Tysabri (natalizumab)

Medical Policy

Section Prescription Drug

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Description

Multiple Sclerosis

Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. Because Tysabri increases the risk of progressive leukoencephalopathy (PML), it is generally recommended for patients who have had an inadequate response to, or unable to tolerate alternate MS therapies. This product is the first humanized monoclonal antibody approved for the treatment of MS. Tysabri acts by preventing the movement of possibly harmful cells from the bloodstream into the central nervous system. The most commonly reported adverse events with Tysabri were infections, hypersensitivity reactions, depression, and gallstones. Tysabri is available as a 300 mg single-use vial and is given intravenously every 4 weeks. The drug will only be prescribed, distributed and infused by prescribers, pharmacies and infusion centers registered with the TOUCH program. (See Appendix for further details of the TOUCH program.)

Multiple Sclerosis (MS) is a demyelinating disease accompanied by a lymphocytic infiltration in lesions. Evidence relating to pathogenesis suggests genetic, infective, and/or immune mechanisms. Tysabri has been investigated in patients with relapsing/remitting MS, where the treatment goals are to decrease the frequency and severity of future attacks and, if possible, to improve the functional deficit to some extent in those same patients. Tysabri was initially FDA approved in November 2004, and was withdrawn by the manufacturer in February 2005 after three patients in the drug’s clinical trials developed progressive leukoencephalopathy (PML), a serious and often fatal viral infection of the brain. In addition, the FDA put clinical trials of the drug on hold in February 2005, based on this information. FDA allowed clinical trials of Tysabri to resume in February 2006, and in March 2006 FDA approved Tysabri to be distributed strictly through a risk management program called the TOUCH program. The safety of Tysabri beyond an infusion period of longer than two years has not been established. Also, Tysabri has not been studied in patients with chronic progressive multiple sclerosis, in children, or in pregnant females with MS. It is not known if patients older than 65 have a different response to Tysabri. Tysabri does not cure MS.
Crohn’s Disease

There is no cure for Crohn’s disease, and treatment regimens are directed toward including remission, maintaining remission and addressing complications. The 5-ASA agents (e.g., mesalamine), antibiotics (e.g., metronidazole), corticosteroids, asathioprine, 6-mercaptopurine, and methotrexate are among several options used in treating Crohn’s disease. The choice of a specific treatment depends on severity, response, and location of the disease.

Biologic-response modifiers may also be used in the treatment of Crohn’s disease. Current biologic-response modifiers approved for use in the treatment of Crohn’s disease include:

- Adalimumab (Humira®
- Certolizumab (Cimzia®
- Infliximab (Remicade®
- Natalizumab (Tysabri®

Ancillary disease or care management interventions that are intended to accompany natalizumab (Tysabri®

The following clinical assessments are performed at three and six months after the first infusion and every six months thereafter to evaluate patients for the presence of adverse effects:

- Liver function tests (including total bilirubin in patients with signs and symptoms of hepatotoxicity)
- Complete blood count (CBC)
- Evaluate for signs and symptoms of progressive multifocal leukoencephalopathy (PML)
- Evaluate for signs and symptoms of infection

The effectiveness of natalizumab (Tysabri®) in Crohn’s disease is primarily determined by evaluation for signs of clinical response, such as decreased symptoms, decreasing frequency of bowel movements, and the decrease of corticosteroids.

Policy

Multiple Sclerosis

Tysabri requires preauthorization in all cases and the following criteria will require strict adherence.

