Clinical Policy: Natalizumab (Tysabri)

Reference Number: IL.ERX.SPA.162
Effective Date: 06.01.21
Last Review Date: 05.21 Revision Log
Line of Business: Illinois Medicaid

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

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), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults
- 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
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Tysabri is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all)**:**

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome, and member is contraindicated to both, or has experienced clinically significant adverse effects to one, of the following at up to maximally indicated doses: an interferon-beta agent (*Betaseron® and Rebif® are preferred agents*), glatiramer (*Copaxone® 20 mg is preferred*);
   b. Relapsing-remitting MS, and failure of the following at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced: dimethyl fumarate (*Tecfidera® brand is preferred*) and any of the following: an interferon-beta agent *(Betaseron and Rebif are preferred agents)* or glatiramer *(Copaxone 20 mg is preferred*);
   **Prior authorization is required for all disease modifying therapies for MS*
   c. Secondary progressive MS;
2. Prescribed by or in consultation with a neurologist;
3. Age ≥ 18 years;
4. Tysabri is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);

5. Documentation of baseline number of relapses per year and expanded disability status scale (EDSS) score;
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 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 a ≥ 3 consecutive month trial of Cimzia® AND Humira®, unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is required for adalimumab and certolizumab*
6. Tysabri is not prescribed concurrently with immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF-α inhibitors (note: aminosalicylates may be continued);
7. Dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: 6 months

C. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Multiple Sclerosis (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
   a. If member has received < 1 year of total treatment: Member is responding positively to therapy;
   b. If member has received ≥ 1 year of total treatment: Member meets one of the following (i, ii, iii, or iv):
      i. Member has not had an increase in the number of relapses per year compared to baseline;
      ii. Member has not had ≥ 2 new MRI-detected lesions;
      iii. Member has not had an increase in EDSS score from baseline;
      iv. Medical justification supports that member is responding positively to therapy;
3. Tysabri is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix D*);
4. If request is for a dose increase, new dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval duration: first re-authorization: 6 months**; second and subsequent re-authorizations:** 12 months

B. Crohn's Disease (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Tysabri is not prescribed concurrently with 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

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;
B. Primary progressive MS.

IV. Appendices/General Information
Appendix A: Abbreviation/Acronym Key

6-MP: 6-mercaptopurine
CD: Crohn's disease
EDSS: expanded disability status scale
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		
Rebif® (interferon beta-1a)	22 mcg or 44 mcg SC TIW	44 mcg TIW
Betaseron® (interferon beta-1b)	250 mcg SC QOD	250 mg QOD
glatiramer acetate (Copaxone®)	20 mg SC QD or 40 mg SC TIW	20 mg/day or 40 mg TIW
dimethyl fumarate (Tecfidera®)	120 mg PO BID for 7 days, followed by 240 mg PO BID	480 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
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
Cimzia® (certolizumab)	Initial dose: 400 mg SC at 0, 2, and 4 weeks	CD: 400 mg every

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Maintenance dose: 400 mg SC every 4 weeks	4 weeks

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®), diroximel fumarate (Vumerity®), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya®), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocrelizumab (Ocrevus®), cladribine (Mavenclad®), siponimod (Mayzent®), ozanimod (Zeposia®), and ofatumumab (Kesimpta®).
- 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

V. 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

VI. Product Availability

Single-use vial: 300 mg/15 mL

VII. References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; June 2020. Available at http://www.tysabri.com. Accessed February 8, 2021.
2. 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.
3. Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. Gastroenterology 2014; 147: 702-705.
4. 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.
5. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	04.19.21	05.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.