thirdwaverx

Utilization Management Medical Policy

Policy: Multiple Sclerosis and Crohn's Disease – Tysabri Utilization Management Medical Policy
- Tysabri® (natalizumab intravenous infusion – Biogen)

Review Date: 11/30/2022

Overview

Tysabri, an integrin receptor antagonist, is indicated for the treatment of:[1]
- Relapsing forms of **multiple sclerosis (MS)** include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease in adults as monotherapy.
- **Crohn's disease**, inducing and maintaining clinical response and remission in adults with moderately to severely active 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)-α.

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML).[1] When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset the risks. Tysabri should not be used in combination with immunosuppressants (e.g., azathioprine, 6-mercaptopurine, cyclosporine, methotrexate) or inhibitors of TNFα. The safety and effectiveness in patients with MS or Crohn's disease < 18 years of age have not been established.

Disease Overview

Multiple Sclerosis

MS is a chronic, inflammatory, demyelinating, autoimmune disease of the central nervous system that impacts almost 1,000,000 people in the US.[2-4] 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.[2-4] Advances in the understanding of the MS disease process, as well as in MRI technology, spurned updated disease course descriptions in 2013,[5] as well as in 2017.[6] The revised disease courses are clinically isolated syndrome, relapsing remitting MS, primary progressive MS, and secondary progressive MS.[2-6] 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.

Crohn's Disease
Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract.[8] The prevalence has been increasing worldwide.[9] 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.[8,9] 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 subcutaneous injection]).

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.[7]

In September 2019, a consensus paper was updated by the MS Coalition that discusses the use of disease-modifying therapies in MS.[2] Many options from various drug classes, involving different mechanisms of action and modes of administration, have shown benefits in patients with MS.

The American College of Gastroenterology has guidelines on management of Crohn's disease in adults (2018).[9] Anti-TNF agents (e.g., infliximab products, adalimumab products, Cimzia) should be used to treat Crohn's disease that is resistant to treatment with corticosteroids, 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 intravenous infusion]) 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 subcutaneous injection or intravenous infusion) 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.[1] Tysabri is available only through a special restricted distribution Risk Evaluation and Mitigation Strategy (REMS) program called 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 indications. 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. In cases where the approval is authorized in months, 1 month is equal to 30 days. 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: Documentation is required for use of Tysabri at initiation for multiple sclerosis as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, magnetic resonance imaging (MRI) reports, and/or other information.

Automation: None.

Recommended Authorization Criteria

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

FDA-Approved Indications

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1. **Multiple Sclerosis.** Approve for 1 year if the patient meets one of the following (A or B)
   - **A)** Initial Therapy. Approve if the patient meets all of the following (i, ii, iii, and iv):
     - i. Patient is ≥ 18 years of age; AND
     - ii. Patient has a relapsing form of multiple sclerosis; AND
       Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
     - iii. Patient meets one of the following (a or b):
       - **a)** According to the prescriber, the patient has experienced inadequate efficacy or significant intolerance to one disease-modifying agent used for multiple sclerosis; OR
         Note: See Appendix for examples.
       - **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) Patient has demonstrated rapidly advancing deterioration(s) in physical functioning **[documentation required]**; OR
           Note: Examples include loss of mobility or lower levels of ambulation and severe changes in strength or coordination.
         - (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 **[documentation required]**; OR
           Note: Examples include new, enlarging, or a high burden of T2 lesions or gadolinium-enhancing lesions.
         - (4) Manifestations of multiple sclerosis-related cognitive impairment **[documentation required]**; AND
     - iv. Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR
   - **B)** Patient is Currently Receiving Tysabri. Approve if the patient meets one of the following criteria (i or ii):
     - i. Patient has been receiving Tysabri for < 1 year. Approve if the patient meets all of the following (a, b, and c):
       - a) Patient is ≥ 18 years of age; AND
       - b) Patient has a relapsing form of multiple sclerosis; AND
         Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease.

c) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis; OR

ii. Patient has been receiving Tysabri for 1 year or more. Approve if the patient meets the following (a, b, c, and d):
   a) Patient is ≥ 18 years of age; AND
   b) Patient has a relapsing form of multiple sclerosis; AND
      Note: Examples of relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive multiple sclerosis.
   c) Patient meets one of the following [(1) or (2)]:
      (1) Patient experienced a beneficial clinical response when assessed by at least one objective measure; OR
      Note: Examples include stabilization or reduced worsening in disease activity as evaluated by magnetic resonance imaging (MRI) [absence or a decrease in gadolinium enhancing lesions, decrease in the number of new or enlarging T2 lesions]; stabilization or reduced worsening on the Expanded Disability Status Scale (EDSS) score; achievement in criteria for No Evidence of Disease Activity-3 (NEDA-3) or NEDA-4; improvement on the fatigue symptom and impact questionnaire-relapsing multiple sclerosis (FSIQ-RMS) scale; reduction or absence of relapses; improvement or maintenance on the six-minute walk test or 12-Item Multiple Sclerosis Walking Scale; improvement on the Multiple Sclerosis Functional Composite (MSFC) score; and/or attenuation of brain volume loss.
      (2) Patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation; AND
   d) Medication is prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis.

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 (A or B):

A) Initial Therapy. Approve for 6 months if the patient meets all of the following (i, ii, iii, and iv):
   i. Patient is ≥ 18 years of age; AND
   ii. Patient has moderately to severely active Crohn's disease; AND
   iii. Patient has tried at least two biologics for Crohn's disease; AND
      Note: Examples include an adalimumab product (Humira, biosimilars), Cimzia (certolizumab pegol subcutaneous injection), an infliximab product (Remicade, biosimilars), Entyvio (vedolizumab intravenous infusion), Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), or Stelara (ustekinzumab subcutaneous injection or intravenous infusion).
      Note: Each biosimilar tried from the same chemical would only count as a trial of one product.
   iv. Tysabri is prescribed by or in consultation with a gastroenterologist; OR

B) Patient is Currently Receiving Tysabri. Approve for 1 year if the patient meets all of the following (i, ii, iii, and iv):
   i. Patient has been established on therapy for at least 6 months; AND

Note: A patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criteria A (Initial Therapy).

ii. Patient is ≥ 18 years of age; AND
iii. Patient meets at least one of the following (a or b):
   a) When assessed by at least one objective measure, patient experienced a beneficial clinical response from baseline (prior to initiating Tysabri); OR
   Note: Examples of objective measures include fecal markers (e.g., renal lactoferrin, fecal calprotectin), serum markers (e.g., C-reactive protein), imaging studies (magnetic resonance enterography [MRE], computed tomograph enterography [CTE]), endoscopic assessment, and/or reduced dose of corticosteroids.
   b) Compared with baseline (prior to initiating Tysabri), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool; AND
iv. Medication 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.

Conditions Not Recommended for Approval

Coverage of Tysabri is not recommended in the following situations:

1. **Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease.** 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.[1]
   Note: Examples include 6-mercaptopurine, azathioprine, cyclosporine, methotrexate, an infliximab product, an adalimumab product, Cimzia, Entyvio, Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]), and Stelara.

2. **Concurrent Use with Other Disease-Modifying Agents Used for Multiple Sclerosis.** These agents are not indicated for use in combination (See Appendix for examples). Additional data are required to determine if use of disease-modifying multiple sclerosis agents in combination is safe and provides added efficacy.

3. **Non-Relapsing Forms of Multiple Sclerosis.** The safety and efficacy of Tysabri have not been established in patients with primary progressive multiple sclerosis.
   Note: An example of a non-relapsing form of multiple sclerosis is primary progressive multiple sclerosis.

4. **Ulcerative Colitis.** Efficacy data with use of Tysabri are limited.[10]

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

1. Tysabri® intravenous infusion [prescribing information]. Cambridge, MA: Biogen; December 2021.
2. A Consensus Paper by the Multiple Sclerosis Coalition. The use of disease-modifying therapies in multiple sclerosis. Updated September 2019. Available at:

