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Policy Number: 025.005

Title: Coverage Determination Policy for Tysabri (Natalizumab)

Regions: ☒ **Texas** ☐ **Florida** ☐ **Indiana** ☐ **New Jersey** ☒ **New Mexico**

Impacted Areas:

- ☒ Network Management/Provider Services
- ☐ Member services
- ☐ Quality Management
- ☐ Credentialing
- ☐ IT
- ☐ Administration
- ☐ Compliance/delegation
- ☒ Utilization Management
- ☐ Case management
- ☐ Disease management
- ☒ Claims
- ☐ Human resources
- ☐ Finance
- ☒ Pharmacy
- ☐ ALL

Available LCD/NCD/LCA: None

Disclaimer:

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Doctors helping patients for more than 25 years

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Coverage Policy Number: 025.005

Line of Business: Medicare Part B

Policy Type: Prior Authorization

Coverage Determination:

*The following criteria are applicable to **ALL** indications:*

- *Tysabri should NOT be initiated in patients with a history of or active progressive multifocal leukoencephalopathy (PML)*
- *Patients should be tested for JC virus before use and during therapy*

Initial/New Requests

Tysabri is medically necessary for inducing and maintaining clinical response and remission in patients with **moderate to severe Crohn's disease (CD)** when **ALL** of the following are met:

A. Diagnosis of moderately to severely active Crohn's disease

B. Inadequate response or intolerance to conventional Crohn's disease therapies

i. Conventional Crohn's disease therapies may include aminosalicylates (such as sulfasalazine and mesalamine), corticosteroids, immunomodulators (such as azathioprine, 6-mercaptopurine and methotrexate)

C. Inadequate response or intolerance to inhibitors of TNF-alpha

i. TNF-inhibitors [(e.g., infliximab (Remicade), adalimumab (Humira), or certolizumab pegol (Cimzia)]

D. Tysabri will NOT be used in combination with ANY of the following:

i. Immunosuppressants (e.g., 6-MP, azathioprine, cyclosporine, or methotrexate)

ii. TNF-inhibitors [(e.g., infliximab (Remicade), adalimumab (Humira), or certolizumab pegol (Cimzia)]

E. Tysabri is initiated according to US FDA labeled dosing for Crohn's disease

Tysabri is medically necessary for the treatment of **relapsing forms of Multiple Sclerosis (MS)** when **ALL** of the following are met:

A. Patient has a diagnosis of relapsing forms of MS (e.g., clinically isolated syndrome, relapsing-remitting disease, active secondary progressive disease)

B. Tysabri will NOT be used in combination with ANY of the following (used as monotherapy):

ii. Disease modifying therapy (e.g., interferon beta preparations, glatiramer acetate, fingolimod, cladribine, siponimod, or teriflunomide)

iii. B cell targeted therapy (e.g. rituximab, belimumab, ofatumumab)

iv. Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)

C. Tysabri is dosed according to US FDA labeled dosing

Renewal/Continuation of Therapy Requests

Crohn's Disease: ALL of the following must be met:

- **A.** Patient has previously received treatment with Tysabri
- **B.** Documentation of positive clinical response to Tysabri therapy
- **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)]
- **D.** Tysabri is dosed according to the US FDA labeled dosing

Multiple Sclerosis, Relapsing forms: ALL of the following must be met:

- **A.** Patient has previously received treatment with Tysabri
- **B.** Documentation of positive clinical response to Tysabri therapy
- **C.** Patient is NOT receiving Tysabri in combination with ANY of the following (used as monotherapy):
    - i. Disease modifying therapy (e.g., interferon beta preparations, glatiramer acetate, fingolimod, cladribine, siponimod, or teriflunomide)
    - ii. B cell targeted therapy (e.g., rituximab, belimumab, ofatumumab)
    - iii. Lymphocyte trafficking blockers (e.g., alemtuzumab, mitoxantrone)
- **D.** Tysabri is dosed according to the US FDA labeled dosing

FDA Approved Dose and Indication

FDA approved indications	Approved Dosing
Crohn's disease (Moderate to Severe)	300mg IV every 4 weeks
Multiple sclerosis, Relapsing forms	300mg IV every 4 weeks

