09-J0000-73

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Subject: Natalizumab (Tysabri®) IV

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DESCRIPTION:

Natalizumab (Tysabri®) is Food and Drug Administration (FDA) approved for the treatment of moderately to severely active Crohn's disease (CD) and relapsing forms of multiple sclerosis (MS) to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. Natalizumab is a humanized monoclonal antibody that binds to alpha-4 integrin expressed on the surface of activated T-cells. Alpha-4 integrin is a selective adhesion molecule that facilitates adhesion and subsequent leukocyte migration into areas of inflammation. Pre-clinical data has demonstrated the benefits of integrin inhibition, including mucosal healing and a reduction of inflammation. Leukocyte adhesion in endothelial cells is a multistep process that involves chemokine receptors and active integrins. Ultimately, natalizumab blocks both alpha-4 subunit of alpha-4 beta-1 (vascular cellular adhesion molecule of VCAM-1) and alpha-4 beta-7 (mucosal addressin [MAD] CAM-1). The site of action is not organ specific and other sites such as the brain, bone marrow, and kidneys are affected. This has led to studies of natalizumab in diverse chronic inflammatory diseases including MS and CD.

Multiple sclerosis (MS) is a chronic disease affecting the central nervous system (CNS). It is characterized by triad of inflammation, demyelination, and scarring of the central nervous system and manifests as pathological (immune-mediated CNS demyelination and axonal injury) and clinical (exacerbations, disability progression) dissemination in time and space. Although the clinical course of the disease is capricious, MS has been categorized into four types: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), secondary progressive (SPMS), and primary progressive (PPMS).The most common type is RRMS, which is characterized by acute attacks followed by periods of remission. An initial attack may present as a clinically isolated syndrome (CIS); individuals presenting with this syndrome are high

risk for subsequent conversion to clinically definite MS (CDMS) when coupled with MRI lesions consistent with MS. Although a cure for MS remains elusive, several treatment options slow the progression of the disease and reduce the frequency of relapses.

In 2018, the American Academy of Neurology published a practice guideline on the use of disease-modifying therapy for adults with multiple sclerosis which includes an assessment of the effectiveness and safety of natalizumab in the treatment of MS. Natalizumab has demonstrated a reduction in measures of disease activity including clinical relapse rate, new and enlarging T2 lesions, and disability progression in patients with relapsing MS. Natalizumab has also shown a reduction in relapses and MRI measures in a sub-group analysis in patients with highly active disease. The guideline discusses increased risk of developing PML in natalizumab-treated patients for patients receiving 2 years or more of treatment, prior use of immunosuppressants, and patients testing positive for anti-John Cunningham virus (JCV) antibodies. Continued monitoring of anti-JCV antibodies is recommended every 6 months to enable early detection of transition to JCV antibody-positive status. Alternative disease-modifying therapy is encouraged for patients who become JCV antibody positive, and the JCV index and patient history is utilized to assist with risk assessment. The guideline recommends against combination therapy (e.g., natalizumab with additional disease modifying therapy), due to safety concerns associated with use.

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract and can manifest as focal or patchy inflammation confined to the bowel wall or result in complications such as fistulas or strictures. Similar to MS, a definitive cure for CD has not been established. The goals of CD therapy are to induce and maintain remission, improve quality of life and prevent complications that may occur. Treatment options are individualized and target disease location, behavior and severity. Tumor necrosis factor (TNF) alpha antagonists have been considered the mainstay in the management of CD. Natalizumab is the first non-TNF alpha antagonist approved for the treatment of CD. It represents an important option for individuals who are intolerant or have lost efficacy to all other treatments including immune modulators and TNF alpha inhibitors. Guidelines from the American College of Gastroenterology recommend use of natalizumab only if anti-JCV antibody is negative and recommend retesting every 6 months.

POSITION STATEMENT:

Site of Care: If natalizumab (Tysabri) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46: Site of Care Policy for Select Specialty Medications.

