BlueCross BlueShield of Alabama

Name of Policy:
Tysabri (natalizumab)

Policy #: 281
Category: Pharmacology

Latest Review Date: October 2013
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Tysabri (natalizumab) is an integrin-4 receptor antagonist labeled for the treatment of multiple sclerosis (MS) and Crohn's disease (CD). Tysabri 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.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. MS is considered an autoimmune disease with both a humoral and cellular component. MS follows a variable course, and the cause is unknown. Most individuals with MS are diagnosed at age 20-40 years. There is a higher incidence of MS in women. There is no cure for MS. Treatment depends on the clinical presentation of the disease. The aim is to slow progression and minimize attacks. Tysabri is used for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The efficacy of Tysabri beyond two years is unknown. Because Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, Tysabri is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate multiple sclerosis therapy. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

Crohn's disease is a serious, often painful inflammatory bowel disorder that affects about 600,000 people in the United States. It can involve intestinal bleeding, diarrhea, weight loss, arthritis, skin problems, fever and anemia. In Crohn's disease, the interaction of the alpha-4 beta-7 integrin with the endothelial receptor NADCAN-1 has been implicated as an important contributor to the chronic inflammation which is the hallmark of this disease condition. The clinical effect in Tysabri with Crohn's disease is thought to be due to a secondary blockade of the molecular interaction of the alpha-4 beta-7 integrin receptor with the NADCAN-1 expressed on the venular endothelium at the inflammatory foci. Tysabri should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α.

Policy:

Tysabri (natalizumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for the treatment of adult patients with moderate-to-severe active Crohn's disease when the following criteria are met:

- Evidence of inflammation as indicated by C-reactive protein; **and**
- An inadequate response to or an inability to tolerate conventional therapies and inhibitors of TNF-alpha.

Tysabri (natalizumab) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for adult patients with multiple sclerosis (MS).

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and

his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

Multiple Sclerosis

Natalizumab is the first alpha4 integrin antagonist in a new class of selective adhesion-molecule inhibitors. It has been evaluated by the manufacturer in two randomized, double-blind, placebo-controlled trials, the AFFIRM study, and the SENTINEL study. The results of these studies are summarized below.

Polman, et al (2006), published the results of a two-year Phase 3 trial of natalizumab in patients with relapsing MS, the AFFIRM study. A randomized, placebo-controlled trial of Tysabri was conducted at ninety-nine clinical centers worldwide in 942 patients from age 18 to 50 years with a diagnosis of relapsing multiple sclerosis. Participants with a score of 0 to 5.0 on the Expanded Disability Status Scale (ratings in the EDSS range from 0 to 10, with higher scores indicating more severe disease); who had undergone MRI showing lesions consistent with multiple sclerosis; and had at least one medically documented relapse within the 12 months before the study began were randomly assigned in a 2:1 ratio to either Tysabri at a 300 mg dose (n=627) or placebo (n=315) by IV infusion every four weeks for up to 116 weeks. The primary endpoints were the rate of clinical relapse at one year and the rate of sustained progression of disability at two years.

Tysabri was found to reduce the risk of sustained progression of disability by 42% over two years ($P<0.001$) and the cumulative probability of progression was 17% in the Tysabri group and 29% with placebo. In addition, Tysabri was found to reduce the rate of clinical relapse at one year by 68% ($P<0.001$) which led to an 83% reduction in the accumulation of new or enlarging lesions over two years ($P<0.001$). The adverse events that were significantly more pronounced in the Tysabri over placebo group were fatigue and allergic reaction. Biogen Idec and Elan Pharmaceuticals supported this study and analyzed the data.

Rudick, et al (2006), published the results of another two-year Phase 3 trial of natalizumab plus interferon beta -1a in patients with relapsing MS, the SENTINEL study. Of 1,171 patients who were randomized, 589 received continued interferon beta-1a in combination with 300 mg of natalizumab, and 582 received continued interferon beta-1a with placebo, IV every four weeks for up to 116 weeks. The main outcome measures 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.

Combination therapy resulted in a 24% reduction in the relative risk of sustained disability progression ($P=0.02$). 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 (0.34 vs. 0.75, $P<0.001$) with fewer new or enlarging

lesions on T2-weighted MRI. Adverse events reported with combination treatment were anxiety, pharyngitis, sinus congestion, and peripheral edema, as well as two cases of PML, one of which was fatal. Biogen Idec and Elan Pharmaceuticals supported this study.

