natalizumab (Tysabri®)

Policy # 00156
Original Effective Date: 09/20/2006
Current Effective Date: 02/12/2024

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Multiple Sclerosis

Based on review of available data, the Company may consider natalizumab (Tysabri®)‡ for the treatment of adult patients with relapsing forms of multiple sclerosis (MS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for the use of natalizumab (Tysabri) for the treatment of patients with relapsing multiple sclerosis (MS) will be considered when ALL of the following criteria are met:

- Patient is an adult with a diagnosis of relapsing multiple sclerosis (i.e., clinically isolated syndrome, relapsing remitting disease, or active secondary progressive disease); AND
- Physician is enrolled in the Tysabri Outreach Unified Commitment to Health (TOUCH®)‡ prescribing program must prescribe medication; AND
- Tysabri is used as monotherapy for relapsing multiple sclerosis (MS).

Crohn's Disease

Based on review of available data, the Company may consider natalizumab (Tysabri) for the induction and maintenance of clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of natalizumab (Tysabri) for the treatment of patients with Crohn's disease (CD) will be considered when ALL of the following criteria are met:

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- Patient is an adult with a diagnosis of moderately to severely active Crohn's disease (CD) with evidence of inflammation; AND
- Patient must have had an inadequate response to, or are unable to tolerate conventional Crohn's disease (CD) therapies such as corticosteroids, 6 mercaptopurine (6MP) or azathioprine AND tumor necrosis factor alpha (TNF- α) inhibitors, such as Humira®‡ or Remicade®‡; AND
- A physician who is enrolled in the Tysabri Outreach Unified Commitment to Health (TOUCH) prescribing program must prescribe medication; AND
- Tysabri is not used in combination with immunosuppressants (e.g. 6 mercaptopurine (6MP), azathioprine, cyclosporine, methotrexate) or inhibitors of TNF-α (e.g. Humira, Remicade) in Crohn's disease (CD).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of natalizumab (Tysabri) when the above listed patient selection criteria are not met to be **investigational.***

Background/Overview

Tysabri is a recombinant monoclonal antibody that is administered every four weeks via intravenous (IV) infusion. The recommended dose is 300 mg by an IV infusion in 100 mL 0.9% sodium chloride over approximately one hour, every four weeks. It is known as an alpha-4 integrin antagonist and belongs to a new selective adhesion molecule (SAM) inhibitor class. Tysabri is indicated as monotherapy for the treatment of patients with relapsing forms of MS. Tysabri is also 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 Crohn's disease therapies and inhibitors of TNF-alpha. It should not be used in combination with other immune system modifying drugs such as interferon beta-1a (Avonex®)‡ because concomitant exposure to these therapies is associated with increased risk for progressive multifocal leukoencephalopathy (PML). Tysabri should also not be used in combination with inhibitors of TNF-alpha.

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Tysabri carries a boxed warning for PML, an opportunistic viral infection that affects the brain and can lead to death or severe disability. Other serious adverse events that have occurred in Tysabri-treated patients include hypersensitivity reactions, such as anaphylaxis and liver injury. Serious opportunistic and other atypical infections have been observed in patients receiving immunosuppressants while on Tysabri, and Tysabri should generally not be used in patients receiving immunosuppressants. Serious herpes infections have also been observed. Common side effects include headache, fatigue, infusion reactions, urinary tract infections, joint and limb pain and rash. Because of these risks, patients, prescribers, pharmacies, and infusion centers must all be enrolled in TOUCH and agree to comply with the company's strict monitoring guidelines. Additionally, they must participate in an extensive educational program designed to inform people about the risks of Tysabri treatment. Tysabri is administered intravenously by trained professionals at infusion centers.

Multiple Sclerosis
Multiple sclerosis is believed to have an immunologic mechanism that is characterized by demyelination in the brain and spinal cord. This is often expressed by symptoms such as visual and oculomotor abnormalities, weakness, urinary dysfunction, and mild cognitive impairment. Often patients will experience remissions and exacerbations. Treatment can include corticosteroids for acute exacerbations and immunomodulatory (disease modifying) drugs to prevent exacerbations. Disease modifying drugs include oral products such as Gilenya®‡, Mayzent®‡, Tecfidera®‡, and Aubagio®‡; subcutaneous and intramuscular injectable products such as Copaxone®‡, Avonex, Rebif®‡, Extavia®‡, Betaseron®‡, and Plegridy®‡; and intravenous infusions such as Ocrevus®‡, Tysabri, Mavenclad®‡, and Lemtrada®‡.

Crohn’s Disease
Crohn's disease is a chronic, inflammatory bowel disease that affects both men and women. There is no cure. Crohn's can cause diarrhea, fever, rectal bleeding, malnutrition, narrowing of the intestinal tract, obstructions, abscesses, cramping and abdominal pain. The disease also can lead to abnormal connections (fistulas) leading from the intestine to the skin or internal organs. Its cause is unknown. There are more than one million people with CD worldwide.