Initiation of natalizumab **meets the definition of medical necessity** when administered for the following conditions when **ALL** indication-specific criteria are met:

A. Multiple Sclerosis (MS)
    1. Member is diagnosed with **ONE** of the following
        a. Relapsing-remitting MS [RRMS]
        b. Active secondary-progressive MS [SPMS]

c. First clinical episode and member has MRI features consistent with MS

2. Natalizumab will **NOT** be used in combination with **ANY** of the following:
    a. Alemtuzumab (Lemtrada)
    b. Cladribine (Mavenclad)
    c. Dimethyl fumarate (Tecfidera)
    d. Diroximel fumarate (Vumerity)
    e. Fingolimod (Gilenya, Tascenso ODT)
    f. Glatiramer acetate (Copaxone, Glatopa)
    g. Interferon beta-1a (Avonex, Rebif)
    h. Interferon beta-1b (Betaseron, Extavia)
    i. Mitoxantrone (Novantrone)
    j. Monomethyl fumarate (Bafiertam)
    k. Ocrelizumab (Ocrevus)
    l. Ofatumumab (Kesimpta)
    m. Ozanimod (Zeposia)
    n. Peg-interferon beta-1a (Plegridy)
    o. Ponesimod (Ponvory)
    p. Rituximab (Rituxan or biosimilars)
    q. Siponimod (Mayzent)
    r. Teriflunomide (Aubagio)
    s. Ublituximab (Briumvi)
3. Natalizumab will be used as monotherapy
4. The dose does not exceed 300 mg every 28 days

B. Crohn's Disease
1. Member's disease is moderately to severely active
2. Member has tested negative for anti-JCV antibodies in the past 6 months
3. Member has an inadequate response to or has a contraindication to **ONE** or more conventional therapies (e.g., sulfasalazine, mesalamine products, aminosalicylate, corticosteroids, immunosuppressants [6-mercaptopurine], azathioprine, methotrexate)
4. Member has an inadequate response to or has a contraindication to **ONE** or more tumor-necrosis factor (TNF)-antagonists (e.g., adalimumab [Humira], infliximab [Remicade], certolizumab [Cimzia])
5. Natalizumab will be used as monotherapy
6. The dose does not exceed 300 mg every 28 days

Approval duration: 1 year

Continuation of natalizumab therapy **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with **EITHER** of the following:
    a. RRMS, active SPMS or clinically isolated syndrome
    b. Moderately to severely active Crohn's disease
2. Member has demonstrated a beneficial response to therapy
3. Member has been tested for anti-JCV antibodies in the past 6 months
4. Authorization/reauthorization for natalizumab has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member previously met all indication-specific initiation criteria
5. Natalizumab will be used as monotherapy
6. The dose does not exceed 300 mg every 28 days

Approval duration: 1 year

Natalizumab IV **does not meet the definition of medical necessity** when administered for all other indications as there is insufficient clinical evidence to support its use, and specifically for the following:

Natalizumab for chronic progressive multiple sclerosis.

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-Approved: Natalizumab is approved as monotherapy for the treatment of patients with relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. Physicians should consider whether the expected benefit is sufficient to offset the risk of developing progressive multifocal leukoencephalopathy (PML).

Additionally, natalizumab is approved in adult patients for the treatment of moderately to severely active CD to induce and maintain clinical response and remission in members with evidence of inflammation who have had an inadequate response to or are unable to tolerate conventional Crohn's disease therapies and TNF-alpha inhibitors. Natalizumab should not be used in combination with immunosuppressants or TNF-alpha inhibitors.

Natalizumab should be administered as a 300 mg intravenous (IV) infusion given over 1 hour every 4 weeks. It should not be administered as an IV bolus or IV push.

Natalizumab should be administered within 8 hours of preparation.

Members should be observed during the infusion and post-infusion for the first 12 infusions for one hour after the infusion is complete. For patients without evidence of hypersensitivity reaction, observe post-infusion according to clinical judgement for the 13th and subsequent infusions.