Progressive Multifocal Leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, has occurred in three patients who received Tysabri in clinical trials. Two cases of PML were observed in the 1869 patients with MS who were treated for a median of 120 weeks and one case occurred in the 1043 patients with Crohn's disease after receiving eight doses.

All three of these cases of PML occurred in patients who were concomitantly exposed to immunomodulators (interferon beta in MS patients) or were immunocompromised due to recent treatment with immunosuppressants (azathioprine in Crohn's disease patient).
Tysabri was initially approved by the FDA in November 2004 for use as monotherapy in patients with relapsing forms of MS. It is also meant for patients who have not responded adequately to, or cannot tolerate, other treatments for MS.

In February 2005, it was withdrawn by the manufacturer after three patients in the drug's clinical trials developed PML. The clinical trials were also put on hold.

In February 2006, the FDA re-examined the clinical trials and confirmed no additional cases of PML and allowed a clinical trial to resume. In March 2006, the FDA consulted with its Advisory Committee about the possibility of making Tysabri available to appropriate MS patients while decreasing the possibility of patients developing PML. The committee recommended a risk-minimization program with mandatory patient registration and periodic follow-up to identify as early as possible any cases of PML and the reason the infection occurs. The manufacturer, Biogen Idec, submitted to the agency a Risk Management Plan, called the TOUCH Prescribing Program, to help ensure the safe use of the product.

On June 5, 2006, the FDA approved an application for resumed marketing of Tysabri with a special distribution program. Biogen Idec, Inc., the company that manufacturers Tysabri, and Elan Pharmaceuticals, Inc. the company that distributes Tysabri, will manage the program.

Tysabri® is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The safety and efficacy of Tysabri® beyond two years are unknown.

Because Tysabri® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, Tysabri® is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been studied.

Tysabri is available only through this special restricted distribution program called the TOUCH Prescribing Program. Under this program, only prescribers, infusion centers, and pharmacies

associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the drug. It may not be given as a home infusion. Also, Tysabri must be administered only to patients who have enrolled in and meet all the conditions of the TOUCH Prescribing Program (1-800-456-2255).

The FDA also recommends an MRI scan should be obtained prior to initiating therapy with Tysabri, as it may be helpful to differentiate subsequent MS symptoms from PML. Healthcare professionals should monitor patients on Tysabri for any new sign or symptom suggestive of PML, and immediately withhold dosing. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, CSF analysis for JC viral DNA are recommended. Patients must be evaluated at three months and six months after the first infusion, and every six months thereafter. The prescribing information does have a black box warning that states Tysabri increases the risk of PML. It states that although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with Tysabri monotherapy.

Pucci et al evaluated the efficacy, tolerability and safety of natalizumab in patients with RRMS. Among the pertinent literature, three studies met the inclusion criteria of methodological quality, comprising a total of 2,223 participants. The results showed that natalizumab treatment reduces the number of patients who experienced relapses and the number of patients who progressed at two years. Also MRI scans showed evidence of a beneficial effect of natalizumab on disease activity. Although information on adverse events (AEs) was limited, as most participants were followed up for two years only, infusion reactions, anxiety, sinus congestion, lower limb swelling, rigors, vaginal inflammation and menstrual disorders were found to be more frequent after natalizumab treatment. However, the number of patients experiencing at least one AE (including severe or serious AEs) did not differ between natalizumab and control groups. On the contrary, significant safety concerns have been raised regarding progressive multifocal leukoencephalopathy (PML), a rare and often fatal viral disease characterized by damage to the white matter of the brain. In the studies included in this review, PML was reported in two patients treated with natalizumab for more than two years. However, the protocol was insufficient to evaluate PML risk as well as other potential rare and long-term AEs (e.g. cancers and other infections) which are important issues in considering the risk/benefit ratio of natalizumab. An independent systematic review of the safety profile of natalizumab is warranted. Natalizumab should be used only by skilled neurologists in MS centers under surveillance programs.

Crohn's disease

The safety and efficacy of Tysabri to treat Crohn's disease was evaluated in three randomized, double-blinded, placebo-controlled clinical trials. One study evaluated 1,414 adult patients with moderately-to-severely active Crohn's disease. Induction of clinical response was evaluated in two studies. In the CD1 study, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. Clinical results were assessed at 10 weeks, and patients with incomplete information were considered as not having clinical response. In 56% of 717 patients receiving Tysabri were in response compared to 49% of the 179 patients receiving

placebo. In a post analysis of the subset of 653 patients with elevated baseline C-reactive protein, 57% of Tysabri patients were in response compared to 45% of those in placebo.