Tysabri infusions may be considered medically necessary when the following criteria are met:

Patients meeting ALL of the following criteria will be considered for Tysabri infusions:

- Diagnosis of relapsing/remitting MS
- At least 18 years of age and less than 65 years of age
- Neurologist documenting the diagnosis
- Functional status is ambulatory
- Not currently receiving any interferon-beta (Rebif, Avonex, Betaseron) or glatiramer acetate (Copaxone) treatment; but must have tried and failed Avonex or Rebif in the previous 180 days.
- Diagnosis of at least two focal neurological deficits (i.e., loss of vision, diplopia, localized numbness or weakness, etc) where the first resolved and the second followed after a period of at least 6 months
- MRI suggestive of MS
- Proof of enrollment in the TOUCH program by prescribing physician, member and location of service (i.e., infusion center)
- Adherence to all rules governing the TOUCH program, including specifically but not limited to:
  - MRI prior to beginning Tysabri to differentiate potential future MS from PML
  - MD evaluation at 3 and 6 mos after first infusion, then every 6 months thereafter
- If requesting ongoing Tysabri infusions, a statement from a neurologist indicating that Tysabri has been effective in decreasing relapses as evidenced by objective data is required.

Tysabri is considered **not medically necessary** as a treatment of MS in patients who have not tried other therapies previously; or who have been helped by, or would be able to tolerate other therapies for MS.

Other applications of Tysabri infusions are considered **investigational**, including but not limited to the following conditions:
- Chronic progressive multiple sclerosis
- Having a medical condition that could weaken the immune system such as leukemia, lymphoma, organ transplant, HIV, AIDS, etc.

**Crohn's Disease**

Tysabri may be considered **medically necessary** for patients with active Crohn's disease when the following criteria have been met:
- elevated baseline C-reactive protein (CRP) levels of ≥6mg/dL.
- Other disease-modifying treatment options are not effective, not tolerated or are contraindicated
- Tysabri use is non-concomitant with tumor necrosis factor-alpha inhibitors (such as infliximab (Remicade® ), adalimumab (Humira® ), and certolizumab pegol (Cimzia® ).
The fact that a Covered Provider may prescribe, order or recommend Tysabri does not, in and of itself, necessarily establish that such service is Medically Necessary.

The term Medically Necessary as defined and used in the policy is strictly limited to the application and interpretation of this policy, and any determination of whether a service is Medically Necessary hereunder is made solely for the purpose of determining whether services rendered are covered services.

Rationale

Effectiveness in Crohn’s Disease

There is good quality evidence supporting the use of natalizumab (Tysabri) in the management of Crohn’s disease, that is supplemented by a Cochrane review.

An elevated C-reactive protein (CRP) level (> 6mg/dL) at initiation of treatment with natalizumab appears to be an indicator of positive response to natalizumab based on a post hoc analysis of an initial trial and a follow up trial that used elevated CRP as an entry criterion.

- The initial pivotal trial (Sanborn et al. 2005 [33]), an enrichment design, that studied natalizumab in the treatment of CD failed to reach its primary endpoint in its first phase (ENACT-I). In a post hoc analysis of trial data, it was determined that there was an association between elevated CRP levels at baseline and response to natalizumab.

- The second pivotal trial (Tragan et al. 2007 [31]) used elevated CRP as an entry criterion. In this follow up trial, there was a statistical difference reported between natalizumab and placebo.

Safety

- Nataluzimab (Tysabri®) is associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a serious brain infection. This was observed in randomized controlled trials with natalizumab (Tysabri® ) and was confirmed in an FDA postmarketing safety analysis. Other disease-modifying medications used in the treatment of Crohn’s disease are not associated with an increased risk of PML. Because of this safety concern, nataluzimab (Tysabri®) is not recommended as a first-line therapy for Crohn’s disease.

- The risk of PML increases with exposure to nataluzimab. The mean duration of treatment was 17.9 doses before onset of PML. Doses higher than 300 mg or frequency more often than every 28 days have not been adequately evaluated. [36]

- Concomitant administration of nataluzimab (Tysabri®) with other disease-modifying agents is not recommended because it may increase the risk of serious infections, including PML.
  - Avoid concomitant administration with immunosuppressive agents (6-mercaptopurine, asathiopurine, cyclosporine, and methotrexate), TNF-alpha inhibitors (adalimumab [Humira® ], infliximab [Remicade® ]), or certolizumab pegol (Cimzia® ).

Nataluzimab (Tysabri®) may be utilized in quantities up to 300mg every 28 days. The safety and efficacy of higher doses in Crohn’s disease has not been established.
References:


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