TYSABRI® (natalizumab)

Policy Number: 2014D0026J
Effective Date: 8/1/2014

Table of Contents **Page**

COVERAGE RATIONALE 1
BENEFIT CONSIDERATIONS 2
CLINICAL EVIDENCE 3
U.S. FOOD AND DRUG ADMINISTRATION (FDA) 8
APPLICABLE CODES 9
REFERENCES 8
POLICY HISTORY/REVISION INFORMATION 11

Related Medical or Drug Policies:
None

Related Coverage Determination Guidelines:
None

INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificates of Coverage (COCs), Schedules of Benefits (SOBs), or Summary Plan Descriptions (SPDs)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this policy. Other Medical Policies, Drug Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Medical Policies, Drug Policies, and Coverage Determination Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

Natalizumab (Tysabri®) is **proven** when **all** of the following are met:
1. Diagnosis of relapsing forms of multiple sclerosis.[1]
2. Baseline cranial MRI performed prior to initial administration[1]
3. Used as monotherapy[1]

Natalizumab is **proven** for inducing and maintaining clinical response and remission in patients with moderate to severe Crohn's disease (CD)[1] who meet **one** of the following criteria:
1. For **induction therapy** when **all** of the following criteria are met:
   a. Evidence of inflammation[1] (e.g., elevated C-reactive protein [CRP], elevated erythrocyte sedimentation rate, presence of fecal leukocytes[5]).
   b. History of inadequate response or intolerance to conventional Crohn's disease therapies and inhibitors of TNF-α.[1] Conventional Crohn's disease therapies may include aminosalicylates (such as mesalamine and sulfasalazine), corticosteroids, immunomodulators (such as azathioprine, 6-mercaptopurine, and

methotrexate) and TNF-inhibitors [e.g., infliximab (Remicade®), adalimumab (Humira®), or certolizumab pegol (Cimzia®)].[5,6] *Refer to Benefit Considerations for specific state guidance*.

c. Patient is not receiving concomitant treatment with immunosuppressants (e.g., 6-MP, azathioprine, cyclosporine, or methotrexate) OR TNF-inhibitors [e.g., infliximab (Remicade), adalimumab (Humira),or certolizumab pegol (Cimzia)].

-OR-

2. For **maintenance therapy** when **all** of the following criteria are met:
   a. Diagnostic and/or clinical documentation (e.g. improved disease activity index) that indicates patient has experienced clinical benefit from receiving (induction) natalizumab therapy by week 12.[1]
   b. Patients with Crohn's disease who start natalizumab while on chronic oral corticosteroids must discontinue chronic steroids within 6 months of starting natalizumab therapy or natalizumab therapy should be discontinued.[1]
   c. Patient is not receiving concomitant treatment with immunosuppressants (e.g., 6-MP, azathioprine, cyclosporine, or methotrexate) **OR** TNF-inhibitors [e.g., Enbrel (etanercept), Humira (adalimumab), or Remicade (infliximab)].

Additional information to support medical necessity review where applicable:
The above indications and criteria also apply to medical necessity review.

Natalizumab is **unproven** for the treatment of other conditions or diseases, including type of MS other than relapsing forms. Statistically robust randomized controlled trials are needed to address the issue of whether natalizumab has sufficient superiority in clinical efficacy compared to other available treatments to justify the substantial inherent clinical risk in its use.

Medicare does not have a National Coverage Determination (NCD) for Tysabri® (natalizumab). Local Coverage Determinations (LCDs) do exist, refer to the LCDs for Drugs and Biologicals (Non Chemotherapy).

In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, section 50 Drugs and Biologicals at: http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf.

(Accessed April 3, 2014)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

The State of New Jersey prohibits requiring failed prior therapy or intolerance to therapy as a requirement for coverage.

