Executive Summary:

Natalizumab is a monoclonal antibody that is thought to act by inhibiting the migration of leukocytes into the CNS, which in theory leads to a reduction of inflammation and demyelination.

Natalizumab is indicated for the treatment of patients with relapsing forms of multiple sclerosis with the goal of reducing the frequency of exacerbations. Additionally, it has been used off label in the treatment of Chron’s Disease.

The pivotal trials of natalizumab in Multiple Sclerosis (MS) are AFFIRM and SENTINEL. The annualized adjusted relapse rate after 13 months of treatment was 0.25 for natalizumab and 0.74 for placebo treated patients (P<0.001) in the AFFIRM trial. In SENTINEL the annualized adjusted relapse rate after 13 months of treatment was 0.36 for a combination of natalizumab/interferon beta-1a and 0.78 for interferon beta-1a only treated patients (P<0.001).

There is uncertainty whether a reduction in relapse rate is related to the prevention of disability.

The most frequently reported serious adverse reactions associated with natalizumab treatment include infections (3.2%), hypersensitivity reactions (1.1%), depression (1%) and cholelithiasis (0.8%). Other reported adverse reactions include headache, fatigue and arthralgias.

PML is a demyelinating disease of the CNS caused by the JC polyoma virus, which is mainly seen in immunocompromised patients. Natalizumab was temporarily withdrawn from the market when there were three reported cases in the SENTINNEL and ENACT I trials.

Patients, prescribers, infusion sites and dispensing pharmacies must be enrolled in the TOUCH™ Program

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating natalizumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Natalizumab is a recombinant humanized (IgG4κ) murine monoclonal antibody directed against alpha-4 integrins. It functions as a selective adhesion molecule inhibitor (SAM). Natalizumab binds to the integrins on the surface of all leukocytes, except neutrophils, inhibiting alpha-4-mediated adhesion of leukocytes to their counter-receptors. By disrupting the molecular interactions, natalizumab prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. This inhibits further recruitment and inflammation of activated immune cells. This leads to a reduction of ensuing inflammation and slows the demyelination process. Although
the specific mechanism by which natalizumab effects MS is unknown, it can cross the blood-
brain barrier and decrease the formation of plaques that are associated with lesions.

Natalizumab is administered as an intravenous infusion over one hour. The pharmacokinetics of
natalizumab were investigated in a study of thirty-six patients with MS randomized to receive 1, 3
or 6 mg/kg or placebo. Following the infusion peak plasma level were reached in two hours. The
peak plasma level and area under the concentration time curve were dose proportional. The
pharmacokinetics in Crohn’s Disease patients was also investigated, utilizing the same dosing
parameters. This study confirmed the linear pharmacokinetics of natalizumab. The mean half-life
is 11 days. The mean time to steady state is 24 weeks with a four week dosing protocol.

**FDA Approved Indication(s) and Off-label Uses**

Natalizumab is a recombinant humanized (IgG4κ) murine monoclonal antibody indicated for the
treatment of patients with relapsing forms of multiple sclerosis with the goal of reducing the
frequency of exacerbations.

Natalizumab has also been used off label in the treatment of Crohn’s disease.

### Current VA National Formulary Alternatives

Alternate immunomodulatory agents used in the treatment of MS include glatiramer acetate,
interferon beta 1a, interferon beta 1b and mitoxantrone. These agents are listed in Table 1 with
current recommendations from the American Academy of Neurology.

**Table 1: American Academy of Neurology Guidelines for use of disease modifying drugs in
MS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction in relapse rate</th>
<th>Reduce disease severity on MRI</th>
<th>Decreases disability progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon B</td>
<td>Established as effective</td>
<td>Probably effective</td>
<td>Probably effective</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Established as effective</td>
<td>Possibly effective</td>
<td>Possibly effective</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Probably effective</td>
<td>NA</td>
<td>Possibly effective</td>
</tr>
<tr>
<td>natalizumab</td>
<td>Established as effective</td>
<td>Established as effective</td>
<td>Established as effective</td>
</tr>
</tbody>
</table>

**Dosage and Administration**

The recommended dose of natalizumab for treatment of relapsing forms of multiple sclerosis is
300 mg intravenously every four weeks. The safety and efficacy of natalizumab beyond two years
of treatment have not been established.

