

**POLICY:** Multiple Sclerosis and Crohn's Disease – Tysabri® (natalizumab injection for intravenous use – Biogen)

**DATE REVIEWED:** 11/13/2019

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## OVERVIEW

Tysabri, an integrin receptor antagonist, is indicated for the treatment of relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults.<sup>1</sup> Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri is also indicated for inducing and maintaining clinical response and remission in adults with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of tumor necrosis factor (TNF)- $\alpha$ .<sup>1</sup> Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNF $\alpha$ . For both indications, the recommended dose of Tysabri is 300 mg by intravenous infusion over approximately 1 hour once every 4 weeks.<sup>1</sup>

## Disease Overview

### Multiple Sclerosis (MS)

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system (CNS) that impacts almost 1,000,000 people in the US.<sup>2</sup> The condition is marked by inflammation and demyelination, as well as degenerative alterations. Patients usually experience relapses and remissions in their neurological symptoms. For most patients, the onset of MS symptoms occurs when patients are 20 to 40 years of age; however, children can get MS and new onset disease can occur in older adults. The MS disease course is heterogeneous but has some patterns. Approximately 85% to 90% of patients have a relapsing pattern at onset. However, this transitions over time in patients who are untreated to a worsening with very few or no relapses or magnetic resonance imaging (MRI) activity (secondary progressive MS). Around 10% to 15% of patients have a steady progression of symptoms over time (primary progressive MS), marked by some clinical manifestations or by MRI activity. Primary progressive MS is generally diagnosed in patients on the upper level of the typical age range (e.g., almost 40 years of age) and the distribution is equivalent among the two genders. Advances in the understanding of the MS disease process, as well as in MRI technology, spurred updated disease course descriptions in 2013,<sup>3</sup> as well as in 2017.<sup>4</sup> The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.<sup>2-4</sup> Clinically isolated syndrome is now more recognized among the course descriptions of MS. It is the first clinical presentation of MS that displays characteristics of inflammatory demyelination that may possibly be MS but has yet to fulfill diagnostic criteria. It is notable that the other MS designations can be further characterized considering whether patients have active disease (or not active), as well as if disease is worsening or stable. Disability in MS is commonly graded on the deterioration of mobility per the Expanded Disability Status Scale (EDSS) an ordinal scale that ranges from 0 to 10, with higher scores indicating greater disability.

Many disease-modifying MS agents are FDA-approved for use in patients with relapsing forms of MS.<sup>2</sup> Options include self-administered injectable agents (e.g., glatiramer acetate products, and interferon beta agents), oral agents (i.e., Tecfidera® [dimethyl fumarate delayed-release capsules], Gilenya® [fingolimod capsules], Mayzent® [siponimod tablets]), Aubagio® [teriflunomide tablets], Mavenclad® [cladribine tablets], Vumerity™ [diroximel fumarate delayed-release capsules]), and intravenously infused agents (i.e.,

Lemtrada® [alemtuzumab injection for intravenous use], Ocrevus® [ocrelizumab injection for intravenous use], and mitoxantrone injection for intravenous use).

### **Crohn's disease**

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.<sup>6</sup> The prevalence has been increasing worldwide.<sup>7</sup> Common symptoms of Crohn's disease include abdominal pain, diarrhea, fatigue, weight loss, fever, anemia, and recurrent fistulas. Adults with Crohn's disease may be at risk of bone fractures, as well as thromboembolism. Other extraintestinal manifestations may occur (e.g., primary sclerosing cholangitis). Younger patients may experience growth failure.<sup>6,7</sup> The chronic intestinal inflammation over time leads to intestinal complications such as strictures, fistulas, and abscesses. Only 20% to 30% of patients with Crohn's disease will have a nonprogressive or indolent course. Therefore, it is appropriate to identify therapies that will achieve adequate control for the patient. Many different therapies are available including corticosteroids, immunomodulators (e.g., azathiopurine, 6-mercaptopurine), and anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol injection for subcutaneous use]).

### **Guidelines**

A practice guideline recommendation regarding disease-modifying agents for adults with MS from the American Academy of Neurology (2018) states to consider Tysabri for patients with MS who have highly active disease.<sup>5</sup>

The American College of Gastroenterology (ACG) has guidelines on management of Crohn's disease in adults (2018).<sup>7</sup> Some of the recommendations are summarized for moderate to severe disease or moderate to high-risk disease. Oral corticosteroids are effective and can be used short-term to alleviate signs and symptoms of moderately to severely active Crohn's disease. Thiopurines (azathiopurine, 6-mercaptopurine) are effective and should be considered for use for steroid-sparing Crohn's disease. Azathioprine and 6-mercaptopurine are effective therapies and should be considered for patients with Crohn's disease for maintenance of remission. Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia® [certolizumab pegol injection for subcutaneous use]) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids. Anti-TNF agents should be given for Crohn's disease refractory to thiopurines or methotrexate. For patients with moderately to severely active Crohn's disease and objective evidence of active disease, anti-integrin therapy (with Entyvio® [vedolizumab injection for intravenous use] with or without an immunomodulator is more effective than placebo and should be considered for use for induction of symptomatic remission in patients with Crohn's disease. Tysabri is more effective than placebo and should be considered to be used for induction of symptomatic response and remission in patients with active Crohn's disease (strong recommendation; high level of evidence). Tysabri should be used for maintenance of Tysabri-induced remission of Crohn's disease only if serum antibody to John Cunningham virus is negative. Stelara® (ustekinumab injection for subcutaneous or intravenous use) should be given for moderate to severe Crohn's disease patients who failed treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors.

