



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Policy Number ..... 6017

Subject **Natalizumab (Tysabri®)**

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## Hyperlink to Related Coverage Policies

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), 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 supercedes** 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers natalizumab (Tysabri®) as medically necessary for either of the following indications:**

- treatment of relapsing forms of multiple sclerosis (MS) where either of the following criteria is met:
  - history of beneficial clinical response to Tysabri for MS
  - failure, contraindication or intolerance to one preferred MS therapy [Avonex, Copaxone, Rebif]
- treatment of moderately to severely active Crohn's disease (CD) where either of the following criteria are met:
  - history of beneficial clinical response to Tysabri for CD
  - failure, contraindication, intolerance, or inadequate response to conventional therapies (i.e. aminosalicylate, corticosteroids, or immunomodulators) **AND** failure or intolerance to Humira

**The dosage, frequency, site of administration, and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to natalizumab (Tysabri®) therapy.**

## **FDA Approved Indications**

### **Multiple Sclerosis (MS)**

Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of MS to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The efficacy of Tysabri beyond two years is unknown. Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate MS therapy. Safety and efficacy in patients with chronic progressive MS have not been studied.

### **Crohn's Disease (CD)**

Tysabri is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active CD with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- $\alpha$ . Tysabri should not be used in combination with immunosuppressants.

## **FDA Recommended Dosing**

### **MS**

Only prescribers registered in the MS TOUCH® Prescribing Program may prescribe Tysabri for MS. The recommended dose of Tysabri for MS is 300 mg intravenous infusion over one hour every four weeks.

### **CD**

Only prescribers registered in the CD TOUCH® Prescribing Program may prescribe Tysabri for CD. The recommended dose of Tysabri for CD 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- $\alpha$ . Aminosalicylates may be continued during treatment with Tysabri. If the patient with CD has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue Tysabri.

## **Black Box Warning**

**Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking Tysabri who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving Tysabri as monotherapy. Because of the risk of PML, Tysabri is available only through a special restricted distribution program called the TOUCH® Prescribing Program. Under the TOUCH® Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, Tysabri must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH® Prescribing Program. Healthcare professionals should monitor patients on Tysabri for any new sign or symptom that may be suggestive of PML. Tysabri dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.**

## **Drug Availability**

Tysabri injection is supplied as 300 mg natalizumab in 15 mL in a sterile, single-use vial free of preservatives. Each package contains a single-use vial.

## **General 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.

Natalizumab has a mean half-life of approximately 10 days. However, the observed time to steady state is approximately 16 to 24 weeks after every 4 weeks of dosing. The pharmacokinetic profile of natalizumab in patients with renal or hepatic insufficiency is not known. Gender and age (range 18 to 62 years) does not affect pharmacokinetic profile. Natalizumab clearance increases three fold in patients with persistent anti-natalizumab antibodies.

## **Clinical Efficacy**

### **MS**

No comparative data with other FDA-approved drugs for MS are available. Two randomized, double-blind, placebo-controlled, phase III trials evaluated the efficacy of natalizumab, as monotherapy and as add-on therapy, in patients with MS who experienced at least one clinical relapse during the prior year. The AFFIRM trial involved 942 individuals with relapsing MS, who received either natalizumab 300mg (n=627) or placebo (n=315) by intravenous infusions every four weeks for more than two years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability as measured by the Expanded Disability Status Scale (EDSS) at two years. Results showed that natalizumab reduced the risk of progression of disability by 42% (p<0.001) and reduced the rate of clinical relapses by 68% (p<0.001) over two years. In addition, natalizumab reduced the development of new or newly enlarging MRI-detected brain lesions by 83% (p<0.001) and the mean number of enhancing (active) MRI lesions by 92% (p<0.001) after the first and second year. The adverse events that Fatigue (27% vs. 21%, p=0.048) and allergic reaction (9 % vs. 4%, p=0.012) were the most common adverse events reported in the natalizumab group compared to the placebo group.

