Clinical Policy: Natalizumab (Tysabri)
Reference Number: ERX.SPA.162
Effective Date: 10.01.16
Last Review Date: 05.18

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 Envolve Pharmacy Solutions™ 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 (Betaseron and Rebif are preferred agents), glatiramer (Glatopa 20 mg and Copaxone 40 mg are preferred agents), or Aubagio;
         b. Tecfidera and Gilenya; *Prior authorization is required for all of these therapies
      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], or methotrexate [MTX]) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. Failure of 2 TNF-α inhibitors (Humira® and Remicade® are preferred), each used for ≥ 3 consecutive months unless contraindicated or clinically significant adverse effects are experienced;  
*Prior authorization is required for Humira and Remicade  
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 ERX.PA.01 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 a health plan affiliated with Envolve Pharmacy Solutions 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 for MS (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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 6 months (whichever is less); or**  
2. Refer to ERX.PA.01 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 – ERX.PA.01 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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
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</thead>
<tbody>
<tr>
<td><strong>MS agents</strong></td>
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</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>| Plegridy® (peginterferon beta-1a) | 125 mcg SC Q2 weeks                      | 125 mcg/2 weeks          |</p>
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Betaseron®, Extavia® (interferon beta-1b)</td>
<td>250 mcg SC QOD</td>
<td>250 mg QOD</td>
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<tr>
<td>Glatiramer acetate (Copaxone®, Glatopa®)</td>
<td>Copaxone: 20 mg SC QD or 40 mg SC TIW Glatopa: 20 mg SC QD</td>
<td>Copaxone: 20 mg/day or 40 mg TIW Glatopa: 20 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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<tr>
<td>Gilenya™ (fingolimod)</td>
<td>0.5 mg PO QD</td>
<td>0.5 mg/day</td>
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<tr>
<td>Tecfidera® (dimethyl fumarate)</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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**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 budesonide (Entocort EC®) 6 – 9 mg PO QD | Various |
| 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 |
| Humira® (adalimumab) | 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 | 40 mg every other week |
| Remicade® (infliximab) | Initial dose: 5 mg/kg IV at weeks 0, 2 and 6 Maintenance dose: 5 mg/kg IV every 8 weeks. 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 |
| Stelara® (ustekinumab) | Weight based dosing IV at initial dose, followed by 90 mg SC every 8 weeks | 90 mg 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**

- **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.

- 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 ocrelizumab (Ocrevus™).

- 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
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<tr>
<td>MS, CD</td>
<td>300 mg IV every 4 weeks</td>
<td>300 mg/4 weeks</td>
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VI. Product Availability

Single-use vial: 300 mg/15 mL

VII. References


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Policy split from USS.SPMN.36 Multiple Sclerosis (MS) Treatments and USS.SPMN.24 Irritable Bowel Disease (IBD) Treatments. Converted to new template. Added dosing criteria. Modified approval duration to 6 months for initial and 12 months for renewal. MS criteria: clarified monotherapy restriction. CD criteria: 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 &quot;corticosteroid, with or without immunomodulator&quot; per 2014 AGA Clinical decision tool. For all trial/failure requirements, indicated that member can also meet criteria if intolerant (as opposed to just contraindicated) to therapy in question. For CD, added poor prognostic indicators as alternative to trial/failure requirement and modified trial/failure requirement to indicate an immunomodulator (as opposed to a corticosteroid with or without an immunomodulator) must be trialed.</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<td>08.16</td>
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Reviews, Revisions, and Approvals

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<th>P&amp;T Approval Date</th>
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<td>11.17</td>
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4Q17 Annual Review
Converted to new template.
Added age requirement as safety and efficacy have not been established in pediatric populations.
MS: Removed requirement for MRI as this is not a specific diagnostic test and involvement of specialist in the care is required. Updated preferencing to require at least one of the highly effective disease-modifying therapies on formulary (Tecfidera or Gilenya). Added PPMS as a diagnosis not covered.
CD: diagnostic criteria modified to require verifiable information; removed poor prognostic indicators; added trial duration of 3 months for thiopurine or MTX

2Q 2018 annual review: for MS: no significant changes; for CD: removed requirements for specific criteria relating to diagnosis, altered specialist requirement to GI specialist, modified trial and failure to require at least one immunomodulator, modified preferencing for biologics, added requirement to not allow concurrent use with immunosuppressants or other TNF-α inhibitor to both initial and continuation approval criteria; 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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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