Clinical Policy: Natalizumab (Tysabri)
Reference Number: HIM.PA.SP17
Effective Date: 06.01.17
Last Review Date: 08.20
Line of Business: HIM

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
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 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):
i. Failure of all of the following at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated (1, 2, 3, and 4):*
   1) Dimethyl fumarate (generic Tecfidera®);
   2) Aubagio®;
   3) Gilenya®;
   4) An interferon-beta agent (Avonex, Betaseron, Rebif, or Plegridy) or glatiramer (Copaxone, Glatopa);

*Prior authorization is required for all disease modifying therapies for MS

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 ≥ 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

1. Refer to HIM.PA.SP60 Biologic DMARDs.

C. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

II. Continued Therapy

A. Multiple Sclerosis (must meet all):

1. Currently receiving medication via Centene 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

1. Refer to HIM.PA.SP60 Biologic DMARDs.

C. 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace.

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 – HIM.PHAR.21 for health insurance marketplace or evidence of coverage documents;

B. Primary progressive MS.

IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

- CD: Crohn’s disease
- EDSS: expanded disability status scale
- FDA: Food and Drug Administration
- MS: multiple sclerosis
- 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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex®, Rebif® (interferon beta-1a)</td>
<td><em>Avonex: 30 mcg IM Q week</em>&lt;br&gt;<em>Rebif: 22 mcg or 44 mcg SC TIW</em></td>
<td><em>Avonex: 30 mcg/week</em>&lt;br&gt;<em>Rebif: 44 mcg TIW</em></td>
</tr>
<tr>
<td>Betaseron® (interferon beta-1b)</td>
<td>250 mcg SC QOD</td>
<td>250 mg QOD</td>
</tr>
<tr>
<td>Plegidy® (peginterferon beta-1a)</td>
<td>125 mcg SC Q2 weeks</td>
<td>125 mcg/2 weeks</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone®, Glatopa®)</td>
<td>20 mg SC QD or 40 mg SC TIW</td>
<td>20 mg/day or 40 mg TIW</td>
</tr>
<tr>
<td>Gilenya® (fingolimod)</td>
<td>0.5 mg PO QD</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>Aubagio (teriflunomide)</td>
<td>7 mg or 14 mg PO QD</td>
<td>14 mg/day</td>
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</tbody>
</table>
**Clinical Policy**

**Natalizumab**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>dimethyl fumarate (Tecfidera)</td>
<td>120 mg PO BID for 7 days, followed by 240 mg PO BID</td>
<td>480 mg/day</td>
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</tbody>
</table>

*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®).
- 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.

**V. Dosage and Administration**

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

**VI. Product Availability**

Single-use vial: 300 mg/15 mL

**VII. References**

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>P&amp;T Approval Date</th>
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</thead>
<tbody>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>01.17</td>
<td>05.17</td>
</tr>
<tr>
<td>2Q 2018 annual review: for MS: removed MRI requirement, added age requirement, updated preferencing to require at least one of the highly effective disease-modifying therapies on formulary (Tecfidera or Gilenya); For CD: removed requirements for specific criteria relating to diagnosis, altered specialist requirement to GI specialist, added age requirement, modified trial and failure of biologic to requirement of Humira and another TNF-α inhibitor; references reviewed and updated.</td>
<td>02.27.18</td>
<td>05.18</td>
</tr>
<tr>
<td>4Q 2018 annual review: modified prescriber specialist from GI specialist to gastroenterologist for CD; added trial and failure of immunosuppressants, or medical necessity for use of biologics in CD; references reviewed and updated.</td>
<td>08.28.18</td>
<td>11.18</td>
</tr>
<tr>
<td>2Q 2019 annual review: 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.</td>
<td>02.19.19</td>
<td>05.19</td>
</tr>
<tr>
<td>RT4: added coverage for CIS and SPMS per updated FDA labeling; references reviewed and updated.</td>
<td>08.16.19</td>
<td></td>
</tr>
<tr>
<td>Revised Crohn’s Disease criteria sets to refer to HIM.PA.SP60 Biologic DMARDs criteria.</td>
<td>12.30.19</td>
<td></td>
</tr>
<tr>
<td>2Q 2020 annual review: MS: added CIS re-directions per SDC; references reviewed and updated.</td>
<td>01.27.20</td>
<td>05.20</td>
</tr>
<tr>
<td>MS: added requirements for documentation of baseline relapses/EDSS and objective measures of positive response upon re-authorization; modified continued approval duration to 6 months for the first re-authorization and 12 months for second/subsequent re-authorizations; references reviewed and updated.</td>
<td>05.27.20</td>
<td>08.20</td>
</tr>
</tbody>
</table>
**Reviews, Revisions, and Approvals**

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per November SDC and prior clinical guidance, for RRMS modified redirection to require generic dimethyl fumarate, Aubagio, Gilenya, and either an interferon-beta agent or glatiramer, unless member has highly active MS, in which Gilenya redirection is maintained.</td>
<td>02.15.21</td>
</tr>
</tbody>
</table>

**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.

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