**Geriatrics.** Clinical trails did not include a sufficient number of patients’ age 65 years and over
to determine if they would respond differently than younger patients.

**Pregnancy.** Category C. Natalizumab should be used cautiously, if at all, in pregnant patients.
Breast Feeding. It is unknown whether natalizumab is excreted in human milk. Because of the potential for adverse effects in breastfeeding infants, a decision must be made weighing the risks to an infant versus the benefits to continuing therapy in the nursing mother.

Renal Insufficiency. The safety and efficacy of natalizumab have not been established in patients with renal insufficiency.

Hepatic Insufficiency. The safety and efficacy of natalizumab have not been established in patients with hepatic insufficiency.

Administration. Infuse each natalizumab dose over one hour. If the solution has been refrigerated, it should be allowed to warm to room temperature prior to infusion. Patients should be monitored closely for one hour post-infusion due to the increased incidence of infusion-related reactions.

Special Considerations. Patients, prescribers, infusion sites and dispensing pharmacies must be enrolled in the TOUCH™ Program4. Due to safety concerns with natalizumab administration, only physicians, infusion centers, and pharmacies that have undergone instruction and certification by the drug's sponsors will be able to prescribe and administer natalizumab. All patients must enroll in the “TOUCH Prescribing Program” by completing an enrollment form. All patients must be thoroughly informed of the purpose and risk of natalizumab therapy, read and sign a detailed consent form and be enrolled in TOUCH. The patient must be evaluated by an informed health professional and sign a consent form before each monthly infusion. Prescribing physicians, infusion sites, and pharmacies may be audited by the FDA as well as by the commercial sponsors. The TOUCH program provides specific guidelines for distinguishing PML from MS including MRI and cerebrospinal fluid assessment for JC virus DNA where PML might be considered. The TOUCH program must be informed when a patient discontinues natalizumab treatment.

Efficacy

Multiple Sclerosis Efficacy Measures5

Disease progression in MS is measured by several scales, with the Kurtzke Expanded Disability Status Scale (EDSS) being the most common. This scale ranges from zero to ten and progresses in increments of 0.5 degree, with higher scores indicating more severe disease. The scale allows for quantification of disability and allows neurologists to assign a functional score to affected systems, including pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other. The rate of relapse is an outcome measure in MS trials that serves as more of a clinical marker of disease state. The presence of gadolinium enhancing lesions on MRI scans also serves as a marker of disease activity.

Multiple Sclerosis

The initial trials of natalizumab involved variable doses of the agent and included the use of a placebo controlled arm. These trials are discussed in Table 2. The three trials6, 7, 8 compared natalizumab to placebo in RRMS and SPMS patients. It is difficult to compare these trials as the same type of outcome data is not reported in the results. The size of the study population and doses used in the trials make extrapolation difficult as well. In 2003, Miller et.al6 conducted a trial in 213 patients with relapsing–remitting or relapsing secondary progressive multiple sclerosis who were randomized to receive 3 mg of intravenous natalizumab per kilogram of body weight (68 patients), 6 mg per kilogram (74 patients), or placebo (71 patients) every 28 days for 6 months. This trial followed patients over a 12 month time period.
The primary efficacy end point utilized monthly gadolinium-enhanced magnetic resonance imaging during the six-month treatment period to measure the number of newly active brain lesions. Clinical outcomes included relapses and self-reported well-being. There were marked reductions in the mean number of new lesions in both natalizumab groups: 9.6 per patient in the placebo group, as compared with 0.7 in the group given 3 mg of natalizumab per kilogram (P<0.001) and 1.1 in the group given 6 mg of natalizumab per kilogram (P<0.001). Twenty-seven patients in the placebo group had relapses, as compared with 13 in the group given 3 mg of natalizumab per kilogram (P=0.02) and 14 in the group given 6 mg of natalizumab per kilogram (P=0.02).

