

Medication Policy Manual

Policy No: dru111

Topic: Tysabri[®], natalizumab

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IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Natalizumab (Tysabri[®]) is a medication used to treat multiple sclerosis or Crohn's disease. It works on the immune system to relieve symptoms of disease. Natalizumab was removed from the market for several months due to significant safety concerns.

Policy/Criteria

I. Most contracts require prior authorization approval of natalizumab prior to coverage. Natalizumab may be considered medically necessary when criterion A or B below is met:

A. **Multiple sclerosis.** Initial authorization for natalizumab may be considered medically necessary for patients meeting all of the following criteria under 1, 2, and 3.

1. A definitive diagnosis of a relapsing form of multiple sclerosis (relapsing-remitting or secondary progressing multiple sclerosis) that has been established by a neurologist or a multiple sclerosis physician specialist (see Appendix A for *American Academy of Neurology* multiple sclerosis definitions).

AND

2. Natalizumab is prescribed by, or in consultation with, a neurologist or a multiple sclerosis physician specialist.

AND

3. When an interferon beta product (Avonex[®], Rebif[®], or Betaseron[®]) OR glatiramer acetate (Copaxone[®]) was documented in clinical notes to be ineffective, contraindicated, or not tolerated. Ineffectiveness is defined as meeting **two** of the following three criteria (a, b or c) during treatment with one of these agents.

a. The patient continues to have clinical relapses (at least two clinical relapses within the past 12 months).

b. The patient continues to have CNS lesion progression as measured by MRI.

c. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility or decreased ability to perform activities of daily living due to disease progression.

OR

B. **Crohn's disease.** Initial authorization for natalizumab may be considered medically necessary for patients meeting all of the following criteria under 1, 2, 3, and 4.

1. A diagnosis of Crohn's disease when at least one of the following criteria a, b, or c is met:

- a. Treatment with an adequate course of systemic corticosteroids (e.g., 40 mg to 60 mg prednisone per day for 7 to 14 days) has been ineffective or is contraindicated.

OR

- b. The patient has been unable to taper off of an adequate course of systemic corticosteroids without experiencing worsening of disease.

OR

- c. The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least two months on an immunomodulatory medication (such as azathioprine, mercaptopurine, cyclosporine, or methotrexate).

AND

2. Infliximab (Remicade[®]) is not effective after at least an initial induction period (5 mg/kg on weeks 0, 2 and 6), except if not tolerated due to documented clinical side effects.

AND

3. Adalimumab (Humira[®]) is not effective after at least an initial 3-dose induction period, except if not tolerated due to documented clinical side effects.

AND

4. Patients have elevated (greater than or equal to 6 mg/dl) baseline C-reactive protein (CRP) levels.

II. Administration, Quantity Limitations, and Authorization Period

- A.** Regence does **not** consider natalizumab to be a self-administered medication.
- B.** When prior authorization is approved, natalizumab may be authorized in quantities up to one 300-mg infusion every 4 weeks.
- C.** Authorization period:
 1. Multiple sclerosis: Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

2. Crohn's disease: Initial authorization shall be for 12 weeks. Subsequent authorization shall be reviewed at least every six months to confirm that current medical necessity criteria are met and that the medication is effective.

III. Natalizumab is considered not medically necessary when used for the following conditions:

A. For the treatment of multiple sclerosis when used in combination with any of the following disease modifying medications:

1. Interferon beta products (Avonex[®], Rebif[®], or Betaseron[®]).

OR

2. Glatiramer acetate (Copaxone[®]).

B. For the treatment of Crohn's disease when used in combination with any of the following:

1. Adalimumab (Humira[®]).

OR

2. Infliximab (Remicade[®]).

OR

3. Certolizumab pegol (Cimzia[®])

C. Ulcerative colitis.

IV. Natalizumab is considered investigational when used for all other conditions, including, but not limited to:

- A.** Primary progressive (PPMS) and progressive relapsing (PRMS) multiple sclerosis.
- B.** Rheumatoid arthritis.

