Clinical Policy: Natalizumab (Tysabri)
Reference Number: PA.CP.PHAR.259
Effective Date: 01/18
Last Review Date: 04/19

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 $\geq 3$ 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 (*Humira® is preferred*) AND one other TNF-α inhibitor (e.g., infliximab [*Inflectra® and Renflexis™ are preferred*, Cimzia®), each used for $\geq 3$ 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*

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>6-MP: 6-mercaptopurine</td>
<td>FDA: Food and Drug Administration</td>
</tr>
<tr>
<td>CD: Crohn’s disease</td>
<td>GI: gastrointestinal</td>
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</table>
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.

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

**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 ocreliuzumab (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**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapsing MS, CD</td>
<td>300 mg IV every 4 weeks</td>
<td>300 mg/4 weeks</td>
</tr>
<tr>
<td></td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
<th>Date</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
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<td></td>
</tr>
</tbody>
</table>

**Reviews, Revisions, and Approvals**

- 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.  
  
  Date: 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.
  
  Date: 04.17 .19
References