Natalizumab for Crohn’s Disease

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Related Coverage Resources

Immunomodulators – Oral and Subcutaneous
(Company Group Benefit Plans)
Immunomodulators – Oral and Subcutaneous
(Individual and Family Plans)
Multiple Sclerosis Therapy

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Medical Necessity Criteria

This coverage policy addresses the use of natalizumab (Tysabri®) for Crohn’s disease. Natalizumab (Tysabri) is also indicated for multiple sclerosis. Use for this indication is addressed in a separate coverage policy (Multiple Sclerosis Therapy). Please refer to the related coverage policy link above.

Natalizumab (Tysabri®) is considered medically necessary when all of the following criteria are met:

- Individual is 18 years of age or older.
- Diagnosis of moderate to severe Crohn’s disease
- Documented failure or inadequate response, contraindication per FDA label, intolerance, or not a candidate for ONE anti-tumor necrosis factor biologic

Initial authorization is up to 12 months.

Natalizumab (Tysabri) is considered medically necessary for continued use when the initial criteria are met. Reauthorization for up to 12 months.
When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Natalizumab (Tysabri) is considered experimental, investigational or unproven for ANY other use including the following:

- Concomitant use with any other biologic including all non-tumor necrosis factor (non-TNF) biologics, anti-TNF biologics, or oral immunomodulatory agents (for example, Otezla or Xeljanz/ Xeljanz XR)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

**FDA Approved Indications**

**Crohn’s Disease (CD)**
Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients 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 CD therapies and inhibitors of TNF-α. Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α [see Warnings and Precautions (5.1)].

**Multiple Sclerosis (MS)**
Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. Tysabri increases the risk of PML. When initiating and continuing treatment with Tysabri, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. See important information regarding the risk of PML with Tysabri [see Warnings and Precautions (5.1)].

**Recommended Dosing**

**FDA Recommended Dosing – Crohn’s Disease**
Only prescribers registered in the CD TOUCH® Prescribing Program may prescribe Tysabri for Crohn’s disease [see Warnings and Precautions (5.2)].

The recommended dose of Tysabri for Crohn’s disease is 300 mg intravenous infusion over one hour every four weeks. Tysabri should not be used with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or concomitant inhibitors of TNF-α. Aminosalicylates may be continued during treatment with Tysabri.

If the patient with Crohn’s disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue Tysabri. For patients with Crohn’s disease who start Tysabri while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of Tysabri has occurred; if the patient with Crohn’s disease cannot be tapered off of oral corticosteroids within six months of starting Tysabri, discontinue Tysabri. Other than the initial six-month taper, prescribers should consider discontinuing Tysabri for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn’s disease.

**Drug Availability – Crohn’s Disease**
Tysabri injection is supplied as 300 mg natalizumab in 15 mL in a single-use vial free of preservatives. Each package contains a single-use vial.

**Tysabri TOUCH Prescribing Program**
Tysabri is available only through a restricted program under a REMS called the TOUCH® Prescribing Program because of the risk of PML.

For prescribers and patients, the TOUCH® Prescribing Program has two components: MS TOUCH® (for patients with multiple sclerosis) and CD TOUCH® (for patients with Crohn’s disease).
Selected requirements of the TOUCH® Prescribing Program include the following:

- Prescribers must be certified and comply with the following:
  - Review the TOUCH Prescribing Program prescriber educational materials, including the full prescribing information.
  - Educate patients on the benefits and risks of treatment with Tysabri, ensure that patients receive the Medication Guide, and encourage them to ask questions.
  - Review complete, and sign the Patient-Prescriber Enrollment Form.
  - Evaluate patients three months after the first infusion, six months after the first infusion, every six months thereafter, and for at least six months after discontinuing Tysabri.
  - Determine every six months whether patients should continue on treatment and, if so, authorize treatment for another six months.
  - Submit to Biogen Idec the “Tysabri Patient Status Report and Reauthorization Questionnaire” six months after initiating treatment and every six months thereafter.
  - Complete an “Initial Discontinuation Questionnaire” when Tysabri is discontinued and a “6-Month Discontinuation Questionnaire” following discontinuation of Tysabri.
  - Report cases of PML, hospitalizations due to opportunistic infections, or deaths to Biogen Idec at 1-800-456-2255 as soon as possible.

- Patients must be enrolled in the TOUCH Prescribing Program, read the Medication Guide, understand the risks associated with Tysabri and complete and sign the Patient-Prescriber Enrollment Form.

- Pharmacies and infusion centers must be specially certified to dispense or infuse Tysabri.

### Background

#### Pharmacology

Natalizumab is an integrin-4 receptor antagonist labeled for the treatment of MS and CD. Natalizumab is a human recombinant immunoglobulin-4 monoclonal antibody directed against the integrin alpha-4 adhesion molecule. It is the first medication of this type in a new class of selective adhesion molecule inhibitors.

Natalizumab binds to the alpha-4 subunit of integrins alpha-4-beta-1 and alpha-4-beta-7 expressed on the surface of leukocytes (except neutrophils). Integrin alpha-4-beta-7 binds to the mucosal vascular addressin cell adhesion molecule-1 (MadCam-1) in the gastrointestinal endothelium. When natalizumab binds to alpha-4 integrins, it disrupts integrin interaction with MadCam-1, preventing the passage of leukocytes into the gut.