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FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA on June 5, 2006 approved an application for resumed marketing of natalizumab (Tysabri) with a special restricted distribution program. Tysabri is a monoclonal antibody for the treatment of patients with relapsing forms of MS. Tysabri is indicated for use as monotherapy because we do not know enough about how its use with other immune modifying drugs could impact risk. A labeling change in December of 2013 removed wording that recommends the use of the drug after the patient has tried alternate therapies for multiple sclerosis. A label change in August 2019 clarified that relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

Tysabri was initially approved by the FDA in November 2004, but was withdrawn by the manufacturer in February 2005 after three patients in the drug's clinical trials developed PML, a serious viral infection of the brain. FDA then put clinical trials of the drug on hold in February 2005, allowing them to resume a year later after confirming that there were no additional cases of PML. In March 2006, FDA consulted its Advisory Committee on drugs for peripheral and central nervous systems about the possibility of making Tysabri available to appropriate MS patients. The Advisory Committee recommended a risk-minimization program with mandatory patient registration and periodic follow-up. In response, the manufacturer, Biogen-Idec, submitted to the agency a Risk Management Plan to help ensure safe use of the product. Tysabri is available only through the Risk Management Plan, called the TOUCH Prescribing Program. In order to receive Tysabri, patients must talk to their doctor and understand the risks and benefits of Tysabri and agree to all of the instructions in the TOUCH Prescribing Program.

The FDA has approved Tysabri (natalizumab) in January 2008 for the treatment of moderate-to-severe CD in patients with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies. CD patients using the drug must be enrolled in a special restricted distribution program called the Crohn's Disease–Tysabri Outreach Unified Commitment to Health (CD TOUCH) Prescribing Program.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration

approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Multiple Sclerosis
Natalizumab's efficacy in MS was assessed in two, two-year, randomized, double blind and placebo-controlled studies. Both trials included MS patients who had at least one relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between zero and 5.0. Neurological evaluations were done every 12 weeks at the time of suspected relapse. Magnetic resonance imaging evaluations were done annually. In both trials, the primary endpoint at two years was the time to onset of sustained increase in disability, defined as a ≥ 1.0 point increase on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5 point increase on the EDSS from baseline EDSS = 0 that was sustained for 12 weeks.

In the first trial patients had not received any interferon beta or glatiramer acetate for at least six months prior and most patients (94%) had never received these agents. In a 2:1 ratio, patients were randomized to receive natalizumab 300mg IV or placebo every four weeks for up to 28 months. The average patient age and disease duration were 36 years and five years, respectively. Sixty-seven percent of patients had EDSS scores ≤ 2.5. After two years of follow-up, there was a 67% reduction in the relapse rate for those given natalizumab. A greater percentage of patients given natalizumab were relapse-free (67%) compared with placebo (41%) at two years. The percentage of patients with a sustained increase in disability was less with natalizumab (17%) compared with placebo (29%), representing a 42% relative risk reduction. MRI endpoints were favorable with natalizumab as the number of new or enlarging lesions detected by T_2-weighted MRI over two years was reduced by 83% as compared with placebo. Over two years, no new or enlarging lesions developed in 57% of patients in the natalizumab group compared with 15% given placebo. A reduced percentage given natalizumab displayed three or more new or enlarging lesions (18%) compared with placebo (68%). Lesions detected by Gd-enhanced MRI were absent in 97% of patients given natalizumab compared with 72% in the placebo group at two years.

In the second trial, MS patients who had experienced one or more relapses while receiving interferon beta-1a (Avonex) 30 mcg intramuscularly (IM) once a week during the year prior were randomized to receive natalizumab 300 mg IV or placebo every four weeks for up to 28 months, while continuing therapy with interferon beta-1a. The average patient age was 39 years and the median disease

duration was seven years. Sixty-five percent of patients had EDSS scores ≤ 2.5. This study ended one month early due to two reports of PML. After a median follow-up of 120 months, use of natalizumab with interferon beta-1a led to a 56% relative reduction in the annualized relapse rate compared with placebo plus interferon beta-1a.The percentage of patients who remained relapse-free was greater for those given natalizumab and interferon beta-1a (54%) compared with placebo plus interferon beta-1a (32%). There was a 24% relative risk reduction in sustained disability progression with natalizumab plus interferon beta-1a (23%) compared with placebo and interferon beta-1a (29%). Magnetic resonance imaging data was also positive for natalizumab in that after 120 months, the percentage of patients with no new or newly enlarging lesions was greater for those given natalizumab and interferon beta-1a (67%) compared with placebo plus interferon beta-1a (30%). The number of new or enlarging lesions over the two years was reduced by 83% with combination therapy.

Crohn's Disease
Induction of clinical response (defined as ≥70-point decrease in CDAI [Crohn's Disease Activity Index] from baseline) was evaluated in two studies. In Study CD1, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. Clinical results were assessed at Week 10, and patients with incomplete information were considered as not having a clinical response. At Week 10, 56% of the 717 patients receiving Tysabri were in response compared to 49% of the 179 patients receiving placebo (treatment effect: 7%; 95% confidence interval (CI): [-1%, 16%]; p=0.067). In the second study, CD2, only patients with elevated CRP were studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg Tysabri or placebo. In Study CD2, in contrast to Study CD1, clinical response and clinical remission (defined as CDAI score <150) were required to be met at both Weeks 8 and 12, rather than at a single time-point; patients with incomplete information were considered as not having a response. In terms of clinical response at weeks 8 and 12: 48% of patients in the Tysabri group had a clinical response vs. 32% in the placebo group. In terms of clinical remission at weeks 8 and 12: 26% of patients in the Tysabri group had a clinical remission vs. 16% in the placebo group. Both of these showed a significant difference.