CLINICAL EVIDENCE

Proven

Relapsing Multiple Sclerosis

Filippini et al conducted a meta-analysis to estimate the relative efficacy and acceptability of interferon ß-1b (IFNß-1b) (Betaseron), interferon ß-1a (IFNß-1a) (Rebif and Avonex), glatiramer acetate, natalizumab, mitoxantrone, methotrexate, cyclophosphamide, azathioprine, intravenous immunoglobulins, and long-term corticosteroids versus placebo or another active agent in participants with multiple sclerosis (MS) and to provide a ranking of the treatments according to their effectiveness and risk-benefit balance.[2] Forty-four trials were included in the review, in which 17,401 participants had been randomized. The pairwise meta-analysis showed that there was high quality evidence that natalizumab and IFNß-1a (Rebif) were effective against recurrence of relapses in RRMS during the first 24 months of treatment compared to placebo (odds ratio (OR) 0.32, 95% confidence interval (CI) 0.24 to 0.43; OR 0.45, 95% CI 0.28 to 0.71, respectively). Additionally, the pairwise meta-analysis suggested, with moderate quality evidence, that natalizumab and IFNß-1a (Rebif) probably decreased the odds of the participants with RRMS having disability progression at two years' follow-up, with an absolute reduction of 14% and 10%, respectively, compared to placebo. Natalizumab and IFNß-1b (Betaseron) were significantly more effective (OR 0.62, 95% CI 0.49 to 0.78; OR 0.35, 95% CI 0.17 to 0.70, respectively) than IFNß-1a (Avonex) in reducing the number of the participants with RRMS who had progression at two years' follow-up, and confidence in this result was graded as moderate. The network meta-analysis provided evidence that the most effective drug appeared to be natalizumab (median OR versus placebo 0.29, 95% credible intervals (CrI) 0.17 to 0.51), followed by IFNß-1a (Rebif) (median OR versus placebo 0.44, 95% CrI 0.24 to 0.70), mitoxantrone (median OR versus placebo 0.43, 95% CrI 0.20 to 0.87), glatiramer acetate (median OR versus placebo 0.48, 95% CrI 0.38 to 0.75), IFNß-1b (Betaseron) (median OR versus placebo 0.48, 95% CrI 0.29 to 0.78). However, our confidence was moderate for direct comparison of mitoxantrone and IFNB-1b vs placebo and very low for direct comparison of glatiramer vs placebo. Authors concluded that on the basis of high quality evidence, natalizumab and IFNß-1a (Rebif) are superior to all other treatments for preventing clinical relapses in RRMS in the short-term (24 months) compared to placebo. Moderate quality evidence supports a protective effect of natalizumab and IFNß-1a (Rebif) against disability progression in RRMS in the short-term compared to placebo. Direct head-to-head comparison(s) between natalizumab and IFNß-1a (Rebif) are still warranted.

A Cochrane review of three studies suggested that treatment with natalizumab (dosage > 3 mg/kg intravenous infusion every 4 weeks) was effective in reducing relapses and disability at 2 years in relapsing-remitting multiple sclerosis (RRMS) patients.[14] The efficacy results showed that treatment with natalizumab was statistically significant for all the primary outcomes and for the secondary ones where data was available. Natalizumab reduced the risk of experiencing at least one new exacerbation at 2 years by about 40% and of experiencing progression at 2 years by about 25% as compared to a control group. Additionally, MRI parameters showed statistical evidence in favor of participants receiving natalizumab. Common natalizumab adverse events reported included infusion reactions, anxiety, sinus congestion, lower limb swelling, rigors, vaginitis and menstrual disorders. Natalizumab was found to be well tolerated and the number of patients experiencing at least one adverse event (including severe and serious AEs) during this period did not differ between natalizumab-treated patients and controls. In the trials reviewed, two cases of PML were documented: one in a patient who had received 29 doses and a second fatal case of PML in another patient after 37 doses of natalizumab. The review protocol was unable 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.

Approval of natalizumab was based on results of two phase III, multi-center, randomized, double-blind, placebo-controlled trials. Both studies enrolled MS patients who had experienced at least one clinical relapse during the previous year. Natalizumab was administered as a 300 mg intravenous infusion every 4 weeks for 28 months.

In the first study (AFFIRM; n=942), patients were randomly assigned to receive either 300 mg natalizumab (n=627) or placebo (n=315).[7] The primary endpoints were the rate of clinical relapse at one year and the rate of sustained progression of disability. The results showed that natalizumab reduced the rate of clinical relapse at one year by 68% (p<0.001) and led to an 83% reduction in the accumulation of new or enlarging hyperintense lesions, as detected by T2-weighted magnetic resonance imaging (MRI), over two years (mean numbers of lesions, 1.9 with natalizumab and 11.0 with placebo; p<0.001). Natalizumab reduced the risk of sustained progression of disability by 42% over two years (hazard ratio, 0.58; 95% confidence interval, 0.43 to 0.77; p<0.001). The cumulative probability of progression was 17% in the natalizumab group and 29% in the placebo group. There were 92% fewer lesions (as detected by gadolinium-enhanced MRI) in the natalizumab group than in the placebo group at both one and two years (p<0.001). The adverse events that were significantly more frequent in the natalizumab group than in the placebo group were fatigue (27% vs. 21%, p=0.048) and allergic reaction (9% vs. 4%, p=0.012). Hypersensitivity reactions of any kind occurred in 25 patients receiving natalizumab (4%), and serious hypersensitivity reactions occurred in 8 patients (1%). In conclusion, natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing multiple sclerosis.