General Background

Tysabri® is a recombinant humanized IgG4-kappa monoclonal antibody which prevents transmigration of leukocytes across the endothelium into the inflamed parenchymal tissue by binding to the alpha-4-subunit of alpha-4-beta-1 and alpha-4-beta-7 integrins on the surface of all leukocytes (except neutrophils) and inhibits the alpha 4-mediated adhesion of leukocytes to their counter-receptors. It blocks the molecular interaction of alpha 4 beta 1-integrin with vascular cell adhesion molecule-1(VCAM-1) on activated vascular endothelial cells, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) on vascular endothelial gastrointestinal cells, and with connecting segment-1 (CS-1). In vivo, Tysabri may also inhibit the interaction of alpha-4 integrin antibodies and ligands extracellularly and on parenchymal cells, inhibiting continued recruitment and inflammatory activity of activated immune cells. The specific mechanisms that Tysabri acts to mitigate disease in Crohn disease and multiple sclerosis are not fully defined. Its clinical effects in Crohn disease may be due to blockade of molecular interactions of the alpha-4-beta-7 integrin receptor with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) expressed on venular endothelium at inflammatory foci. In multiple sclerosis, Tysabri clinical effects may be due to the interruption of the molecular interaction of alpha-4-neta-1 integrin expressed by inflammatory cells with vascular cell adhesion molecule-1 (VCAM-1) on vascular endothelial cells and with connecting segment-1 (CS-1) or osteopontin expressed by brain parenchymal cells.

Tysabri is indicated for inducing and maintaining clinical response and remission among adults with moderately to severely active Crohn disease who have evidence of inflammation and have had an inadequate response to or are unable to tolerate conventional therapies and inhibitors of TNF-alpha; however, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF-alpha.

Tysabri is also indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis (MS).

Black Box Warnings:

Tysabri increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Risk factors for PML include therapy duration, prior immunosuppressant use, and presence of anti-JC virus antibodies. Because of the risk of PML, Tysabri is available only through a restricted distribution program called the TOUCH® Prescribing Program. Patients should be monitored for any new sign or symptom that may be suggestive of PML and interrupt therapy at the first sign or symptom suggestive of PML. For diagnosis, a gadolinium-enhanced MRI scan of the brain and, if indicated, cerebrospinal fluid analysis for JC viral DNA are recommended

Tysabri (Tysabri®) is available only through the TOUCH® Prescribing Program to prescribers, infusion centers, and pharmacies associated with infusion centers registered through the program. Additionally, Tysabri® can only be prescribed to patients who are enrolled in and meet all the requirements of the program.

