These Clinical Guidelines have been created using resources that were current as of the "Reviewed" date noted at the beginning of the document. Clinicians should refer to the manufacturer's Prescribing Information (or equivalent) for the most up-to-date information. While CarepathRx has published these Clinical Guidelines after a close review of available literature and a clinical review process, given the evolving nature and complexity of modern pharmaceutical products, CarepathRx does not and cannot warrant or guarantee that these Clinical Guidelines reflect the objectively best or highest standard of care at any given time.

Nothing within these Clinical Guidelines is intended to supersede or interfere with any individual clinician's decision-making or professional judgment with respect to either (1) prescribing or dispensing the drug or product in question or (2) the overall treatment plan for an individual patient.

GUIDELINES FOR IN-HOME INTRAVENOUS NATALIZUMAB (TYSABRI) THERAPY

Section: Clinical Guidelines
Compliance: ACHC Infusion Pharmacy
ACHC Standards:
URAC Standards:
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Effective: 6/1/2023
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Revised:
Approved by, Title and Date Approved: Kathleen Patrick, President, 6/1/2023

I. BACKGROUND

Natalizumab (Tysabri) is a recombinant humanized IgG4-kappa monoclonal antibody that acts as an integrin receptor antagonist. Natalizumab is indicated for the treatment of multiple sclerosis and Crohn's disease in adult patients. Mechanistically, natalizumab 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, natalizumab 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 following outlines the procedures for servicing patients in need of in-home natalizumab infusions.

II. PATIENT ACCEPTANCE CRITERIA

A. All candidates for home care service must be evaluated by the clinician(s) and deemed appropriate to receive home care based upon the dispensing pharmacy's admission criteria. In addition, patients will need enrolled and must comply with the TOUCH® REMS program through their provider.

B. The decision to administer a first dose in the home by an infusion nurse will be determined on a case-by-case basis and reviewed by nursing and pharmacy management. The following criteria will be evaluated:
   a. Prescriber preference
   b. Allergy profile
   c. Age ≥18 years
   d. Other relevant social and/or medical history
   e. No previous short exposure to natalizumab (1 to 2 infusions) followed by an extended period without treatment. These patients re-exposed to natalizumab are at a much higher risk of developing antibodies and/or hypersensitivity reactions

C. Physician orders for natalizumab must include:
   a. Drug and dose

b. Route of administration
c. Frequency of administration
d. Length of observation period. (See Nursing Procedure section for post infusion monitoring observation periods)
e. Emergency medications per protocol
f. Orders for pre-medications, if applicable
g. Line care protocol
h. Routine lab monitoring, if applicable

D. Only prescribers registered in the MS TOUCH® or CD TOUCH® Prescribing Programs may prescribe natalizumab for multiple sclerosis or Crohn's disease respectively. Natalizumab is available through a restricted program under a REMS called TOUCH Prescribing Program because of the risk of PML (Progressive Multifocal Leukoencephalopathy). Prescribers must be certified and comply with the following:
(1) Review the TOUCH® Prescribing Program prescriber educational materials, including the full prescribing information.
(2) Educate patients on the benefits and risks of treatment with natalizumab, ensure that patients receive the Medication Guide, and encourage them to ask questions.
(3) Review, complete, and sign the Patient-Prescriber Enrollment Form.
(4) Evaluate patients three months after the first infusion, six months after the first infusion, every six months thereafter, and for at least six months after discontinuing natalizumab.
(5) Determine every six months whether patients should continue on treatment and, if so, authorize treatment for another six months.
(6) Submit to Biogen the "TYSABRI Patient Status Report and Reauthorization Questionnaire" six months after initiating treatment and every six months thereafter.
(7) Complete an "Initial Discontinuation Questionnaire" when natalizumab is discontinued, and a "6-Month Discontinuation Questionnaire" following discontinuation of natalizumab.
(8) Report cases of PML, hospitalizations due to opportunistic infections, and deaths to Biogen at 1-800-456-2255 as soon as possible.

E. Baseline labs or tests prior to starting therapy

F. Pharmacies and infusion centers must be specifically certified with the TOUCH® program to dispense or infuse natalizumab. During intake process, the clinical pharmacist will be responsible confirming the patient and provider are both enrolled in the TOUCH® program prior to dispensing natalizumab.

G. Dispensing pharmacy treatment protocol for anaphylaxis will be instituted unless a more comprehensive patient-specific orders are provided by physician. See policy NUR012 (Appendix A).