Maintenance therapy was evaluated in Study CD3. In this study, 331 patients from Study CD1 that had had a clinical response to Tysabri at both Weeks 10 and 12 were re-randomized 1:1 to treatment with continuing monthly infusions of either 300 mg Tysabri or placebo. Maintenance of response was assessed by the proportion of patients who did not lose clinical response at any study visit for

an additional 6 and 12 months of treatment (i.e., Month 9 and Month 15 after initial treatment with Tysabri). The study also assessed the proportion of patients who did not lose clinical remission at any study visit within the subset of those who were in remission at study entry. Requiring maintenance of response or remission at each visit, as opposed to just at Month 9 or Month 15, may result in lower proportions meeting endpoint criteria, and may make a comparison of these results with those of other products used to treat CD misleading. In terms of the maintenance of clinical response through month 9: 61% of the patients in the Tysabri group maintained a clinical response vs. 29% of patients in the placebo group (statistically significant). At month 15, 54% in the Tysabri group had maintained a response vs. 20% in the placebo group. In terms of maintenance of a clinical remission through month 9: 45% of patients in the Tysabri group maintained a clinical remission through month 9 vs. 26% of those in the placebo group (statistically significant). At month 15, 40% of patients in the Tysabri group maintained a clinical remission vs. 15% of those in the placebo group.

References

1. American Society of Health-System Pharmacists. AHFS Drug Information 2008. Natalizumab.
2. Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER). Drug Information. Natalizumab (Tysabri) Information. Last updated 1/20/2012.
3. Polman, Chris et al. A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis. N Engl J Med 2006; 354:899-910.
4. Rudick, Richard et al. Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis. N Engl J Med 2006; 354:911-23.
5. Tysabri [Package Insert]. Biogen Idec. Cambridge, MA. Updated 8/2019.

Policy History

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09/06/2006	Medical Director review
09/20/2006	Medical Policy Committee approval
12/12/2007	Medical Director review
12/19/2007	Medical Policy Committee approval
03/12/2008	Medical Director review

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03/19/2008	Medical Policy Committee approval. Added new FDA information. Tysabri is now eligible for Crohn's disease patients with criteria.
03/04/2009	Medical Director review
03/18/2009	Medical Policy Committee approval. Added FDA Black Box Warning to FDA section. No change to coverage eligibility.
03/05/2010	Medical Director review
03/19/2010	Medical Policy Committee approval. No change to coverage.
03/03/2011	Medical Policy Committee review
03/16/2011	Medical Policy Implementation Committee approval. No change to coverage.
03/01/2012	Medical Policy Committee review
03/21/2012	Medical Policy Implementation Committee approval. No change to coverage.
03/07/2013	Medical Policy Committee review
03/20/2013	Medical Policy Implementation Committee approval. Clarified patient selection criteria to say adult for MS and CD (it said it in the intro and is on the call tree already). Removed Note saying that it is used only as monotherapy and replaced that with patient selection criteria for both CD and MS. Cleaned up the When Services Are Considered Investigational section to make it easier to read and to capture it all in one sentence.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Changed wording for MS to include failure of the newer oral agents as these agents are new. Changed wording in CD to match Call tree. Updated background, rationale/source.
01/09/2014	Medical Policy Committee review
01/15/2014	Medical Policy Implementation Committee approval. Removed the requirement that the patient try an alternative MS therapy prior to Tysabri to coincide with the new wording in the package insert.
01/08/2015	Medical Policy Committee review
01/21/2015	Medical Policy Implementation Committee approval. No change to coverage.
01/07/2016	Medical Policy Committee review
01/22/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
01/05/2017	Medical Policy Committee review
01/18/2017	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2018	Medical Policy Committee review

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01/17/2018	Medical Policy Implementation Committee approval. No change to coverage.
01/10/2019	Medical Policy Committee review
01/23/2019	Medical Policy Implementation Committee approval. No change to coverage.
01/03/2020	Medical Policy Committee review
01/08/2020	Medical Policy Implementation Committee approval. Updated background information to reflect current practice for multiple sclerosis and updated indication to include the FDA clarification of the definition of relapsing disease.
01/07/2021	Medical Policy Committee review
01/13/2021	Medical Policy Implementation Committee approval. No change to coverage.
01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. No change to coverage.
01/05/2023	Medical Policy Committee review
01/11/2023	Medical Policy Implementation Committee approval. No change to coverage.
01/04/2024	Medical Policy Committee review
01/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 01/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not

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contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.
Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J2323
ICD-10 Diagnosis	All related Diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment,

would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.