Clinical Evidence

Crohn's disease

Tysabri was effective in inducing response and maintaining remission at weeks 8 through 12 among patients with moderately to severely active Crohn disease and C-reactive protein elevation. The Efficacy of Tysabri in Crohn's Disease Response and Remission (ENCORE) trial (n=509) was a global, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial. Adults (41% male, mean age 38 years) with at least 6 months history of moderately to severely active Crohn disease were randomized to receive 3 intravenous infusion of Tysabri 300 mg (n=259) or placebo (n=250) at weeks 0, 4, and 8; with follow-up through week 12. Patients were required to have baseline Crohn's Disease Activity Index (CDAI) scores between 220 to 450 points (with higher scores indicating more severe disease activity), and active inflammation characterized by elevated C-reactive protein (CRP) concentrations (greater than 2.87 mg/L). Concurrent therapies for Crohn disease were permitted. The primary endpoint was the proportion of participants achieving a clinical response at weeks 8 and 12, defined as a reduction in the CDAI score of at least 70 points from baseline; while secondary endpoints evaluated the proportion of participants achieving a clinical remission, defined as a CDAI score of less than 150 at both weeks 8 and 12, and those in response or remission at week 12. The study met the primary endpoint in a statistically greater proportion of Tysabri-treated patients achieving clinical response relative to placebo-treated individuals (48% vs 32%; difference, 16%; 95% confidence interval (CI), 7% to 24%; p less than 0.001) at week 8 sustained through week 12. Similarly, a larger proportion of patients treated with Tysabri achieved remission compared with those treated with placebo at weeks 8 through 12 (26% vs 16%; difference, 10%; 95% CI, 3% to 18%; p=0.002). At week 12, clinical response was sustained in 60% Tysabri-treated patients and 44% placebo-treated patients (p less than 0.001), while remission occurred among 38% and 25% patients in the respective treatment group (p=0.001). Treatment benefits were evident at week 4 following the initial infusion, with the greatest improvement in CDAI score observed at week 12 (4 weeks after completion of 3 infusions) (-118 Tysabri vs -68 for placebo; p less than 0.001). The median time to clinical response was 31 days (95% CI, 30 to 56 days) for Tysabri-treated patients compared with 57 days (95% CI, 57 to 64 days) (p less than 0.001). The serum CRP concentrations improved from a mean baseline value of 23 mg/L to 15 mg/dL among patients treated with Tysabri, but worsened from 23.4 mg/L to 24.7 mg/L for those treated with placebo at week 12 (p less than 0.001 compared with placebo). Tysabri was associated with higher incidence of headache (29% vs 21%; p less than 0.05), nausea (15% vs 12%), abdominal pain (12% vs 9%), nasopharyngitis (11% vs 6%; p less than 0.05), infection (35% vs 30%), hypersensitivity reaction (4% vs less than 1%; p less than 0.05), and development of anti-Tysabri antibodies (9.5% vs less than 1%; p less than 0.05) compared with placebo. In contrast, exacerbation of Crohn’s disease occurred more frequently with placebo than with Tysabri (6% vs 3%; p less than 0.05).

Multiple sclerosis, Relapsing forms

According to an analysis of a large prospective observational cohort, second-line therapy with Tysabri was more effective than fingolimod for patients with relapsing-remitting MS previously treated with either interferon beta or glatiramer acetate (N=578). Tysabri was associated with a significantly greater drop from baseline in the annualized relapse rate (1.5 to 0.2 relapses/year vs 1.3 to 0.4 relapses/year), and the rate of sustained disability regression was 2.8 times higher compared with fingolimod. However, there was no difference between treatment groups for the rate of sustained disability progression.

Tysabri significantly reduced relapse rate (1-year, 21.1% vs 30.4%; 2-year, 30.9% vs 41.7%) and development of new gadolinium-enhancing (1-year, 9.3% vs 29.8% year; 2-year, 9.1% vs 22.1%) and T2 lesions (1-year, 10.6% vs 29.6%; 2-year, 16.9% vs 34.1%) on MRI, compared with fingolimod in an observational study (N=629). Approximately 12% of the patients were treatment naive, 84% had 1 or more relapse and 42% had 2 or more relapses in the year prior to Tysabri or fingolimod initiation. There was no difference between treatments for the rate of disability progression.

Second-line Tysabri significantly reduced the annualized relapse rate from baseline (1.5 to 0.2 relapses/year vs 1.3 to 0.4 relapses/year), and the rate of sustained disability regression was 2.8 times higher, compared with fingolimod in another observational study over a mean follow-up of 12 months in patients previously treated with either interferon beta or glatiramer acetate (N=578). There was no difference between treatment groups for the rate of sustained disability progression.

NOTE: Vitamin D supplementation in vitamin D insufficient, relapsing-remitting MS patients is associated with increased 25-hydroxyvitamin D (25(OH)D) levels and has been shown to decrease rate of relapse.

HCPCS Code

HCPCS Code	Description
J2323	Tysabri injection, 1mg

Dosage Form & Route of Administration	
20mg/ml solution	IV

Diagnosis Codes

Diagnosis Code	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

Acronyms

TNF-alpha = Tumor Necrosis Factor alpha

CDAI=Crohn's Disease Activity Index

6-MP = Mercaptopurine

CS-1 = Connecting Segment-1

VCAM-1 = Vascular Cell Adhesion Molecule-1

MAdCAM-1 = Mucosal Addressin Cell Adhesion Molecule-1

MS = Multiple Sclerosis

PML = Progressive Multifocal Leukoencephalopathy

REMS = Risk Evaluation and Mitigation Strategy

NCD = National Coverage Determination

LCD = Local Coverage Determination

JC = (John Cunningham)

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