Clinical Policy: Natalizumab (Tysabri)
Reference Number: CP.PHAR.259
Effective Date: 08.01.16
Last Review Date: 08.20
Line of Business: 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.

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 (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 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 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): CP.PMN.53 for Medicaid.

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 (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 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 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): CP.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 – CP.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 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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<td></td>
</tr>
</tbody>
</table>
| Avonex®, Rebif® (interferon beta-1a) | Avonex: 30 mcg IM Q week  
Rebif: 22 mcg or 44 mcg SC TIW | Avonex: 30 mcg/week  
Rebif: 44 mcg TIW |
<p>| Betaseron® (interferon beta-1b)    | 250 mcg SC QOD                                      | 250 mcg QOD             |
| Plegridy® (peginterferon beta-1a)  | 125 mcg SC Q2 weeks                                 | 125 mcg/2 weeks         |
| glatiramer acetate (Copaxone®, Glatopa®) | 20 mg SC QD or 40 mg SC TIW | 20 mg/day or 40 mg TIW |
| Aubagio® (teriflunomide)           | 7 mg or 14 mg PO QD                                 | 14 mg/day               |
| Gilena® (fingolimod)              | 0.5 mg PO QD                                        | 0.5 mg/day              |
| dimethyl fumarate (Tecfidera®)     | 120 mg PO BID for 7 days, followed by 240 mg PO BID | 480 mg/day              |
| <strong>CD agents</strong>                      |                                                     |                         |
| 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 | Various |
|                                   | budesonide (Entocort EC®) 6 – 9 mg PO QD            |                         |
| methotrexate (Otrexup®, Rasuvo)*   | 15 – 25 mg/week IM or SC                            | 30 mg/week              |
| Pentasa® (mesalamine)             | 1,000 mg PO QID                                     | 4 g/day                 |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<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</td>
<td>400 mg every 4 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 400 mg SC every 4 weeks</td>
<td></td>
</tr>
<tr>
<td>Humira® (adalimumab)</td>
<td>Initial dose: 160 mg SC on Day 1, then 80 mg SC on Day 15</td>
<td>40 mg every other week</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 40 mg SC every other week starting on Day 29</td>
<td></td>
</tr>
<tr>
<td>Renflexis®, Inflectra®, Infliximab</td>
<td>Initial dose: 5 mg/kg IV at weeks 0, 2 and 6</td>
<td>10 mg/kg every 8 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 5 mg/kg IV every 8 weeks.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response</td>
<td></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®, Rebița®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plengiridag™), dimethyl fumarate (Tecfidera®), diroximel fumarate (Vumerity™), monomethyl fumarate (Bafiertam™), fingolimod (Gilenya®), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab
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(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.
- 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

<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 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>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>
</tr>
</thead>
<tbody>
<tr>
<td>J2323</td>
<td>Injection, natalizumab, 1 mg</td>
</tr>
</tbody>
</table>

Reviews, Revisions, and Approvals
Policy split from CP.PHAR.18 MS Treatments and CP.PHAR.87.IBD Treatment_4_.
MS criteria: added max dosing, clarified monotherapy restriction, removed re-authorization requirement for documented adherence, 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”.
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.

All indications: Removed both contraindications and reasons to
discontinue.

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).

CD: modified poor prognostic indicator list to match AGA guidelines.

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.

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.

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.

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.

RT4: added coverage for CIS and SPMS per updated FDA labeling;
references reviewed and updated.

2Q 2020 annual review: MS: added CIS re-directions per SDC;
references reviewed and updated.

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-
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Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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</thead>
<tbody>
<tr>
<td>authorization and 12 months for second/subsequent re-authorizations; references reviewed and updated.</td>
<td></td>
</tr>
<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>01.11.21</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.

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.

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**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.

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