III. PHARMACOLOGY OVERVIEW

***Refer to manufacturer's full Prescribing Information for most up to date information**

A. Indications:

a. Multiple sclerosis: monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults.
b. Crohn's disease: indicated for moderate to severe disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF-α inhibitors. In Crohn's disease, natalizumab should not be used in combination with immunosuppresants or TNF-α inhibitors.

B. Dosage: 300 mg IV over one hour every 4 weeks for both indications
C. Contraindications
a. Hypersensitivity to natalizumab or any component of the product
b. History of or active progressive multifocal leukoencephalopathy

D. Warnings and Precautions
a. **Progressive Multifocal Leukoencephalopathy (PML)**: an opportunistic viral infection of the brain caused by the John Cunningham virus (JCV) that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability, has occurred in patients who have received natalizumab. Three factors are known to increase the risk of PML in natalizumab treated patients have been identified:
(1) The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk of developing PML.
(2) Longer treatment of duration, especially beyond 2 years
(3) Prior treatment with an immunosuppressant (ex: azathioprine, methotrexate, cyclophosphamide)

These factors should be considered in the context of expected benefit when initiating and continuing treatment with natalizumab.

Table 1: Estimated United States Incidence of PML Stratified by Risk Factor

Anti-JCV Antibody Negative	TYSABRI Exposure	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1/10,000	1-24 months	<1/1,000	1/1,000
	25-48 months	2/1,000	6/1,000
	49-72 months	4/1,000	7/1,000
	73-96 months	2/1,000	6/1,000

Notes: The risk estimates are based on postmarketing data in the United States from approximately 100,000 TYSABRI exposed patients.
The anti-JCV antibody status was determined using an anti-JCV antibody test (ELISA) that has been analytically and clinically validated and is configured with detection and inhibition steps to confirm the presence of JCV-specific antibodies with an analytical false negative rate of 3%.

b. **Herpes infections:**
(1) Herpes encephalitis and meningitis: Natalizumab increases the risk of encephalitis and meningitis caused by herpes simplex and varicella zoster viruses. Serious, life-threatening, and sometimes fatal cases have been reported in the post-marketing setting in multiple sclerosis patients receiving natalizumab. Laboratory confirmation in those cases was based on positive PCR for viral DNA in the cerebrospinal fluid. The duration of treatment with natalizumab prior to onset ranged from a few months to

several years. Monitor patients receiving natalizumab for signs and symptoms of meningitis and encephalitis. If herpes encephalitis or meningitis occurs, natalizumab should be discontinued, and appropriate treatment for herpes encephalitis/meningitis should be administered.

(2) Acute Retinal Necrosis (ARN): ARN is a fulminant viral infection of the retina caused by the family of herpes viruses. A higher risk of ARN has been observed in patients being administered natalizumab. Patients presenting with eye symptoms, including decreased visual acuity, redness, or eye pain, should be referred for retinal screening for ARN. Some ARN cases occurred in patients with central nervous system (CNS) herpes infections (e.g., herpes meningitis or encephalitis). Serious cases of ARN led to blindness of one or both eyes in some patients. Following clinical diagnosis of ARN, consider discontinuation of natalizumab. The treatment reported in ARN cases included anti-viral therapy and, in some cases, surgery.

c. **Hepatotoxicity**: Clinically significant liver injury, including acute liver failure requiring transplant, has been reported in patients treated with natalizumab in the post-marketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon re-challenge, providing evidence that natalizumab caused the injury. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Natalizumab should be discontinued in patients with jaundice or other evidence of significant liver injury.

d. **Hypersensitivity/Antibody formation**: Hypersensitivity reactions have occurred in patients receiving natalizumab, including serious systemic reactions (e.g., anaphylaxis), which occurred at an incidence of <1%. These reactions usually occur within two hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to natalizumab. If a hypersensitivity reaction occurs, discontinue administration of natalizumab, and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with natalizumab. Hypersensitivity reactions were more frequent in patients with antibodies to natalizumab compared to patients who did not develop antibodies to natalizumab in both MS and CD studies. Therefore, the possibility of antibodies to natalizumab should be considered in patients who have hypersensitivity reactions. Patients who receive natalizumab for a short exposure (1 to 2 infusions) followed by an extended period without treatment are at higher risk of developing anti-natalizumab antibodies and/or hypersensitivity reactions on re-exposure, compared to patients who received regularly scheduled treatment. Given that patients with persistent antibodies to natalizumab experience reduced efficacy, and that hypersensitivity reactions are more common in such patients, consideration should be given to testing for the presence of antibodies in patients who wish to recommence therapy following a dose interruption. Following a period of dose interruption, patients testing

negative for antibodies prior to re-dosing have a risk of antibody development with re-treatment that is similar to natalizumab naïve patients.