The two major trials evaluating the safety and efficacy of natalizumab include the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) trial which evaluated natalizumab as monotherapy and The Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) evaluating combination therapy with interferon beta-1a (Avonex®). These trials are compared in Table 3.

The AFFIRM trial randomized 627 patients to receive natalizumab with the placebo arm enrolling 315. Natalizumab therapy significantly reduced by 68% the frequency of clinical exacerbations at 1 year, as well as delayed by 42% the sustained progression of disability over 2 years. The primary endpoint of this study was a 2 year measure of progression, 29% in the placebo arm vs. 17% in those patients treated with natalizumab. (p<0.001). The AFFIRM trial has an NNT of 8 for sustained increase in disability and an NNT of 2 for no new or enlarging hyperintense T-2 lesions developed over a 2 yr period.

The SENTINEL trial randomized patients to receive natalizumab/interferon beta 1a or placebo/interferon beta 1a. Patients enrolled in this trial had relapsing remitting MS, with at least one relapse while on treatment with interferon beta 1a. All patients continued on their current interferon beta 1a dosing regimen with those randomized to the natalizumab group receiving 300 mg of natalizumab (n=589) every 4 weeks for up to 28 months. SENTINEL attrition was high (14%); 12% of patients allocated to receive the added natalizumab and 16% of patients assigned to get the placebo withdrew.
### Table 2 Trials of natalizumab vs. placebo in mixed RRMS and SPMS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient demographics</th>
<th>N dose</th>
<th>Mean change in EDSS</th>
<th>Total Relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miller, 2003</td>
<td>N=213, mean EDSS 4.3, mean relapse 2 yrs prior to trial 3.0</td>
<td>3 mg/kg or 6 mg/kg every 28 days for 6 months</td>
<td>3 mg/kg -0.14</td>
<td>3 mg/kg 3 (4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg/kg -0.03 Placebo 0.03</td>
<td></td>
<td>6 mg/kg 8 (11%)</td>
</tr>
<tr>
<td>Tubridy, 1999</td>
<td>N=72, mean EDSS 4.8, ≥ 2 relapses in 18 months prior to study</td>
<td>3 mg/kg every 28 days</td>
<td>3 mg/kg -0.02</td>
<td>Placebo 18 (21%)</td>
</tr>
<tr>
<td>Shermata, 1999</td>
<td>N=28, mean EDSS ≤5.5, mean relapse 2 yrs prior to trial 0.7-2.3</td>
<td>Dose ranging study, 0.03-3.0 mg/kg</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

### Table 3 Clinical Trials of natalizumab in relapsing remitting multiple sclerosis

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Demographics</th>
<th>Drug</th>
<th>Duration</th>
<th>Annualized relapse rate*</th>
<th>Proportion of relapse free patients*</th>
<th>Probability of disease progression*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td>N=942, mean EDDS 2.3, mean relapse rate 1.52/yr</td>
<td>N 300 mg every 4 weeks vs. placebo</td>
<td>Up to 116 weeks</td>
<td>0.23 vs. 0.73, p&lt;0.001</td>
<td>67% vs. 41%, p&lt;0.001</td>
<td>17% vs. 29%, p&lt;0.001</td>
</tr>
<tr>
<td>SENTINEL</td>
<td>N=1171, mean EDDS 2.4, mean relapse rate 1.47/yr</td>
<td>N 300 mg every 4 weeks with 30ug IFN β1a weekly vs. 30ug IFN β1a weekly with placebo</td>
<td>Up to 116 weeks</td>
<td>0.34 vs. 0.75, p=0.001</td>
<td>61% vs. 37%, p&lt;0.001</td>
<td>23% vs. 29%, p=0.02</td>
</tr>
</tbody>
</table>

