is not prescribed concurrently with one of the following (a or b):
   a. MS: other disease modifying therapies (*see Appendix D*);
   b. CD: immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors (note: aminosalicylates may be continued);
4. If request is for a dose increase, new dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 12 months

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;

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

2. Refer to PA.CP.PMN.53**.**

III. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

6-MP: 6-mercaptopurine
CD: Crohn's disease
FDA: Food and Drug Administration
GI: gastrointestinal

MS: multiple sclerosis
MTX: methotrexate
TNF-α: tumor necrosis factor-α

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
MS agents		
Gilenya® (fingolimod)	0.5 mg PO QD	0.5 mg/day
CD agents		
6-mercaptopurine (Purixan®)*	50 mg PO QD or 1.5 – 2 mg/kg/day PO	2 mg/kg/day
azathioprine (Azasan®, Imuran®)*	1.5 – 2 mg/kg/day PO	2.5 mg/kg/day
corticosteroids*	prednisone 40 mg PO QD for 2 weeks or IV 50 – 100 mg Q6H for 1 week budesonide (Entocort EC®) 6 – 9 mg PO QD	Various
methotrexate (Otrexup®, Rasuvo)*	15 – 25 mg/week IM or SC	30 mg/week
Pentasa® (mesalamine)	1,000 mg PO QID	4 g/day
tacrolimus (Prograf®)*	0.27 mg/kg/day PO in divided doses or 0.15 – 0.29 mg/kg/day PO	N/A
Cimzia® (certolizumab)	Initial dose: 400 mg SC at 0, 2, and 4 weeks Maintenance dose: 400 mg SC every 4 weeks	400 mg every 4 weeks
Humira® (adalimumab)	Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15 Maintenance dose: 40 mg SC every other week starting on Day 29	40 mg every other week
Renflexis®, Inflectra® (infliximab)	Initial dose: 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 5 mg/kg IV every 8 weeks.	10 mg/kg every 8 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response	

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.
**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients who have or have had progressive multifocal leukoencephalopathy
  - Patients who have had a hypersensitivity reaction to Tysabri
- Boxed warning(s): progressive multifocal leukoencephalopathy

Appendix D: General Information

- Because of the risk of progressive multifocal leukoencephalopathy, Tysabri is only available through a REMS program called the TOUCH® Prescribing Program.
- Disease-modifying therapies for MS are: glatiramer acetate (Copaxone®, Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), and ocreliuzmab (Ocrevus™).
- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya, Tysabri, and Lemtrada for patients with highly active MS. Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.
- Definition of failure of MTX or DMARDs
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.

Appendix E: Medical Justification

- The following may be considered for medical justification supporting inability to use an immunomodulator for Crohn's disease:
  - Inability to induce short-term symptomatic remission with a 3-month trial of systemic glucocorticoids
  - High-risk factors for intestinal complications may include:

- Initial extensive ileal, ileocolonic, or proximal GI involvement
- Initial extensive perianal/severe rectal disease
- Fistulizing disease (e.g., perianal, enterocutaneous, and rectovaginal fistulas)
- Deep ulcerations
- Penetrating, stricturing or stenosis disease and/or phenotype
- Intestinal obstruction or abscess

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Relapsing MS, CD	300 mg IV every 4 weeks In CD, discontinue in patients who have not experienced therapeutic benefit by 12 weeks of induction therapy and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy	300 mg/4 weeks

V. Product Availability

Single-use vial: 300 mg/15 mL

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
2Q 2018 annual review: for CD: removed requirements for specific criteria relating to diagnosis, changed trial and failure duration to 3 consecutive months, added brand names of preferred agents for trial and failure; references reviewed and updated.	02.27.18	
2Q 2019 annual review: added trial and failure of immunosuppressants, or medical necessity for use of biologics in CD; for MS: modified trial/failure requirement from 2 preferred agents to just Gilenya (the only preferred agent recommended as first-line for highly active disease) per updated AAN MS guidelines which now recommend Tysabri as first-line for highly active disease; references reviewed and updated.	04.17.19	

References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; April 2018. Available at http://www.tysabri.com. Accessed February 4, 2019.
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. March 2017. Accessed February 4, 2019.
3. Lichtenstein GR, Loftus Jr. EV, Isaacs KI, Regueiro MD, Gerson LB, and Sands BE. ACG clinical guideline: management of Crohn's disease in adults. Am J Gastroenterol. 2018; 113:481-517.
4. Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology 2014; 147: 702-705.
5. 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.
6. 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(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904.