In the second study (SENTINEL; n=1,171), natalizumab 300 mg IV (589 patients) or placebo (582 patients) every 4 weeks was added to interferon beta-1a (Avonex®).[8] The primary end points were the rate of clinical relapse at 1 year and the cumulative probability of disability progression sustained for 12 weeks, as measured by the Expanded Disability Status Scale, at 2 years. 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) and with fewer new or enlarging lesions on T(2)-weighted magnetic resonance imaging (0.9 vs. 5.4, p<0.001). The results showed that combination therapy resulted in a 24% reduction in the relative risk of sustained disability progression (hazard ratio, 0.76; 95% confidence interval, 0.61 to 0.96; 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. Adverse events associated with combination therapy were anxiety, pharyngitis, sinus congestion, and peripheral edema. Two cases of progressive multifocal leukoencephalopathy, one of which was fatal, were diagnosed in natalizumab-treated patients. In conclusion, natalizumab added to interferon beta-1a was significantly more effective than interferon beta-1a alone in patients with relapsing multiple sclerosis.

In a randomized, double-blind trial, 213 patients with relapsing-remitting or relapsing secondary progressive MS were randomized to receive 3 mg/kg of intravenous natalizumab, 6 mg/kg or placebo every 28 days for 6 months.[9] The primary endpoint was the number of new brain lesions on monthly gadolinium-enhanced magnetic resonance imaging during the six-month period. The two natalizumab-treated groups had significantly fewer new gadolinium-enhanced lesions per patient than the placebo-treated group. There was no significant difference between the two natalizumab groups. In addition, treatment with natalizumab resulted in a significant reduction in the frequency of relapse and an increased perception of well-being among the patients.

The effect of natalizumab on the progression of disability and its effect in direct comparison with existing therapies are not yet known.

Crohn's Disease

A Cochrane systemic review of four studies suggested that natalizumab (300 mg or 3 to 4 mg/kg) was effective for induction of clinical response and remission in patients with moderately to severely active Crohn's disease.[10] This benefit was 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. The authors concluded that 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 developing PML by testing for the appearance of JC virus in plasma.

Induction of clinical response for natalizumab was evaluated in two studies, CD1 and CD2. In the CD1 study, 896 patients were randomized at a 4:1 ratio to receive three monthly infusions of 300 mg of natalizumab or placebo.[11] At Week 10, 56% of the 717 patients receiving natalizumab and 49% of the 179 patients receiving placebo showed a response (defined as 70-point decrease in CDAI from baseline). CD2, conducted only on patients (n=509) with an elevated C-reactive protein (CRP), randomized (1:1) patients to receive 3 monthly infusions of 300 mg of natalizumab or placebo.[12] Clinical response (70-point decrease in CDAI from baseline) and clinical remission (defined as CDAI score < 150) were required at Weeks 8 and 12. Clinical response and clinical remission at both 8 and 12 weeks was seen in 48% and 26% of the natalizumab and 32% and 16% of the placebo groups respectively ($p<0.005$).

Maintenance therapy was evaluated in study CD3.[11] This study included 331 patients from CD1 that had a clinical response to natalizumab at both weeks 10 and 12. They were re-randomized 1:1 to monthly natalizumab 300 mg or placebo. Clinical response and clinical remission were maintained in 61% and 45% of the natalizumab and 29% and 26% of the placebo groups respectively ($p<0.005$) at 6 months. At 12 months, clinical response and clinical remission were maintained in 54% and 40% of the natalizumab and 20% and 15% of the placebo groups respectively.