In the second induction study, the CD2, only patients with elevated serum C-reactive protein was studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg of Tysabri or placebo. In this study compared to the prior study, clinical response and clinical remission was required to be met at both weeks eight and twelve rather than at a single time period of ten weeks. Patients with incomplete information were considered as not having a response. Study CD1 and CD2 for subgroups defined by prior use of or by inadequate response to prior therapies, the treatment effect genuinely similar to that seen in the whole study population. Patients with inadequate response inhibitors or TNFA appeared to have lower clinical response and lower clinical remission in both the treatment and placebo groups. For patients in study CD2 with an inadequate response to prior treatment with inhibitors of TNA-A clinical response at both weeks eight and 12 were seen in 38% of those randomized to Tysabri and clinical remissions at both weeks eight and 12 were seen 17%.

The CD3 study evaluated maintenance therapy. In this study, 331 patients from the CD1 that had a clinical response at weeks 10 and 12 were re-randomized to continue treatment or receive placebo.

For subgroups in the study, defined by prior use of or inadequate response to prior therapies, the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither condominant immunosuppressants nor condominant corticosteroids the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors with TNA-A appeared to have lower maintenance of clinical response and lower maintenance of clinical remission in both the treatment and placebo groups. For patients in study CD3 with an inadequate response to prior treatment with induction of TNA-alpha maintenance of clinical response through month nine were seen in 52% of those randomized with Tysabri and maintenance of clinical remission through month nine were seen in 30% of the patients.

MacDonald et al performed a systematic review to determine the efficacy and safety of natalizumab for induction of remission in Crohn’s disease. Only randomized controlled trials comparing natalizumab to a placebo or control therapy for the induction of remission in Crohn's disease were included. Data were analyzed using Review Manager (RevMan 4.2.8). All data were analyzed on an intention-to-treat basis. For pooled data, summary test statistics were derived using the relative risk and 95% confidence intervals. Pooled data from the four included studies suggest that natalizumab (300 mg or 3 to 4 mg/kg) is effective for induction of clinical response and remission in patients with moderately to severely active Crohn's disease. This benefit is statistically significant for one, two and three infusion treatments. There was a trend toward increased benefit with additional infusions of natalizumab. Natalizumab appears to provide greater benefit for patient subgroups characterized by objective confirmation of active inflammation or chronically active disease despite conventional therapies. These subgroup analyses demonstrated significantly greater clinical response and remission rates for natalizumab compared with placebo in patients with elevated C-reactive protein levels, active disease despite the use of immunosuppressants, or prior anti-tumor necrosis factor therapy. These benefits were

apparent for both short term (one infusion) and longer term treatment (two or three infusions). Natalizumab was generally well tolerated and the safety profile observed in the four included studies was similar. Adverse events occurred infrequently and were experienced by a similar proportion of natalizumab and placebo treated patients. There were no statistically significant differences between natalizumab and placebo treated patients in the proportions of patients who withdrew due to adverse events or those who experienced serious adverse events. The included trials lacked adequate power to detect serious adverse events that occur infrequently. Recently, two patients with multiple sclerosis treated with natalizumab in combination with interferon beta-1a and one patient with Crohn's disease treated with natalizumab in combination with azathioprine developed progressive multifocal leukoencephalopathy (PML) resulting in two patient deaths. A retrospective investigation was conducted to assess the risk of PML in natalizumab treated patients and no new cases were identified. Pooled data suggest that natalizumab is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease. The clinical benefit of induction therapy with natalizumab in Crohn's disease should be weighed against the potential risk of serious adverse events. Preliminary data from the retrospective investigation of adverse events associated with natalizumab suggest that it may be possible to identify patients at risk for PML by testing for the appearance of JC virus in plasma.

Practice Guidelines and Position Statements

According to the 2008 American Academy of Neurology Practice Guideline on the use of natalizumab for the treatment of multiple sclerosis, natalizumab has been demonstrated to reduce measures of disease activity and to improve measures of disease severity in patients with relapsing-remitting (RR) MS. The guideline also states that the relative efficacy of natalizumab compared to current disease-modifying therapies cannot be defined accurately. Similarly, the value of natalizumab in the treatment of secondary progressive (SP) MS is unknown. The value of combination therapy using natalizumab and interferon in the treatment of RRMS is also unknown. There is an increased risk of developing progressive multifocal leukoencephalopathy (PML) in natalizumab-treated patients and possibly an increased risk of other opportunistic infections.