Note: In CD, discontinue natalizumab therapy in members that have not experienced therapeutic benefit by 12 weeks of induction therapy, and in members that cannot discontinue chronic concomitant steroids within six months of starting therapy.

Recommended Dose Adjustments: At this time, dosage adjustments for renal and hepatic impairment are not indicated and it appears that no dosage adjustments are required. Natalizumab has not been adequately studied in members less than 18 years of age or over the age of 65. Natalizumab is not indicated for use in pediatric members.

Concomitant therapy: Do not use with concomitant immunosuppressants (eg, azathioprine, cyclosporine, methotrexate, 6-mercaptopurine) or concomitant inhibitors of TNF-alpha. Aminosalicylates may be continued during treatment with natalizumab.

Drug Availability: Natalizumab is available as a concentrated solution that must be diluted prior to IV infusion. The injection is supplied as a 300 mg natalizumab in 15 mL (20 mg/mL) in a sterile, single-use, preservative-free vial.

Note: Natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Only prescribers, patients, and infusion centers enrolled in the TOUCH Prescribing Program can prescribe, receive, and infuse natalizumab. Contact the TOUCH Prescribing Program by phone (1-800-456-2255). Additional information on the TOUCH Prescribing Program is located online at www.TOUCHprogram.com

PRECAUTIONS:

Boxed Warning

Natalizumab increases the risk of PML, an opportunistic viral infection of the brain that usually leads to death or severe disability.

Members should be closely monitored and natalizumab therapy should be withheld immediately at the first sign or symptom suggestive of PML.

An MRI scan should be obtained prior to natalizumab therapy initiation.

Treatment duration, prior immunosuppressant use, and presence of anti-JC virus antibodies are associated with increased risk of PML.

Because of the increased risk of PML, natalizumab is available only through a special restricted distribution program called the TOUCH Prescribing Program and must be administered only to members enrolled in this program.

CONTRAINDICATIONS

Natalizumab is contraindicated in members who have or have had progressive multifocal leukoencephalopathy (PML) and in members who have had a hypersensitivity reaction to natalizumab.

Warnings/Precautions

Herpes infections: Natalizumab increases the risk of developing encephalitis and meningitis by herpes simplex and varicella zoster viruses.: Life-threatening and fatal cases have occurred. Acute retinal necrosis has also occurred that can result in blindness. Discontinue and treat appropriately.

Hypersensitivity reactions: The use of natalizumab has been associated with serious hypersensitivity reactions (incidence <1%). Most reactions occur within two hours of the start of the infusion and symptoms often include urticarial, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Patients experiencing hypersensitivity should not be re-challenged.

Immunosuppression/Infection: Natalizumab therapy may increase the risk of infection. The most common types observed in clinical trials were pneumonia, urinary tract infection, gastroenteritis, vaginal infection, tonsillitis, and herpes infection.

Pregnancy and Nursing:

> There is a lack of well-controlled trials of natalizumab in pregnant women. There is potential for fetal harm based on animal studies.Natalizumab is excreted in human breast milk. Due to unknown potential for effects of exposure in the infant, the risk and benefit of breastfeeding and treatment with natalizumab should be considered.

Hepatotoxicity: Significant liver injury, including liver failure requiring transplant has occurred. Natalizumab has been associated with reports of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, which occurred as early as six days following initiation of therapy. Natalizumab should be discontinued in patients with jaundice or evidence of liver injury.

Thrombocytopenia: Monitory for bleeding abnormalities and discontinue in patients with thrombocytopenia.

BILLING/CODING INFORMATION:

The following codes may be used to describe natalizumab therapy:

HCPCS Coding

J2323	Injection, natalizumab, 1mg

ICD-10 Diagnosis Codes That Support Medical Necessity

G35	Multiple sclerosis
K50.00 – K50.919	Crohn's disease (regional enteritis)

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Clinically isolated syndrome (CIS): the first clinical presentation of disease that shows characteristics of inflammatory demyelination that could be MS but has yet to fulfill criteria of dissemination in time.

