

Clinical Policy: Natalizumab (Tysabri)

Reference Number: LA.PHAR.259

Effective Date:

Last Review Date: 01.21

Line of Business: Medicaid

[Coding Implications](#)

[Revision Log](#)

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

Prior authorization is required. Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections 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 (Avonex®, Betaseron®, Rebif®, or Plegridy®), glatiramer (Copaxone®, Glatopa®);
 - b. Relapsing-remitting MS, and one of the following (i or ii):

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- i. Failure of two of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated: Aubagio[®], dimethyl fumarate (Tecfidera[®]), Gilenya[®], an interferon-beta agent (Avonex, Betaseron, Rebif, or Plegridy), glatiramer (Copaxone, Glatopa);
 - ii. Member has highly active MS and failure of Gilenya[®] at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - c. Secondary progressive MS;
 - 2. Prescribed by or in consultation with a neurologist;
 - 3. Age \geq 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 \geq 18 years;
 - 4. Member meets one of the following (a or b):
 - a. Failure of a \geq 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 AND one other TNF- α inhibitor (e.g., infliximab [Inflectra[®] and Renflexis[™]], Cimzia[®]), each used for \geq 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced;
**Prior authorization may be required for adalimumab and TNF- α inhibitors*
 - 6. Tysabri is not prescribed concurrently with immunosuppressants (e.g., azathioprine, cyclosporine, 6-MP, MTX) or TNF- α inhibitors (note: aminosaliclates 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 the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.

II. Continued Therapy

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A. Multiple Sclerosis (must meet all):

1. Currently receiving medication via Louisiana Healthcare Connections benefit 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 (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 Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. Tysabri is not prescribed concurrently 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 Louisiana Healthcare Connections benefit and documentation supports positive response to therapy.
Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.

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 –LA.PMN.53 for Medicaid 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 require prior authorization.

<u>Drug Name</u>	<u>Dosing Regimen</u>	<u>Dose Limit/ Maximum Dose</u>
<u>MS agents</u>		
<u>Avonex[®], Rebif[®]</u> <u>(interferon beta-1a)</u>	<u>Avonex: 30 mcg IM Q week</u> <u>Rebif: 22 mcg or 44 mcg SC TIW</u>	<u>Avonex: 30 mcg/week</u> <u>Rebif: 44 mcg TIW</u>
<u>Betaseron[®] (interferon beta-1b)</u>	<u>250 mcg SC QOD</u>	<u>250 mg QOD</u>
<u>Plegridy[®] (peginterferon beta-1a)</u>	<u>125 mcg SC Q2 weeks</u>	<u>125 mcg/2 weeks</u>
<u>glatiramer acetate</u> <u>(Copaxone[®], Glatopa[®])</u>	<u>20 mg SC QD or 40 mg SC TIW</u>	<u>20 mg/day or 40 mg TIW</u>
<u>Aubagio[®]</u> <u>(teriflunomide)</u>	<u>7 mg or 14 mg PO QD</u>	<u>14 mg/day</u>
<u>Gilenya[®] (fingolimod)</u>	<u>0.5 mg PO QD</u>	<u>0.5 mg/day</u>
<u>dimethyl fumarate</u> <u>(Tecfidera[®])</u>	<u>120 mg PO BID for 7 days,</u> <u>followed by 240 mg PO BID</u>	<u>480 mg/day</u>
<u>CD agents</u>		
<u>6-mercaptopurine</u> <u>(Purixan[®])*</u>	<u>50 mg PO QD or 1.5 – 2</u> <u>mg/kg/day PO</u>	<u>2 mg/kg/day</u>
<u>azathioprine (Azasan[®],</u> <u>Imuran[®])*</u>	<u>1.5 – 2 mg/kg/day PO</u>	<u>2.5 mg/kg/day</u>
<u>corticosteroids*</u>	<u>prednisone 40 mg PO QD for 2</u> <u>weeks or IV 50 – 100 mg Q6H for</u> <u>1 week</u> <u>budesonide (Entocort EC[®]) 6 – 9</u> <u>mg PO QD</u>	<u>Various</u>
<u>methotrexate (Otrexup[®],</u> <u>Rasuvo)*</u>	<u>15 – 25 mg/week IM or SC</u>	<u>30 mg/week</u>
<u>Pentasa[®] (mesalamine)</u>	<u>1,000 mg PO QID</u>	<u>4 g/day</u>
<u>tacrolimus (Prograf[®])*</u>	<u>0.27 mg/kg/day PO in divided</u> <u>doses or 0.15 – 0.29 mg/kg/day</u> <u>PO</u>	<u>N/A</u>

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<u>Drug Name</u>	<u>Dosing Regimen</u>	<u>Dose Limit/ Maximum Dose</u>
<u>Cimzia® (certolizumab)</u>	<u>Initial dose: 400 mg SC at 0, 2, and 4 weeks</u> <u>Maintenance dose: 400 mg SC every 4 weeks</u>	<u>400 mg every 4 weeks</u>
<u>Humira® (adalimumab)</u>	<u>Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15</u> <u>Maintenance dose: 40 mg SC every other week starting on Day 29</u>	<u>40 mg every other week</u>
<u>Renflexis®, Inflectra® (infliximab)</u>	<u>Initial dose: 5 mg/kg IV at weeks 0, 2 and 6</u> <u>Maintenance dose: 5 mg/kg IV every 8 weeks.</u> <u>Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response</u>	<u>10 mg/kg every 8 weeks</u>

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®), and ozanimod (Zeposia®).

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- 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.
- Of the disease-modifying therapies for MS that are FDA-labeled for CIS, only the interferon products, glatiramer, and Aubagio have demonstrated any efficacy in decreasing the risk of conversion to MS compared to placebo. This is supported by the AAN 2018 MS guidelines.
- 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.
- Per the American Academy of Neurology 2018 MS practice guidelines, 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.

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

<u>Indication</u>	<u>Dosing Regimen</u>	<u>Maximum Dose</u>
<u>Relapsing MS, CD</u>	<u>300 mg IV every 4 weeks</u> <u>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</u>	<u>300 mg/4 weeks</u>

VI. Product Availability

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Single-use vial: 300 mg/15 mL

VII. References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; August 2019. Available at <http://www.tysabri.com>. Accessed January 27, 2020.
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. Updated June 2019. Accessed January 27, 2020.
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>.

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.

<u>HCPCS Codes</u>	<u>Description</u>
J2323	Injection, natalizumab, 1 mg

<u>Reviews, Revisions, and Approvals</u>	<u>Date</u>
<u>Converted corporate to local policy</u>	01.21

Important Reminder

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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. LHCC 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.

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 LHCC administrative policies and procedures.

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