# Clinical Policy: Natalizumab (Tysabri)

Reference Number: CP.PHAR.259
Effective Date: 07.01.16
Last Review Date: 05.18
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)
- 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.*

It is the policy of health plans affiliated with Centene Corporation® that Tysabri is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

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

1. Diagnosis of relapsing-remitting 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. Tysabri is not prescribed concurrently with other disease modifying therapies for MS (*see Appendix C*);
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 gastrointestinal (GI) specialist;
3. Age ≥ 18 years;
4. 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;
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. 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 CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

## II. Continued Therapy

**A. All Indications in Section I** (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
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 C*);
   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 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.PMN.53 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 – CP.PMN.53 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
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*** | | |
| Avonex®, Rebif® (interferon beta-1a) | *Avonex*: 30 mcg IM Q week<br>*Rebif*: 22 mcg or 44 mcg SC TIW | *Avonex*: 30 mcg/week<br>*Rebif*: 44 mcg TIW |
| Plegridy® (peginterferon beta-1a) | 125 mcg SC Q2 weeks | 125 mcg/2 weeks |
| Betaseron®, Extavia® (interferon beta-1b) | 250 mcg SC QOD | 250 mg QOD |
| glatiramer acetate (Copaxone®, Glatopa®) | *Copaxone*: 20 mg SC QD or 40 mg SC TIW<br>*Glatopa*: 20 mg SC QD | *Copaxone*: 20 mg/day or 40 mg TIW<br>*Glatopa*: 20 mg/day |
| Gilenya™ (fingolimod) | 0.5 mg PO QD | 0.5 mg/day |
| Tecfidera® (dimethyl fumarate) | 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<br><br>budesonide (Entocort EC®) 6 – 9 mg PO QD | Various |

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

- Disease-modifying therapies for MS are: daclizumab (Zinbryta®), 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™).
- Contraindications:
  - Tysabri is contraindicated in patients who have or have had PML. Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability.
- 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.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| MS, CD | 300 mg IV every 4 weeks | 300 mg/4 weeks |

## VI. Product Availability

Single-use vial: 300 mg/15 mL

## VII. References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; August 2017. Available at http://www.tysabri.com. Accessed February 27, 2018.
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 January 5, 2018.
3. 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.
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.

**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 | P&T Approval Date |
|---|---|---|
| Policy split from CP.PHAR.18 MS Treatments and CP.PHAR.87.IBD Treatment_4_.<br>MS criteria: added max dosing, clarified monotherapy restriction, removed re-authorization requirement for documented adherence, | 06.16 | 07.16 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 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".<br>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. | | |
| 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.<br>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).<br>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 | |
| 2Q 2018 annual review: for CD: removed requirements for specific criteria relating to diagnosis, altered specialist requirement to GI specialist, 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 | 05.18 |

**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.



**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.