According to the National Multiple Sclerosis Society’s National Opinion Paper on patient access to Tysabri (natalizumab), patients in all three of the following groups are considered candidates for Tysabri as long as they continue to have relapses:

- Relapsing-Remitting MS (RRMS), which involves periodic relapses, followed by partial or complete recovery.
- Secondary-Progressive MS (SPMS) in those patients who were initially diagnosed with RRMS and convert to a course of steady progression several years later, but continue to have relapses.
- Progressive-Relapsing MS (PRMS), which is characterized by disease progression from onset with relapses superimposed along the way.

Patients with Primary-Progressive MS (which is progressive from onset and has no relapses) and those with SPMS and PRMS who are no longer experiencing relapses are not considered candidates for Tysabri

According to the American College of Gastroenterology Practice Guidelines for the Management of Crohn's Disease in Adults (ACG Practice Guideline), patients with moderate-severe disease usually have a Crohn's Disease Activity Index (CDAI) of 220-450. They have failed to respond to treatment for mild-moderate disease, or have more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia

The CDAI is the sum of the following clinical or laboratory variables after multiplying by their weighting factor given in parentheses:

- Number of liquid or soft stools each day for seven days (2)
- Abdominal pain graded from 0-3 in severity each day for seven days (5)
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days (7)
- Presence of complications, where one point is added for each complication (20). Complications include:
    - the presence of joint pains (arthralgia) or frank arthritis
    - inflammation of the iris or uveitis
    - presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers
    - anal fissures, fistulae, or abscesses
    - other fistulae (e.g., enterocutaneous, vesicle, vaginal)
    - fever (> 37.8° C) during the previous week.
- Taking diphenoxylate/atropine [Lomotil®] or opiates for diarrhea (30)
- Presence of an abdominal mass where 0 = none, 2 = questionable, 5 = definite (10);
- Absolute deviation of hematocrit from 47% in males and 42% in females (6)
- Percentage deviation from standard body weight (1)

The ACG Practice Guideline states that natalizumab is effective in the treatment of patients with moderate to severely active Crohn's disease who have had an inadequate response or are unable to tolerate conventional Crohn's disease therapies and anti-TNF monoclonal antibody therapy.

Key Words:

Tysabri (natalizumab), multiple sclerosis (MS), progressive multifocal leukoencephalopathy (PML), Crohn’s disease

Approved by Governing Bodies:

In November 2004, Tysabri was initially approved by the FDA.
In February 2005, Tysabri was withdrawn by the manufacturer after three patients developed PML.
In February 2006, clinical trials were resumed.
In March 2006, the FDA Advisory Committee on drugs for peripheral and central nervous system made recommendations and the TOUCH prescribing program was developed.
On June 5, 2006, the FDA approved resumed marketing of Tysabri with the special restricted distribution program.

On January 14, 2008, the FDA approved to treat adult patients who suffer from moderate-to-severely active Crohn's disease with evidence of inflammation.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.
Lowe's Precertification Requirement—**Effective for dates of service on or after February 1, 2010** please contact Care Continuum at 866-240-4734 or fax the prescription with accompanying clinical information to 877-540-6223 for precertification. (This Blue Cross and Blue Shield of Alabama's medical policy does not apply for Lowe's members for dates of service on or after February 1, 2010. This policy was in effect for Lowe's prior to February 1, 2010).

Current Coding:

HCPCS:

J2323 Injection, Natalizumab, 1 mg

Previous Coding:

HCPCS:

Q4079 Injection, natalizumab, 1 mg **(deleted 12/31/2007)**

References:

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Policy History:

Medical Policy Group, June 2006 **(3)**
Medical Policy Administration Committee, July 2006
Available for comment July 18-August 31, 2006
Medical Policy Group, October 2006 **(3)**
Medical Policy Administration Committee, October 2006
Available for comment October 6-November 20, 2006
Medical Policy Group, March 2008 **(3)**
Medical Policy Administration Committee May 2008
Available for comment April 25-June 8, 2008
Medical Policy Group, April 2010 **(1):** No new updates
Medical Policy Group, October 2013 **(1)**: Update to Key Points and References; removed ICD-9 diagnosis codes; no change to policy statement.