Progressive multifocal leukoencephalopathy (PML): an opportunistic viral infection of the brain that usually leads to death or severe disability.

Primary-progressive multiple sclerosis (PPMS): Steadily progressive course from onset; occurs in 10-15% of patients with MS.

Relapsing-remitting multiple sclerosis (RRMS): Characterized by acute attacks followed by periods of remission; primary form of MS that occurs in approximately 85% of patients.

Secondary-progressive multiple sclerosis (SPMS): An initial period of RRMS, followed by a steadily progressive course, with acute relapses (active disease) or without acute relapses (not active disease); 75-85% of patients diagnosed with RRMS will transition to SPMS.

RELATED GUIDELINES:

Alemtuzumab (Lemtrada), 09-J2000-27

Adalimumab (Humira®), 09-J0000-46

Certolizumab Pegol (Cimzia®), 09-J0000-77

Cladribine (Mavenclad), 09-J3000-34

Dalfampridine (Ampyra™) Oral, 09-J1000-23

Dimethyl Fumarate (Tecfidera), Diroximel fumarate (Vumerity), and Monomethyl fumarate (Bafiertam), 09-J1000-96

Fingolimod (Gilenya™, Tascenso ODT), 09-J1000-30

Infliximab (Remicade®), 09-J0000-39

Multiple Sclerosis Self Injectable Therapy, 09-J1000-39

Ocrelizumab (Ocrevus®), 09-J2000-78

Ofatumumab (Kesimpta), 09-J3000-84

Ozanimod (Zeposia), 09-J3000-70

Siponimod (Mayzent), 09-J3000-35

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/24.

GUIDELINE UPDATE INFORMATION:

03/15/08	New Medical Coverage Guideline.
09/15/08	Revision to guideline; consisting of revising boxed warnings regarding PML and indication under Position Statement and adding 3 new ICD-9 codes.
03/15/09	Review and revision to guideline; consisting of updating references.
02/15/10	Review and revision to guideline; consisting of revising the boxed warnings and updating references.
02/15/11	Review and revision to guideline; consisting of updating coding and references.

02/15/12	Review and revision to guideline; consisting of updating the position statement, dosage, precautions, coding, related guidelines and references.
10/15/12	Review and revision to guideline; consisting of revision of description section, position statement, and precautions/warnings section; added contraindications section, updated references.
10/15/13	Review and revision to guideline; consisting of revising position statement, updating references, program exceptions, related guidelines and definitions.
01/01/14	Revision to guideline; consisting of updating the position statement.
10/15/15	Review and revision to guideline; consisting of updating position statement, references.
11/01/15	Revision: ICD-9 Codes deleted.
01/01/17	Review and revision to guideline; consisting of updating position statement and references.
05/15/17	Review and revision to guideline; consisting of updating position statement and references.
10/15/17	Review and revision to guideline; consisting of updating position statement and references.
11/15/17	Review and revision to guideline; consisting of updating position statement.
12/15/18	Review and revision to guideline; consisting of updating position statement and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
11/15/19	Review and revision to guideline; consisting of updating description, position statement and references.
01/15/20	Revision to guideline; consisting of updating the position statement.
07/01/20	Revision to guideline; consisting of updating the position statement.
10/01/20	Revision to guideline; consisting of updating the position statement.
03/15/21	Revision to guideline; consisting of updating the position statement.
10/15/22	Review and revision to guideline; consisting of updating agents not used in combination. Updated administration, warnings, and references.
04/15/23	Revision to guideline; consisting of updating the step requirements in the position statement. Updated medications not to be used in combination.
05/15/23	Revision to guideline; consisting of updating the position statement to include generic teriflunomide.
11/15/23	Review and revision to guideline; consisting of updating the position statement to include Glatopa.
07/15/24	Review and revision to guideline; consisting of updating the position statement to remove step requirement.