e. **Immunosuppression/Infections**: Natalizumab may increase the risk of infections including pneumonias, urinary tract infections, gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections. Concurrent use of antineoplastic, immunosuppressant, or immune-modulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of natalizumab alone. The safety and efficacy of natalizumab in combination with antineoplastic, immunosuppressant, or immune-modulating agents have not been established. Patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not ordinarily be treated with natalizumab. The risk of PML is also increased in patients who have been treated with an immunosuppressant prior to receiving natalizumab. For patients with Crohn's disease who start natalizumab while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within six months, discontinue natalizumab.

f. **Thrombocytopenia:** Cases of thrombocytopenia, including immune thrombocytopenic purpura (ITP), have been reported with the use of natalizumab in the post-marketing setting. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Delay in the diagnosis and treatment of thrombocytopenia may lead to serious and life-threatening sequelae. If thrombocytopenia is suspected, natalizumab should be discontinued. Cases of neonatal thrombocytopenia, at times associated with anemia, have been reported in newborns within utero exposure to natalizumab. A CBC should be obtained in neonates within utero exposure to natalizumab.

g. **Immunizations**: No data are available on the effects of vaccination in patients receiving natalizumab. No data are available on the secondary transmission of infection by live vaccines in patients receiving natalizumab.

E. Pharmacokinetics
   a. Volume of distribution: 4.5-5.7 L
   b. Elimination half-life: 10- 11 days

F. Adverse Reactions:
   a. Dermatologic: Rash (6-12%)
   b. Gastrointestinal: Abdominal discomfort (11%), diarrhea (10%), gastroenteritis (11%), nausea (17%)
   c. Musculoskeletal: arthralgia (8-19%), pain in limb (16%)
   d. Neurologic: headache (32-38%)
   e. Psychiatric: depression (19%)
   f. Renal: urinary tract infection (3-21%)
   g. Respiratory: lower respiratory tract infection (17%), upper respiratory tract infection (22%)

h. Other: fatigue (10-27%)

G. Drug Interactions: Because of the potential for increased risk of PML and other infections, Crohn's disease patients receiving natalizumab should not be treated with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF-α, and corticosteroids should be tapered in those patients with Crohn's disease who are on chronic corticosteroids when they start natalizumab therapy. Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with natalizumab.

IV. ADMINISTRATION GUIDELINES

A. TOUCH On-Line (www.touchprogram.com) is as Web-based tool designed to maintain compliance with the TOUCH® REMS program. Access and documentation within the portal will be overseen by the authorized pharmacy.

B. A few hours before the scheduled infusion, the home infusion nurse may call the patient to recommend removal of the natalizumab carton from the refrigerator. Advise the patient or caregiver to place them on a surface that is not exposed to direct sunlight.

C. Administration- IV infusions should be given immediately after reconstitution and dilution. Use within 1 hour of preparation per current USP Immediate-Use Guidelines.

D. Duration

a. Multiple Sclerosis: Evaluate at 3 and 6 months after first infusion and every 6 months thereafter to determine whether treatment should be continued for another 6 months.

b. Crohn's Disease: Evaluate 3 and 6 months after first infusion and every 6 months thereafter to determine whether treatment should be continued for another 6 months.

E. Dose Adjustment: No dose adjustments for renal or hepatic impairment

V. NURSING PROCEDURE

A. Supplies may include but are not limited to:

A. Alcohol Swabs
B. Gloves
C. Dressing change kit
D. IV Pole
E. IV Start Kit
F. Peripheral IV catheter (ex. 22 Gauge x1" and 24 Gauge x ¾" for patients needing peripheral access)
G. Port access needle (ex. 22 Gauge x ¾ to 1" safe step for patients with a port)
H. Tape
I. Extension set 8"
J. IV injection cap
K. IV administration set (dial-a-flow or gravity)
L. Syringes (20mL) with needles (20 G x 1")
M. Sharps container
N. TOUCH® Pre-Infusion Checklist
O. Medication Guide

B. Prescription items:

a. Natalizumab drug vials
b. Bag of sodium chloride 0.9% for dilution 100mL

c. 0.9% sodium chloride saline flushes

C. TOUCH® REMS Requirements
   a. A printed copy of the patient instruction letter explaining storage instructions and infusion information.
   b. A printed copy of the *TYSABRI Patient Medication Guide*, which will be included with the **original** shipment for patients to read prior to the infusion.