The second trial, SENTINEL study, was a two-year, randomized, multi-center, placebo-controlled, double-blind study of 1,171 Avonex<sup>®</sup> (interferon beta-1a)-treated patients in 124 clinical trial sites worldwide. Patients treated with interferon beta-1a who continued to experience disease activity were randomized to add natalizumab 300mg (n=589) or placebo (n=582) to their regimen of interferon beta-1a every four weeks for up to 116 weeks. The primary end points were the rate of clinical relapse at one year and the cumulative probability of disability progression sustained for 12 weeks, as measured by the EDSS at two years. After one year, participants who had added natalizumab to interferon beta-1a experienced a 54% reduction in the rate of clinical relapses compared to those on placebo and interferon beta-1a, which was also maintained at two years with a 55% reduction. The combination therapy resulted in a 24% decrease in the risk of sustained disability progression (p=0.02). MRI scans showed an 83% reduction in the natalizumab plus interferon beta-1a group in enlarging MRI lesions, and an 89% reduction in lesions showing active inflammation. Kaplan-Meier estimates of the cumulative probability of progression at two years were 23% with combination therapy and 29% with interferon beta-1a alone. Combination therapy was associated with a lower annualized rate of relapse over a two-year period than was interferon beta-1a alone (p<0.001). MRI scans showed an 83% reduction in the combination therapy in enlarging MRI lesions, and an 89% reduction in lesions showing active inflammation. Adverse events associated with combination therapy were anxiety, pharyngitis, sinus congestion, and peripheral edema. Two cases of PML, one of which was fatal, were diagnosed in those on combination therapy.

### **CD**

Overall clinical response rate for natalizumab ranges from 48% to 49% compared to placebo at 32% to 56%. Clinical remission rate for natalizumab ranges from 26% to 37% compared to placebo at 16% to 30%. These results are based on two phase III induction trials (ENACT-1 and ENCORE). A significant effect over placebo for both clinical response and clinical remission was demonstrated in the ENCORE trial but not the ENACT-1 trial. In both the trials, 34% to 38% of patients were using concomitant immunosuppressants and 37% to 42% were using concomitant corticosteroids. The overall clinical response rate for natalizumab is 61% compared to placebo at 28%, p<0.05. The clinical remission rate for natalizumab is 44% compared to placebo at 26%, p<0.05. These results are based on one phase III maintenance trial (ENACT-2). Corticosteroids were discontinued in 58% of natalizumab-treated patients compared to 28% of placebo-treated patients at week 36, p<0.001.

Progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the John Cunningham (JC) virus, and which typically only occurs in patients that are immunocompromised, has occurred in three patients who received natalizumab in clinical trials. The absolute risk for PML in patients treated with natalizumab cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified. All three cases of PML occurred in patients who were concomitantly exposed to

immunomodulators (interferon beta in the patients with multiple sclerosis) or were immunocompromised due to recent treatment with immunosuppressants (e.g., azathioprine in the patient with Crohn's disease).

### Adverse Reactions

The most common adverse events observed with natalizumab include headache, fatigue, infusion-related reactions, infection, and nausea. Study withdrawal rates for natalizumab ranged from 2% to 8% compared to placebo at 3% to 7%. Serious adverse reactions associated with natalizumab include infections, including progressive multifocal leukoencephalopathy, hepatotoxicity, and infusion related reactions. Natalizumab is contraindicated in patients with current or previous PML, or in patients with a previous hypersensitivity reaction to the medication. Natalizumab carries a black box warning for the increased risk of PML.

Do not use natalizumab in combination with other immunosuppressant medications or anti-TNF agents because of the risk for serious infection. Aminosalicylates may be given during natalizumab treatment. Taper corticosteroids as soon as benefit from natalizumab therapy is observed. Stop natalizumab therapy if corticosteroids cannot be discontinued within 6 months of starting treatment or if a patient requires additional corticosteroid therapy that exceeds 3 months per year. No data are available regarding the vaccination (live or attenuated) of patients treated with natalizumab.

Hypersensitivity reactions have occurred in patients receiving natalizumab, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within two hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to natalizumab. If a hypersensitivity reaction occurs, discontinue administration of natalizumab and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with natalizumab. Hypersensitivity reactions were more frequent in patients with antibodies to natalizumab compared to patients who did not develop antibodies to natalizumab in both MS and CD studies. Therefore, the possibility of antibodies to natalizumab should be considered in patients who have hypersensitivity reactions.

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### Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

HCPCS Codes	Description
J2323	Injection, natalizumab, 1 mg

ICD-9-CM Diagnosis Codes	Description
340	Multiple sclerosis
555.9	Regional enteritis, unspecified site

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	2/15/2008	6017	Natalizumab (Tysabri®)
Great-West Healthcare	3/2008	P04.109.2	Tysabri

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