### **Safety**

Tysabri has a Boxed Warning regarding the risk of PML. Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called the TOUCH® Prescribing Program, which requires registration by the prescribers, patients, infusion centers, and pharmacies associated with infusion centers.<sup>1</sup> Tysabri must be administered only to patients enrolled in and who meet all the conditions of the TOUCH Prescribing Program.

## POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Tysabri. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tysabri as well as the monitoring required for adverse events and long-term efficacy, approval requires Tysabri to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Documentation:** In the *Multiple Sclerosis – Tysabri Prior Authorization Policy*, documentation is required for initiation of therapy where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes and magnetic resonance imaging (MRI) reports.

## RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Tysabri is recommended in those who meet one of the following criteria:

### FDA-Approved Indications

1. **Multiple Sclerosis (MS).** Approve for 1 year if the patient meets one of the following criteria (A or B)
  - A) **Initial Therapy.** Approve if the patient meets all of the following criteria (i, ii, iii and iv):
    - i. The patient is  $\geq 18$  years of age; AND
    - ii. The patient has a relapsing form of multiple sclerosis (MS); AND
    - iii. Tysabri is prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis (MS) and/or a neurologist; AND
    - iv. The patient meets one of the following (a or b):
      - a) According to the prescriber the patient has had an inadequate response or is unable to tolerate one disease-modifying agent used for MS. Note: Examples of disease-modifying agents for multiple sclerosis include Avonex (interferon beta-1a for intramuscular [IM] injection), Rebif (interferon beta-1a for subcutaneous [SC] injection), Betaseron (interferon beta-1b for SC injection), Extavia (interferon beta-1b for SC injection), Copaxone/Glatopa (glatiramer acetate injection for SC use), glatiramer acetate injection, Plegridy (peginterferon beta-1a SC injection), Gilenya (fingolimod capsules), Aubagio (teriflunomide tablets), Tecfidera (dimethyl fumarate delayed-release capsules), Mavenclad (cladribine tablets), Mayzent (siponimod tablets), Vumerity (diroximel fumarate delayed-release capsules), Lemtrada (alemtuzumab injection for intravenous use), and Ocrevus (ocrelizumab injection for IV use); OR
      - b) According to the prescriber the patient has highly-active or aggressive multiple sclerosis by meeting one of the following (1, 2, 3, or 4):
        1. The patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination) **[documentation required]**; OR
        2. Disabling relapse(s) with suboptimal response to systemic corticosteroids **[documentation required]**; OR
        3. Magnetic resonance imaging [MRI] findings suggest highly-active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions) **[documentation required]**; OR
        4. Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; OR

- D) Patients currently receiving Tysabri.** Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
- i.** The patient is  $\geq 18$  years of age; AND
  - ii.** The patient has a relapsing form of multiple sclerosis (MS); AND
  - iii.** Tysabri is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist.

**Dosing.** Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

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**2. Crohn's Disease.** Approve for the duration noted below if the patient meets one of the following criteria (A or B):

- A) Initial Therapy.** Approve for 3 months if the patient meets all of the following criteria (i, ii, iii, or iv):
- i.** The patient is  $\geq 18$  years of age; AND
  - ii.** Patient has moderately to severely active Crohn's disease; AND
  - iii.** Tysabri is prescribed by or in consultation with a gastroenterologist; AND
  - iv.** Patient has tried at least two biologics for Crohn's disease: Note: Examples include an adalimumab product, Cimzia (certolizumab pegol for SC injection), an infliximab product, Entyvio (vedolizumab injection for IV use), or Stelara (ustekinumab for SC injection or for IV infusion); OR
- B) For patients currently receiving Tysabri.** Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
- i.** The patient is  $\geq 18$  years of age; AND
  - ii.** The patient has had a response (e.g., reduced number of liquid/soft stools, reduced abdominal pain, less use of antidiarrheal agents) as determined by the prescriber; AND
  - iii.** Tysabri is prescribed by or in consultation with a gastroenterologist.