A double-blind, placebo-controlled trial was conducted in 248 patients with moderate-to-severe Crohn's disease.[13] Patients were randomly assigned to receive one of four treatments administered 4 weeks apart: two infusions of placebo; one infusion of natalizumab 3 mg/kg followed by placebo; two infusions of natalizumab 3 mg/kg; or two infusions of natalizumab 6 mg/kg. Outcomes included reductions in scores for the Crohn's Disease Activity Index (CDAI), the health-related quality of life, and C-reactive protein levels. The group given two infusions of 6 mg/kg did not have a significantly higher rate of clinical remission (defined by a score of less than 150 on the CDAI) than the placebo group at week 6. However, both groups that received two infusions of natalizumab had higher remission rates than the placebo group at multiple time points. Natalizumab also produced a significant improvement in response rates (defined by a reduction of at least 70 points in the score on the CDAI). The highest remission rate was 44% and the highest response rate was 71% (at week 6 in the group given two infusions of 3 mg/kg). Overall, the two infusions of natalizumab 6 mg/kg and of 3 mg/kg had similar effects. The quality of life improved in all natalizumab groups; C-reactive protein levels improved in groups receiving two infusions of natalizumab.

Professional Societies

In 2008, the American Academy of Neurology conducted an assessment regarding the use of natalizumab (Tysabri) for the treatment of multiple sclerosis. A summary of their conclusions and recommendations are below:[4]

Conclusions:*

1. Natalizumab reduces measures of disease activity such as clinical relapse rate, Gd-enhancement, and new and enlarging T2 lesions in patients with relapsing MS (Class I studies, Level A).

2. Natalizumab improves measures of disease severity such as the EDSS progression rate and the T2-hyperintense and T1-hypointense lesion burden seen on MRI in patients with relapsing MS (Class I studies, Level A).

3. The relative efficacy of natalizumab compared to other available disease-modifying therapies is unknown (Level U).

4. The value of natalizumab in the treatment of SPMS is unknown (Level U).

5. The SENTINEL trial provides evidence for the value of adding natalizumab to patients already receiving IFNβ-1a, 30 µg, IM once weekly (one Class I study, Level B). It provides no information either about the value of adding IFNβ therapy to patients already receiving natalizumab in the treatment of RRMS or about the value of continuing IFNβ therapy once natalizumab therapy is started (Level U).

6. There is an increased risk of developing PML in natalizumab-treated patients (Level A for combination therapy, Level C for monotherapy). The two cases seen in MS were treated with a combination of natalizumab and IFNβ-1a, but the fact that PML occurred only with combination therapy may be a chance development. There may also be an increased risk of other opportunistic infections (Level C). On the basis of clinical trial data, the PML risk has been estimated to be 1 person for every 1,000 patients treated for an average of 17.9 months, although this estimate could change in either direction with more patient-years of exposure.

Recommendations:

1. Because of the possibility that natalizumab therapy may be responsible for the increased risk of PML, it is recommended that natalizumab be reserved for use in selected patients with relapsing remitting disease who have failed other therapies either through continued disease activity or medication intolerance, or who have a particularly aggressive initial disease course. This recommendation is very similar to that of the FDA.

2. Similarly, because combination therapy with IFNβ and natalizumab may increase the risk of PML, it should not be used. There are also no data to support the use of natalizumab combined with other disease-modifying agents as compared to natalizumab alone. The use of natalizumab in combination with agents not inducing immune suppression should be reserved for properly controlled and monitored clinical trials.

*Classification of Recommendations:

A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*

B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)

C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)

U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).

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.[15]

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.[5]

The CDAI[16] 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 1 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.[5]

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Tysabri (natalizumab) is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis. Tysabri increases the risk of PML and therefore, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk when initiating and continuing treatment with Tysabri. In multiple sclerosis patients, an MRI scan should be obtained prior to initiating therapy with Tysabri. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.[1]

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. In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on Tysabri therapy are uncommon.[1]

The FDA issued a Drug Safety Communication dated February 5, 2010 to communicate that the risk of developing progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection associated with the use of Tysabri, increases with the number of Tysabri infusions received. This safety information, based on reports of 31 confirmed cases of PML received by the FDA as of January 21, 2010, is included in the Tysabri drug label and patient Medication Guide. However, based on the available information, the FDA believes that the clinical benefits of Tysabri continue to outweigh the potential risks.[17]