https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. Accessed on July 12, 2022.
3. McGinley MP, Goldschmidt C, Rae-Grant AD. Diagnosis and treatment of multiple sclerosis. A review. *JAMA*. 2021;325(8):765-779.
4. No authors listed. Drugs for multiple sclerosis. *Med Lett Drugs Ther*. 2021;63(1620):42-48.
5. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83:278-286.
6. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
7. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-788.
8. Torres J, Mehandru S, Solombel JF, Peyrin-Biroulet L. Crohn's disease. *Lancet*. 2017;389(10080):1741-1755.
9. 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.
10. Gordon FH, Hamilton MI, Donoghue S, et al. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. *Aliment Pharmacol Ther*. 2002;16:699-705.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Multiple Sclerosis:** For the initial therapy requirement that the patient try one disease-modifying agent used for multiple sclerosis, examples of medications used for multiple sclerosis were changed from a Note to an Appendix and Ponvory was added to the list of examples. Also, the citing of the medication routes were updated, as well as generic availability. Regarding highly aggressive multiple sclerosis, the examples regarding rapidly advancing deterioration in physical functioning and magnetic resonance imaging suggest highly active or aggressive multiple sclerosis were moved from the criteria to a Note. **Conditions Not Recommended for Approval:** Regarding Concurrent Use with Other Disease-Modifying Agents for Multiple Sclerosis, examples provided in the Note were changed to an Appendix and Ponvory was added to the list. Also, the citing of the medication routes were updated, as well as generic availability.	12/08/2021
Selected Revision	**Multiple Sclerosis:** For patients currently receiving therapy, the criteria were divided among patients receiving therapy for < 1 year and those receiving Tysabri for 1 year or more. For a patient receiving Tysabri for 1 year or more, response criteria were developed for reauthorization in which the patient either experienced a beneficial clinical response when assessed by at least one objective measure (with examples provided in a Note), or the patient experienced stabilization, slowed progression, or improvement in at least one symptom such as motor function, fatigue, vision, bowel/bladder function, spasticity, walking/gait, or pain/numbness/tingling sensation. For the specialist requirement, the criteria was changed from "prescribed by or in consultation with a physician who specializes in the treatment of multiple sclerosis and/or a neurologist" to "prescribed by or in consultation with a neurologist or a physician who specializes in the treatment of multiple sclerosis." **Crohn's Disease:** The Note which contains a list of biologics for use in Crohn's Disease was updated to now include Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]).	07/20/2022
Selected Revision	**Crohn's Disease:** The duration of initial therapy was changed from 3 months to 6 months. To the Note that has a list of medication examples, the statement was added that a previous trial of the requested biologic (or a biosimilar of the requested biologic) does not count. For a patient currently receiving criteria, it was added as a criterion that the patient has been established on therapy for at least 6 months. A Note was also added that for a patient who has received < 6 months of therapy or who is restarting therapy is reviewed under criterion A (Initial Therapy). Criteria were also added in this section that a patient has experienced a beneficial clinical response from baseline (prior to initiating Tysabri) by at least one objective measure (with examples provided in the criteria as a note) or compared with baseline (prior to initiating Tysabri), patient experienced an improvement in at least one symptom, such as decreased pain, fatigue, stool frequency, and/or blood in stool. The previous criteria and Note that asked if the patient has had a response as determined by the prescriber were removed (replaced with the criteria above). **Conditions Not Recommended for Approval:** To the clinical situation of Concurrent Use with an Immunosuppressant Agent in Patients with Crohn's Disease, Skyrizi (risankizumab-rzaa intravenous infusion, risankizumab-rzaa subcutaneous injection [on-body injector]) was added to the Note that lists the medications that should not be used concomitantly.	07/27/2022
Annual Revision	No criteria changes.	11/23/2022

APPENDIX

Medication	Mode of Administration
Aubagio® (teriflunomide tablets)	Oral
Avonex® (interferon beta-1a intramuscular injection)	Injection (self-administered)
Bafiertam® (monomethyl fumarate delayed-release capsules)	Oral
Betaseron® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Copaxone® (glatiramer acetate subcutaneous injection, generic)	Injection (self-administered)
Extavia® (interferon beta-1b subcutaneous injection)	Injection (self-administered)
Gilenya® (fingolimod capsules, generic)	Oral
Glatopa® (glatiramer acetate subcutaneous injection)	Injection (self-administered)
Kesimpta® (ofatumumab subcutaneous injection)	Injection (self-administered)
Lemtrada® (alemtuzumab intravenous infusion)	Intravenous infusion
Mavenclad® (cladribine tablets)	Oral
Mayzent® (siponimod tablets)	Oral
Ocrevus® (ocrelizumab intravenous infusion)	Intravenous infusion
Plegridy® (peginterferon beta-1a subcutaneous or intramuscular injection)	Injection (self-administered)
Ponvory® (ponesimod tablets)	Oral
Rebif® (interferon beta-1a subcutaneous injection)	Injection (self-administered)
Tecfidera® (dimethyl fumarate delayed-release capsules, generic)	Oral
Tysabri® (natalizumab intravenous infusion)	Intravenous infusion
Vumerity® (diroximel fumarate delayed-release capsules)	Oral
Zeposia® (ozanimod capsules)	Oral