#### Professional Societies/Organizations

**Crohn's Disease**

**American College of Gastroenterology (ACG) Clinical Guideline: Management of Crohn’s Disease in Adults**

Recommendations for immunomodulatory therapies are as follows:

- **Moderate to severe disease/moderate to high risk disease**
  - Infliximab, adalimumab, or certolizumab pegol are recommended in those who have not responded to treatment with a corticosteroid or an immunosuppressive agent
  - Use of infliximab concomitantly with an immunomodulator is more efficacious than monotherapy with either agent in individuals naïve to these medications
  - Vedolizumab with or without use of an immunomodulator should be considered for induction of remission in individuals with moderately to severely active Crohn's disease with evidence of active disease
  - Natalizumab should be a consideration for induction of symptomatic response and remission in active Crohn's disease
  - Natalizumab should be used to maintain natalizumab-induced remission of Crohn's disease only if antibodies are negative to John Cunningham (JC) virus
  - Ustekinumab should be used in individuals with moderate to severe Crohn’s disease who have not responded to corticosteroids, thiopurines, methotrexate or anti-TNF inhibitors, or who are anti-TNF naïve
Severe/fulminant disease
- Infliximab, adalimumab, and certolizumab pegol may be used to treat severely active Crohn’s disease
- Infliximab may be used to treat fulminant Crohn’s disease

Perianal/fistulizing disease
- Infliximab should be considered for treatment of perianal fistulas in Crohn’s disease
- Infliximab should be a consideration for treatment of enterocutaneous and rectovaginal fistulas in Crohn’s disease
- Adalimumab and certolizumab pegol should be a consideration to treat perianal fistulas in Crohn’s disease

Maintenance Therapy of Luminal Crohn’s Disease
- Anti-TNF therapy should be used for maintenance therapy of anti-TNF induced remission (specifically Infliximab, adalimumab and certolizumab pegol)
- Although monotherapy with anti-TNFs is efficacious in maintaining anti-TNF induced remissions, consideration should be given to concomitant use with azathioprine/6-mercaptopurine or methotrexate due to the risk for immunogenicity and loss of response
- Vedolizumab therapy should be utilized to maintain vedolizumab-induced remissions of Crohn’s disease
- Natalizumab therapy should be a consideration for maintenance of natalizumab-induced remissions in Crohn’s disease if John Cunningham (JC) virus is negative
- Ustekinumab therapy should be used to maintain ustekinumab-induced remissions of Crohn’s disease

(Lichtenstein, 2018)

American Gastroenterological Association (AGA) Guideline on the Use of Thiopurines, Methotrexate, and Anti–TNF-α Biologic Drugs for the Induction and Maintenance of Remission in Inflammatory Crohn’s Disease
The AGA provides recommendations for the induction and maintenance of remission in inflammatory Crohn’s disease. Specifically addressing biologic therapy, the recommendations are as follows:

Induction of Remission in patients with moderately to severely active Crohn’s disease:
- Anti-TNF biologics are recommended.
- If monotherapy is utilized, anti-TNF biologics are preferred over thiopurine monotherapy.
- If combination therapy is utilized, anti-TNF biologics combined with thiopurines is the suggested regimen.

Maintenance of Remission
- It is recommended to use an anti-TNF biologic to maintain remission which was induced by corticosteroids or an anti-TNF biologic.
- The AGA is neutral regarding use of combination therapy of an anti-TNF biologic plus a thiopurine compared to either class alone to maintain remission which was achieved by use of a combination of these classes. (Terdiman, 2013)

European Evidence-based Consensus (ECCO) on the Diagnosis and Management of Crohn’s Disease
The third ECCO evidence based consensus group stated guidelines were, in part, revisited in order to recognize the Crohn’s Disease indication for vedolizumab along with its clinical data. Several recommendations were provided by the ECCO guidelines on the use of vedolizumab in the treatment of Crohn’s Disease. They are as follows:
- Moderately active localised ileocaecal Crohn’s disease: Treat with budesonide or with systemic corticosteroids; Anti-TNFs could be used as an alternative for those patients that are steroid-refractory or intolerant; In patients refractory to steroids or Anti-TNFs, vedolizumab is an alternative. (Gomollón, 2017)
• Active colonic Crohn’s Disease: Treat with systemic corticosteroids; AntiTNFs is appropriate in those who have relapsed; In patients refractory to steroids or AntiTNFs, vedolizumab is an alternative. (Gomollón, 2017)

If remission has been achieved with the combination then maintenance with the same regimen is recommended. Therefore, maintenance treatment with vedolizumab is appropriate in patients achieving remission with vedolizumab. (Gomollón, 2017)

The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative
No recommendations are available for natalizumab or Crohn’s disease.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)
There are no CMS National Coverage Determinations for natalizumab.

Off Label Uses
AHFS Drug Information 2019 Edition does not support any off-label uses of natalizumab.

Coding/ Billing Information

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<tr>
<th>HCPCS Codes</th>
<th>Description</th>
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<td>J2323</td>
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Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

References