The FDA issued a second Drug Safety Communication dated April 22, 2011 to provide a safety update on PML associated with Tysabri.[10] The Tysabri label has been revised to include new information about the risk of PML. The updated drug label includes a table summarizing rates of PML with Tysabri use according to the number of infusions (duration of exposure). The new label also includes information on a newly identified PML risk factor. Patients who took an immune system suppressing medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, and mycophenolate) prior to taking Tysabri have been shown to be at an increased risk for developing PML. Based on the available information to date, the FDA continues to believe that the benefits of taking Tysabri outweigh the potential risks.[18]

The FDA issued a third Drug Safety Communication dated January 1, 2012 to provide a safety update on risk factors for developing PML.[19] Testing positive for anti-JC virus (JCV) antibodies has been identified as a risk factor for progressive multifocal leukoencephalopathy (PML). The risks and benefits of continuing treatment with Tysabri should be carefully considered in those patients who are found to be anti-JCV antibody positive and have one or more of the other known risk factors for PML. Patients with all three known risk factors have an estimated risk of PML of 11/1,000 users. The risk factors are:

- The presence of anti-JCV antibodies.
- Longer duration of Tysabri treatment, especially beyond 2 years.
- Prior treatment with an immunosuppressant medication (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, or mycophenolate mofetil).

A patient's anti-JCV antibody status may be determined using an anti-JCV antibody detection test that has been analytically and clinically validated, and has been ordered by a healthcare professional. The Stratify JCV Antibody ELISA test was cleared by FDA on January 20, 2012.[20,21]

Tysabri is available only through a risk minimization plan called Tysabri Outreach Unified Commitment to Health (the TOUCH™ Prescribing Program) which registers prescribers, infusion centers, and pharmacies associated with infusion centers. Additionally, Tysabri can only be prescribed to patients who are enrolled in and meet all the requirements of the program.[1]

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document

HCPCS Code	Description
J2323	Injection, natalizumab, 1 mg

Proven ICD-9 Code	Description
340	Multiple sclerosis
555.0	Regional enteritis of small intestine
555.1	Regional enteritis of large intestine
555.2	Regional enteritis of small intestine with large intestine
555.9	Regional enteritis of unspecified site

ICD-10 Codes (Preview Draft)
In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2015***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. **The effective date for ICD-10 code set implementation is subject to change.*

ICD-10 Diagnosis Code (Effective 10/01/15)	Description
G35	Multiple sclerosis
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess

K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications

REFERENCES

1. Tysabri [package insert]. Biogen Idec, Inc: Cambridge, MA; December 2013.

2. Filippini G1, Del Giovane C, Vacchi L, et al. Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2013 Jun 6;6:CD008933. doi: 10.1002/14651858.CD008933.pub2.

3. Goodin DS, Frohman EM, Garmany JP, et al. Disease modifying therapies in multiple sclerosis: Report of the Therapeutics and Technology Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. Neurology 2002;58;169.

4. Goodin DS, Cohen BA, et al. Assessment: The use of natalizumab (Tysabri) for the treatment of multiple sclerosis (an evidence-based review) Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008;71;766-773.

5. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. ACG Practice Guidelines. Management of Crohn's Disease in Adults. Am J Gastroenterol. 2009;104(2):465-83.

6. Crohn’s Disease information page. National Digestive Diseases Information Clearinghouse (NDDIC) Web site. Available at http://digestive.niddk.nih.gov/ddiseases/pubs/crohns/. Accessed April 29, 2011.

7. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):899-910.

8. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006 Mar 2;354(9):911-23.

9. Miller DH, Khan OA, Sheremata WA, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. N Eng J Med 2003;34815-23.

10. MacDonald JK,McDonald JWD.Natalizumab for induction of remission in Crohn’s disease. CochraneDatabase of Systematic Reviews 2007, Issue 1. Art. No.: CD006097. DOI: 10.1002/14651858.CD006097.pub2.

11. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab Induction and Maintenance Therapy for Crohn’s Disease. N Engl J Med 2005;353(18):1912-25.

12. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the Treatment of Active Crohn's Disease: Results of the ENCORE Trial. Gastroenterology 2007;132(5):1672-83.

13. Ghosh S, Goldin E, Gordon FH, et al. Natalizumab for active Crohn's disease. N Engl J Med 2003;348:24-32.

14. Pucci E, Giuliani G, Solari A, et al. Natalizumab for relapsing remitting multiple sclerosis. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD007621. doi: 10.1002/14651858.CD007621.pub2.