Position Statement

Summary

- Natalizumab is a monoclonal antibody used:
 - * As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability when there has been inadequate response to, or intolerance to, alternate MS therapies. ^[1]
 - * For inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation when there has been inadequate response to, or intolerance of, conventional CD therapies and TNF- α inhibitors. ^[1]
- Natalizumab is not recommended as a first-line option due to potentially serious safety concerns.
 - * Package labeling for natalizumab includes a Black Box Warning describing an increased risk of progressive multifocal leukoencephalopathy (PML) with its use. ^[1]
 - * Natalizumab was temporarily withdrawn from the market in 2005 due to several cases of PML reported in patients who were receiving natalizumab.
 - * Because of these safety concerns, distribution of natalizumab is restricted. Only prescribers registered in the CD TOUCH™ or MS TOUCH™ programs may prescribe natalizumab for CD or MS, respectively. ^[1]
- Natalizumab is considered a disease modifying multiple sclerosis treatment. Other disease modifying multiple sclerosis treatments include interferon beta products (Avonex[®], Rebif[®] or Betaseron[®]) and glatiramer acetate (Copaxone[®]). ^[1]
- No studies have shown that the efficacy of natalizumab is superior to other disease modifying therapies in the treatment of either multiple sclerosis or Crohn's disease.

Clinical Efficacy

MULTIPLE SCLEROSIS

- Natalizumab was evaluated in two randomized, double-blind, placebo-controlled studies:^[1]
 - * Subjects had relapsing remitting multiple sclerosis (RRMS) with at least one clinical relapse within the past year and a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.
 - * The median duration of treatment was 120 weeks.
 - * Treatment with natalizumab decreased the time to sustained disability and decreased the annualized relapse rate relative to placebo.
- Natalizumab has only been shown to be safe and effective in the treatment of relapsing forms of multiple sclerosis.^[2-4, 14-16] There are no data to support the use of natalizumab in non-relapsing forms of multiple sclerosis.
- There are no data to support that natalizumab has superior clinical outcomes or is more effective compared to other less costly multiple sclerosis treatment options (interferon beta-1a [Avonex[®], Rebif[®]], interferon beta-1b [Betaseron[®]], or glatiramer acetate [Copaxone[®]]). In addition, the long term safety and efficacy of natalizumab is unknown.
- Natalizumab in combination with any other disease modifying multiple sclerosis treatment medication (interferon beta products or glatiramer acetate) has not been shown to be more effective than natalizumab alone in the treatment of multiple sclerosis, and may be contraindicated.

CROHN'S DISEASE

- FDA-approval of natalizumab in Crohn's Disease (CD) was based on three trials; two in induction of clinical response/remission and one in the maintenance of remission.^[1]
 - * Patients in the induction trials had moderately to severely active CD (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450).
 - * In one of the two induction studies, significant differences in response to natalizumab were only observed in the subgroup of patients with elevated C-reactive protein (CRP) levels. The second induction study used elevated CRP as an entry criterion.
 - * The treatment effect in the induction studies ranged from approximately 13 to 15%. In other words, for every 7 to 8 patients treated with natalizumab over the 10 to 12 week induction period, one patient had a response to therapy.

- * In the trial that looked at maintenance of response of CD over 9 to 15 months, the treatment effect was approximately 33%. In other words, for every three patients who initially responded to natalizumab therapy, one patient had a sustained response over the 9 to 15 month follow up period.
- Concomitant use natalizumab with immunosuppressives (6-mercaptopurine, azathioprine, cyclosporine, and methotrexate) or inhibitors of TNF- α (e.g., infliximab and adalimumab) is not recommended due to potential concerns with safety. ^[1]
- Natalizumab is generally considered a last-line agent for Crohn's disease due to lack of comparative efficacy with other therapies and its potential for serious safety risks.
 - * Steroids, immunosuppressives, and inhibitors of TNF- α are recommended prior to prescribing natalizumab. ^[1]
 - * A study demonstrating the efficacy of adalimumab in patients in whom infliximab was not effective is the basis for recommending both adalimumab and infliximab prior to natalizumab.
 - A randomized, placebo-controlled study comparing adalimumab with placebo in 325 patients with Crohn's disease who had lost response to treatment with, or were intolerant to, previous infliximab therapy demonstrated induction of remission in 21% versus 7% of patients who had received adalimumab and placebo, respectively (p<0.001, ABI 14%, NNT=8). ^[22]
- One small trial (n = 79) studied the concomitant use of natalizumab and infliximab in patients who did not achieve remission of their CD after 12 weeks of infliximab. ^[19]
 - * The trial was not powered to detect differences in efficacy between treatment groups.
 - * There were not enough patients in the study to determine whether there were differences in uncommon or rare adverse effects between treatment groups.
 - * Natalizumab package labeling warns against use of this combination. ^[1]
- Natalizumab should be discontinued in patients with CD: ^[1]
 - * Who do not achieve therapeutic benefit after 12 weeks of induction therapy.
 - * Who cannot discontinue chronic concomitant steroids within six months of starting therapy.