D. How Supplied:
   a. Natalizumab injection, a sterile, preservative-free, colorless and clear to slightly opalescent solution for dilution prior to intravenous infusion, is supplied as one 300 mg/15 mL (20 mg/mL) single-dose vial per carton (NDC 64406-008-01)
   b. TYSABRI is available only through registered infusion centers or pharmacies participating in the TOUCH® Prescribing Program.

E. Storage and Handling

Vials must be refrigerated between 2°C to 8°C (36°F to 46°F). Do not use beyond the expiration date stamped on the carton and vial label. Do not freeze. Protect from light.

F. Compatibility: Compatible with 0.9% normal saline. No other diluents may be used to prepare natalizumab diluted solution.

G. Procedures:
   a. Explain the reasoning for the visit and use of natalizumab. Drug should **NOT** be prepared until the *Pre-Infusion Patient Checklist* has been successfully completed.
   b. Confirm the patient has read the *TYSABRI Patient Medication Guide* and review the YES/NO questions on the *Pre-Infusion Patient Checklist*:
      (1) Over the past month, have you had any new or worsening medical problems (such as new or sudden changes in your thinking, eyesight, balance, strength, or other problems) that have persisted over several days?
      (2) Do you have a medical condition that can weaken your immune system, such as HIV infection or AIDS, leukemia or lymphoma, or an organ transplant that may suggest that your body is not able to fight infections well?
      (3) In the past month, have you taken medicines to treat cancer or MS or any other medicines that weaken your immune system?
   c. If the patient answers "Yes" to questions 1, 2, or 3, contact the prescriber to review and confirm authorization for infusion.
   d. If the patient answers "No" to questions 1, 2, and 3, or if the home infusion nurse receives authorization from the prescriber to infusion, proceed with natalizumab administration.
   e. Counsel patients on warnings, precautions, and potential side effects including but not limited to: rash, nausea, diarrhea, abdominal pain, headache, risk of infection, PML, hepatotoxicity, hypersensitivity reactions, and thrombocytopenia.
   f. Don gloves.
   g. Establish venous access prior to preparation of drug.

h. Prepare Product
   (1) Visually inspect vials prior to preparation. Natalizumab is a colorless, clear to slightly opalescent solution. Inspect the natalizumab vial for particulate material and discoloration prior to dilution. Do not use the vial if particulates are observed and/or the liquid in the vial is discolored.
   (2) Withdraw 15 mL of natalizumab from the vial using a sterile needle and syringe.
   (3) Inject natalizumab into a 100mL 0.9% sodium chloride bag. Gently invert solution it mix completely. Do not shake.

i. Infusion Rates: administer over approximately 1 hour (~ 5 mg/ minute; 115mL/hr)

j. Post infusion monitoring:
   (1) For patients who have received < 6 natalizumab infusions, observe for 60 minutes.
   (2) For patients who have received $\geq$ 6 consecutive, uninterrupted infusions, confirm with the prescriber whether the post-infusion observation time can be reduced to 30 minutes or should remain 60 minutes.
   (3) For patients who have received 12 infusions without evidence of a hypersensitivity reaction, Bas for the 13th and subsequent infusions for 30 minutes post infusion or per clinical judgement.

k. The *Pre-Infusion Patient Checklist* must be submitted to TOUCH® On-line with 1 business day after the infusion. TOUCH® On-line information may be forwarded to the appropriate authorized pharmacy representative for documentation in TOUCH® On-line if direct access is not available. Record the length of post-infusion observation time in the patient record and on the TOUCH® Pre-Infusion Patient Checklist.