15. Expert Opinion Paper of the National Clinical Advisory Board of the National Multiple Sclerosis Society. Treatment Recommendations for Physicians: Patient Access to Tysabri. 2008. Available at http://www.nationalmssociety.org/for-professionals/healthcare-professionals/publications/expert-opinion-papers/index.aspx.

16. Yoshida EM. The Crohn's Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: A review of instruments to assess Crohn's disease. Can J Gastroenterol. 1999. 13(1):65-73.

17. U.S. Food and Drug Administration Drug Safety Communication: Risk of Progressive Multifocal Encephalopathy (PML) with the use of Tysabri (natalizumab). http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199872.htm. Accessed May 25, 2010.

18. U.S. Food and Drug Administration Drug Safety Communication: Safety Update on Progressive Multifocal Encephalopathy (PML) associated with Tysabri (natalizumab). http://www.fda.gov/Drugs/DrugSafety/ucm252045.htm. Accessed April 26, 2011.

19. U.S. Food and Drug Administration Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab). http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=anti-JCV antibody&utm_content=1#table. Accessed April 11, 2012.

20. U.S. Food and Drug Administration News Release: FDA permits marketing of first test for risk of rare brain infection in some people treated with Tysabri. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm288471.htm. Accessed April 11, 2012.

21. Stratify JCV™ Antibody Elisa [package insert]. Focus Diagnostics: Cypress, CA: January 2011. http://www.focusdx.com/focus/jcv.pdf. Accessed April 11, 2012.

POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
8/1/2014	Policy revised per annual review. Revised Coverage Rationale for MS criteria to include baseline cranial MRI requirement. Clarified unproven indications to include non-relapsing forms of MS. Updated CMS, Clinical Evidence, U.S.FDA, and References. Approved by the National Pharmacy & Therapeutics Committee on 5/21/2014. Policy 2013D0026I archived.
7/1/2013	Policy revised per annual review. Revised Coverage Rationale to remove age requirement and include additional criteria for CD. Updated Benefits Consideration, Clinical Evidence, U.S.FDA, and References. Approved by the National Pharmacy & Therapeutics Committee on 5/21/2013. Policy

	2012D0026H archived.
9/1/2012	Policy revised per annual review. No change to proven indications but expanded clinical criteria. Added FDA Drug Safety Communication and anti-JCV antibody detection testing. Clinical evidence and References updated. Added list of applicable ICD-10 codes (preview draft) in preparation for the transition from ICD-9 to ICD-10 medical coding on 10/01/14. Approved by the National Pharmacy & Therapeutics Committee on 7/10/2012. Policy 2011D0026G archived.
9/1/2011	Policy revised per annual review. Created Additional Information section within the Coverage Rationale to describe FDA labeled uses. Updated Clinical Evidence and References. Added an FDA Drug Safety Communication. Approved by the National Pharmacy & Therapeutics Committee on 7/12/2011. Policy 2010D0026F archived.
8/30/2010	Policy revised per annual review with additional clinical evidence for CD. Added AAN and NMSS guidelines into the Professional Societies section. Incorporated a Hayes Health Technology Brief into the Technology Assessment Section. Added FDA Section which includes approved indications, a Drug Safety Communication, and information regarding the TOUCH program. Expired code Q4079 removed. Approved by the National Pharmacy & Therapeutics Committee on 8/11/2010. Policy 2009D0026E archived.
12/30/2009	Policy revised. Added evidence of inflammation and inadequate response or intolerance to conventional therapies and anti-TNF agents to moderate to severe Crohn's disease proven use in Coverage Rationale. Information from ACG's Practice Guidelines added to the Professional Societies section. Removed ulcerative colitis ICD-9 codes 556.0-556.3, 556.5, 556.6, and 556.9. Approved by National Pharmacy & Therapeutics Committee on 8/11/2009. Policy 2009D0026D archived.
4/16/2009	Policy updated. Approved by National Pharmacy & Therapeutics Committee on 2/12/2009. Policy 2008D0026C archived.
4/4/2008	Policy update. Approved by National Pharmacy & Therapeutics Committee on 1/22/2008. Policy 2006D0026B archived.
1/3/2008	Code J2323 added to policy as directed by Manager of Coding and Integrity. Q4079 expired per CMS 12/31/2007.
8/8/2006	ICD-9D and HCPCS codes added, per direction from the Reimbursement Medical Policy Operations Manager. Approved 7/11/2006.