Safety

- Several cases of progressive multifocal leukoencephalopathy (PML), a progressive demyelinating disease of the CNS, have been associated with natalizumab use. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. ^[1]

- After its initial approval, natalizumab was withdrawn from the market for approximately one year while a task force investigated several cases of PML. ^[13]
 - * Three patients contracted PML while receiving natalizumab. ^[13]
 - * These patients had received a mean of 17.9 monthly doses of natalizumab. ^[13]
 - * The estimated incidence of PML with exposure to natalizumab is 1 case per 1000. ^[13]
- Additional cases of PML have been reported with natalizumab since its reintroduction to the market. ^[23]
- Natalizumab product labeling contains a Black Box Warning describing the increased risk of PML, which may lead to death or severe disability. ^[1]
- Because of the risk of PML, distribution of natalizumab is restricted via the TOUCH™ Prescribing Program.
 - * Providers must register to prescribe, distribute, or infuse natalizumab.
 - * Only patients who are registered with and who meet all the conditions of either the MS or CD TOUCH™ programs are eligible to receive natalizumab.
 - * For more information, go to www.tysabri.com or call 1 (800) 456-2255.
- The most common side effects observed in patients receiving natalizumab include: infections, acute hypersensitivity reactions, depression, and cholelithiasis (gall stones). ^[1]
- There are several case reports of patients who developed melanoma after starting treatment with natalizumab. ^[21] Although cause-effect has not been established, clinicians should be aware of this potential risk, especially when considering therapy for patients with a history of melanoma.
- A warning was recently added to the natalizumab prescribing information regarding the potential for liver injury. In some patients this occurred as early as six days after an initial dose. ^[1]

Dosing and administration

- Natalizumab is administered as an intravenous infusion (300 mg) once every 28 days in the treatment of multiple sclerosis. ^[1] The safety and efficacy of natalizumab at doses higher than 300 mg every 28 days have not been adequately evaluated. ^[1]

Natalizumab – Use in Other Conditions

- The TOUCH™ Prescribing Program currently prevents off-label use of natalizumab.
- Authors of a small, open-label study in 10 patients with active ulcerative colitis reported clinical benefit at 4 weeks with administration of natalizumab. ^[12] Large, well-designed trials are needed before safety and efficacy are established for this indication.
- There are no data available to support the safety and efficacy of natalizumab in the treatment of rheumatoid arthritis.

Appendix A: Multiple Sclerosis Forms/Clinical Courses Definitions ^[6]

Relapsing-remitting (RRMS)	Characterized by acute relapses that are followed by some degree of recovery; patients do not develop worsening of disability between relapses. The American Academy of Neurology (AAN) defines RRMS as the first clinical course of MS and is characterized by self-limited attacks of neurologic dysfunction. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. The AAN defines SPMS as the second clinical course which begins as RRMS, but at some point the attack rate is reduced and the course becomes characterized by a steady deterioration in function unrelated to acute attacks.
Primary progressive (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.
Progressive relapsing (PRMS)	Defined as primary progressive patients who develop acute relapses well after disease onset. The AAN defines PRMS as the fourth clinical type which also begins with a progressive course although these patients also experience occasional attacks.

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Cross References
Self Administered Injectables dru110
Betaseron [®] , interferon beta-1b dru108
Cimzia [®] , certolizumab pegol dru160
Humira [®] , adalimumab dru081
Remicade [®] , infliximab dru036

Codes	Number	Description
HCPCS	J2323	Injection, natalizumab, 1 mg
HCPCS	J3590	Unclassified Biologics