VI. CLINICAL MONITORING

A. Prior to therapy:
   a. Baseline CBC and CMP
   b. Anti-JCV antibodies
   c. Assess if patient is up-to-date on vaccinations
   d. No current, active infections
   e. TOUCH® Pre-Infusion Questions

B. During and after infusion
   a. Signs and symptoms of hypersensitivity reactions
   b. Monitor for infections including Herpes infections and PML
   c. Hepatotoxicity including liver function tests and jaundice
   d. Monitor for signs and symptoms of thrombocytopenia. Symptoms of thrombocytopenia may include easy bruising, abnormal bleeding, and petechiae. Routine CBC.
   e. Monitor for efficacy: evaluate at 3 and 6 months after first infusion and every 6 months thereafter to determine whether treatment should be continued for another 6 months
      (1) Crohn's disease: Assess for worsening symptoms including abdominal pain, cramps, changes in stool, changes in weight, and frequency of flares
      (2) Multiple Sclerosis: Assess neurological and musculoskeletal MS symptoms including vision issues (blurred or double vision), dizziness, increased lack of coordination, increased loss of balance, unsteady gait,

trouble walking, numbness, incontinence, bowel irregularities, tremors, fatigue, and heat sensitivity.

Please refer to the package insert for the most up to date guidance on this medication.

REFERENCES:

Tysabri [package insert]. Cambridge, MA. Biogen, Inc. 2004

APPENDIX A: ANAPHYLAXIS KIT INTRUCTIONS

Emergency Medication After Your Infusion

Please call your pharmacy if you have any questions or concerns. In the event of an emergency, always call 911.

Your nurse will tell you when you need to use Emergency Medications.
The epinephrine dose will be noted on the Anaphylaxis Protocol included with your kit.

Start with a clean work surface and clean hands.

Open the supply bag labeled Anaphylaxis Kit Contents.

You will need:

1. **Bag containing Pills** (2 Acetaminophen and 2 Diphenhydramine)
2. **Bag containing Alcohol Prep Pads**
3. **Bag labeled IM Epinephrine**

All other contents will not be needed.

Open the IM Epinephrine Bag

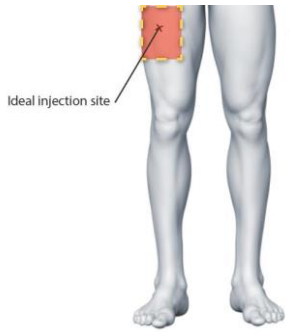
1. **Remove 1 of each item**
    a. 1 -syringe
    b. 1 – brown labeled filter needle (BD Filter Needle)- **for ampul use only**
    c. 1 – black labeled safety needle (Magellan Hypodermic Safety Needle 22G x 1”)
    d. 1 ampul of epinephrine

Prepare IM (intramuscular) injection of Epinephrine:

1. **Attach the brown filtered needle to syringe**
    a. Be careful to not touch the tip of the syringe or the needle.
2. Using an **alcohol swab, wipe the neck of the epinephrine ampul.**
3. Holding the ampul upright, **swirl and flick the ampul until all fluid flows to the bottom chamber** (the top chamber should be empty).
4. Using a new alcohol wipe, grasp the neck of the ampul and with your other hand grasp the bottom chamber of the ampul. **Quickly snap the top of the ampul off, directing the snap way from you.**

5. **Place the tip of the brown filter needle inside the ampul**. Tilting the ampul, **withdraw dose of medication into the syringe** by gently pulling back on the plunger. Be careful to not pull the plunger out of the syringe.
6. Remove the needle from the ampul and h**old the syringe upright** with the needle pointing upward. **Gently tap the side of the syringe to bring any air to the top of the syringe.**
7. **Push the air out of the syringe by gently pushing on the plunger**.
8. Replace the cap on the brown filter needle. Discard remainder in ampul.
9. **Remove the brown filter needle and place the black safety needle onto the syringe.**

Give your IM Epinephrine injection



1. **Grasp your leg muscle at the outer mid-thigh** and **cleanse the area** with a new alcohol wipe.
2. **Push the needle into your leg muscle straight** in at a 90-degree angle.
3. **Inject the medication** by depressing the plunger in a slow and steady motion.
4. **Remove the needle** and wipe the site with the alcohol wipe.
5. May repeat dose every 5 minutes (**maximum 3 doses**) if ordered per protocol.

Take the pills by mouth.

a. 2 – Acetaminophen
b. 2 – Diphenhydramine

Place all trash in the bag the pills came in and take with you when you seek medical care. **Give the bag to the nurse or EMT**, so your doctor will know what medication you already took. They will properly dispose of the syringe and needles.
Call 911 or have someone drive you to the emergency department.