**Dosing in Crohn's Disease.** Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks.

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**CONDITIONS NOT RECOMMENDED FOR APPROVAL**

Tysabri has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

- 1. Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease.** Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab product, an adalimumab product, Cimzia, Entyvio and Stelara. Ordinarily, patients who are receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune function should not take Tysabri.<sup>1</sup>
- 2. Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis (MS).** Note: Examples of disease-modifying agents used for multiple sclerosis include—Betaseron<sup>®</sup>/Extavia<sup>®</sup> (interferon beta-1b injection), Rebif<sup>®</sup> (interferon beta-1a injection [subcutaneous]), Copaxone<sup>®</sup>/Glatopa<sup>®</sup> (glatiramer acetate injection), glatiramer acetate injection, Avonex<sup>®</sup> (interferon beta-1a injection [intramuscular]), Lemtrada<sup>®</sup> (alemtuzumab injection for intravenous use), Plegridy<sup>®</sup>

(peginterferon beta-1a injection), Gilenya® (fingolimod tablets), Aubagio® (teriflunomide tablets), Tecfidera® (dimethyl fumarate delayed-release capsules), Vumerity™ (diroximel fumarate delayed-release capsules), Mayzent® (siponimod tablets), Mavenclad® (cladribine tablets), and Ocrevus® (ocrelizumab injection for intravenous use). Tysabri is only indicated as monotherapy due to an increased risk of PML.<sup>1</sup>

3. **Non-Relapsing Forms of Multiple Sclerosis.** Note: An example of a non-relapsing form of multiple sclerosis (MS) is primary progressive MS. The safety and efficacy of Tysabri have not been established in patients with primary progressive MS.
4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.<sup>8</sup>
5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

## REFERENCES

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6. Torres J, Mehandru S, Solombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017;389(10080):1741-1755.
7. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: management of Crohn's Disease in Adults. *Am J Gastroenterol*. 2018;113:481-517.
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**HISTORY**

<b>Type of Revision</b>	<b>Summary of Changes*</b>	<b>Date Reviewed</b>
Annual revision	Removed Zinbrya from the list of medications in which Tysabri should not be used with concomitantly since the agent was removed from the market. Also, the option of Zinbrya was deleted from the listing of MS disease modifying agents which count as a trial. The approval duration for indications regarding MS were changed from 3 years to 1 year. Also, the approval duration in an adult with Crohn's disease who are currently receiving Tysabri were changed from 3 years to 1 year. For patients with highly-active or aggressive MS, the criteria were revised such that patients must meet one of the following with documentation required: the patient has demonstrated rapidly-advancing deterioration(s) in physical functioning (e.g., loss of mobility/or lower levels of ambulation, severe changes in strength or coordination); OR the patient has disabling relapse(s) with suboptimal response to systemic corticosteroids [documentation required]; OR magnetic resonance imaging [MRI] findings suggest highly-active or aggressive multiple sclerosis (e.g., new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions);OR the patient has manifestations of multiple sclerosis-related cognitive impairment. For patient currently receiving Tysabri with relapsing forms of MS, the criteria were added which require that the patient has a relapsing form of MS (relapsing forms of MS are relapsing-remitting MS [RRMS], secondary-progressive MS with relapses [SPMS], and progressive-relapsing MS [PRMS]) and that Tysabri is prescribed by, or in consultation with, a physician who specializes in the treatment of MS and/or a neurologist. For patients with Crohns disease who are currently receiving Tysabri, the criterion was added that the agent be prescribed by a gastroenterologist. The notation of "in an adult" was removed from the title of the diagnosis regarding MS and Crohn's disease. Waste management and initial/extended approval sections were removed.	10/31/2018
Annual revision	<p>The Duration of Therapy and Labs/Diagnostics sections were removed. The following criteria changes were made:</p> <ol style="list-style-type: none"> <li><b>1. Multiple Sclerosis:</b> The notation of "Relapsing Forms" was removed from the stated indication. Criteria were revised such that the example of relapsing forms of multiple sclerosis were removed. The word "prescriber" replaced the phrase "prescribing physician" in applicable criteria. Vumerity and glatiramer acetate were added as medication alternatives that count toward the requirement of a trial of one disease-modifying agent used for multiple sclerosis.</li> <li><b>2. Crohn's Disease:</b> Regarding the requirement that patients have moderate or severely active Crohn's disease, patients no longer are required to have "evidence of inflammation, that is C-reactive protein", as this is no longer recommended in related guidelines. The word "prescriber" replaced the phrase "prescribing physician" in applicable criteria.</li> <li><b>3. Conditions Not Recommended for Approval:</b> "Children with Multiple Sclerosis or Crohn's Disease" was removed as this is duplicative to the age requirement in the approval criteria. Regarding "Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis", the examples of glatiramer acetate injection, Vumerity, Mavenclad, and Mayzent were added. The condition that stated "Primary Progressive (Chronic Progressive Multiple Sclerosis)" was changed to state "Non-Relapsing Forms of Multiple Sclerosis" with a note that an example is Primary Progressive Multiple Sclerosis. The condition of "Immune Compromised Patients with Multiple Sclerosis or Crohn's Disease" was removed.</li> <li><b>4. Dosing:</b> The dosing for patients with Multiple Sclerosis and Crohn's Disease was changed from 300 mg by intravenous infusion over 1 hour once every 4 weeks" to "Approve up to 300 mg given by intravenous infusion administered no more frequently than once every 4 weeks."</li> </ol>	11/13/2019
Update	02/07/2020: No criteria changes. Added Crohn's Disease to the name on the title of the policy.	--