Criteria for Use
Natalizumab in Multiple Sclerosis
VHA Pharmacy Benefits Management Service and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation. For a full discussion of natalizumab please refer to the monograph at http://vaww.national.cmop.va.gov/PBM/Clinical%20Guidance/Drug%20Monographs/Natalizumab.doc

Exclusion Criteria (if any box is checked the patient DOES NOT qualify for natalizumab)

- Patient has not been enrolled in and met all conditions of the TOUCH™ Prescribing Program
- Patient is diagnosed with primary progressive multiple sclerosis
- Patient has secondary progressive MS with no clinical or MRI evidence of relapses
- Patient is currently responsive to and tolerating another immunomodulatory treatment for MS
- Patient has current or prior history of progressive multifocal leukoencephalopathy (PML);
- Patient has a medical condition which significantly compromises the immune system including HIV infection or AIDS, leukemia, or lymphoma or organ transplantation;
- Patient is currently receiving or has received in the previous three months chronic antineoplastics or immunosuppressants (ie; adalimumab, alefacept alemtuzumab, anakinra, azathioprine, cladribine, cyclophosphamide, cyclosporine, daclizumab, efalizumab, etanercept, fludarabine phosphate, infliximab, intravenous immunoglobulin leflunomide, mercaptopurine, methotrexate, mycophenolate mofetil, mycophenolic acid, pemetrexed, rituximab, trastuzumab.
- Patient is receiving concurrent immune system modifying drugs to treat MS (ie; interferon beta-1B, glatiramer acetate, interferon beta 1A, mitoxantrone)
- Providers may exclude patients with melanoma or at high risk of developing melanoma or other cancers if in their judgment treatment would pose a significant risk to the patient (for more information refer to www.va.gov/ms)

Inclusion Criteria

- Patient has relapsing MS characterized by disease activity defined as one or more relapses in the two years prior to therapy or gadolinium positive lesions on MRI, or new T2 lesions
- Patients’ currently receiving immunosuppressants or antineoplastics (see list above in exclusion criteria) should generally have a washout period of at least 3 months prior to initiation of natalizumab.
- Patients receiving an interferon beta, glatiramer acetate, or corticosteroids should generally have a washout period of at least 2 weeks prior to initiation of natalizumab.
- Patient must be enrolled in the TOUCH Online program
- Patient must have a JC virus test prior to initiation of natalizumab. Patients who are JC negative should be retested every 3-6 months as patients can seroconvert during therapy.
- For seropositive patients who have been counseled regarding risks of continuing natalizumab and who have decided with their physician to continue natalizumab, a MRI should be obtained every 3-6 months

# An appropriate washout time from previous DMT is unknown. Various time periods have been reported, from 2 weeks - 6 months. In patients who have received prior DMT agents, a baseline MRI is recommended prior to initiating natalizumab. The risks of a longer washout period should be weighed against the risks of another relapse.

Dosage Recommendations

The recommended dose of natalizumab for relapsing forms of MS is 300 mg by IV infusion over one hour every four weeks
Monitoring

- Patients should be observed during the infusion and for one hour after the infusion for signs or symptoms consistent with a hypersensitivity reaction. These reactions usually occur within 2 hours of the start of the infusion.
- There have been anecdotal reports of elevated hepatic transaminases and total bilirubin as early as six days post infusion. Liver enzymes and bilirubin should be monitored prior to each dose of natalizumab during the first year of therapy (for more information refer to www.va.gov/ms).
- Natalizumab induces increases in circulating leukocytes (including lymphocytes, monocytes, eosinophils, and basophils). It does not affect the number of circulating neutrophils.
- Patients switching from natalizumab to another DMT for MS may also warrant retesting of serum JCV antibody status. Ques Diagnosis Test Req Form
- Since natalizumab has been causally linked with progressive multifocal leukoencephalopathy (PML), suspected cases should be investigated with a gadolinium enhanced MRI and when indicated a cerebrospinal fluid exam for JC viral DNA.
- Three risk factors (treatment duration >2 years, prior chemotherapy use, and JC virus antibody seropositivity) have been identified and can assist in evaluating a patient’s risk of developing PML. Chemotherapy use refers to agents such as methotrexate, azathioprine, cyclosporine, mycophenolate mofetil and cyclophosphamide, not first line DMT therapy for MS such as interferon-beta or glatiramer.

Table 1: Estimated PML Incidence Stratified by Risk Factor

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Negative**</th>
<th>TYSABRI Exposure†</th>
<th>Anti-JCV Antibody Positive*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No Prior Immunosuppressant Use</td>
<td>Prior Immunosuppressant Use</td>
</tr>
<tr>
<td>&lt;1/1,000</td>
<td>1/1,000</td>
<td>1/1,000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>3/1,000</td>
<td>13/1,000</td>
</tr>
<tr>
<td>49-72 months</td>
<td>7/1,000</td>
<td>9/1,000</td>
</tr>
</tbody>
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Notes: *Based on US postmarketing PML data as of September 3, 2013, and TYSABRI use data as of August 31, 2013. **Calculation based on 2 cases of anti-JCV antibody negative PML in patients exposed for at least 1 month of therapy as of September 3, 2013. Data for anti-JCV antibody negative patients reflects worldwide exposure. †Data beyond 6 years of treatment are limited. 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%.

- Patients on natalizumab should be evaluated at 3 months and 6 months after the first infusion and at least every 6 months after that for clinical response, side effects, and any symptoms suggesting PML as well as a decision to continue natalizumab therapy.
- An annual brain MRI by CMSC Protocol (www.va.gov/ms) is highly recommended
- If a case of PML is confirmed, contact the appropriate MSCoE Associate Clinical Director or Director and enter the data into VA ADERS. Refer to TMS program; VA ADERS - Adverse Drug Event Reporting System for Pharmacist https://www.tms.va.gov/learning/user/catalog/createSearchResults.do or contact local facility pharmacy for assistance.

a Relapsing Forms of MS include: Relapsing, remitting MS: A clinical course of MS characterized by clearly defined, acute attacks with full or partial recovery and no disease progression between attacks. Secondary progressive MS with superimposed relapses: A clinical course of MS that shows steady progression but with superimposed acute relapses, after an initial relapsing-remitting course. Progressive-relapsing MS: A clinical course of MS that shows disease progression from the beginning, but with clear, acute relapses, with or without full recovery from those relapses.

b gadolinium should not be used in patients with CrCl ≤30 ml/min or those on dialysis.