* outcome at 2 years, natalizumab vs. placebo, N=natalizumab, IFN β1a= interferon beta 1a, Avonex®

### Crohn's Disease Efficacy Measures

The Crohn's Disease Activity Index or CDAI\(^{11}\) is a research tool used to quantify the symptoms of patients with Crohn’s Disease. This equation numerically simplified and utilizes eight selected...
variables. Index values of 150 and below are associated with quiescent disease; values above that indicate active disease, and values above 450 are seen with extremely severe disease. The index consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI and include the following: Number of liquid or soft stools each day for seven days, abdominal pain (graded from 0-3 on severity) each day for seven days, general well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days, presence of complications*, taking diphenoxylate/atropine or opiates for diarrhea, presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite), hematocrit of <0.47 in men and <0.42 in women, and percentage deviation from standard weight. Remission of Crohn's disease is defined as a fall in the CDAI of less than 150. Severe disease was defined as a value of greater than 450. Most major research studies on medications in Crohn's disease define response as a fall of the CDAI of greater than 70 points.

**Crohn's Disease**

Natalizumab has been used as both induction and maintenance therapy for Crohn's Disease. In the ENACT-I (Evaluation of Natalizumab in Active Crohn’s Disease Therapy)\textsuperscript{12}, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4, and 8. The primary outcome was response, defined by a decrease in the Crohn's Disease Activity Index (CDAI) score of at least 70 points, at week 10. This trial determined that the natalizumab and placebo groups had similar rates of response (56 percent and 49 percent, respectively; P=0.05) and remission (37 percent and 30 percent, respectively; P=0.12) at 10 weeks. Additionally, natalizumab induced significantly greater clinical response in patients previously treated with infliximab (p=0.004). Response and remission was also greater in natalizumab treated patients who had both received prior infliximab and had active inflammation during the study. THE ENACT-II trial\textsuperscript{12} evaluated a 6 month regimen of monthly natalizumab or placebo on maintaining response and/or remission in patients who had responded to natalizumab in the ENACT-I trial. In the ENACT-II trial, 339 patients who had a response to natalizumab in the first trial were randomly reassigned to receive 300 mg of natalizumab or placebo every four weeks through week 56. The primary outcome was a sustained response through week 36. A secondary outcome in both trials was disease remission (a CDAI score of less than 150). Continuing natalizumab in the second trial resulted in higher rates of sustained response (61 percent vs. 28 percent, P<0.001) and remission (44 percent vs. 26 percent, P=0.003) through week 36 than did switching to placebo. Serious adverse events occurred in 7 percent of each group in the first trial and in 10 percent of the placebo group and 8 percent of the natalizumab group in ENACT-II.

Ghosh et al;\textsuperscript{13} conducted a double-blind, placebo-controlled trial of natalizumab in 248 patients with moderate-to-severe Crohn's disease. Patients were randomly assigned to receive one of four treatments: two infusions of placebo; one infusion of 3 mg of natalizumab per kilogram of body weight, followed by placebo; two infusions of 3 mg of natalizumab per kilogram; or two infusions of 6 mg of natalizumab per kilogram. Infusions were given four weeks apart. Outcomes included changes in scores for the Crohn's Disease Activity Index (higher scores indicate more severe disease), the health-related quality of life, and C-reactive protein levels. The group randomized to receive two infusions of 6 mg of natalizumab per kilogram did not have a significantly higher rate of clinical remission (defined by a score of less than 150 on the Crohn's Disease Activity Index) than the placebo group at week 6 (the prospectively defined primary end point in the efficacy analysis). However, both groups that received two infusions of natalizumab had higher remission rates than the placebo group at multiple time points. Natalizumab produced a significant improvement in response rates (defined by a reduction of at least 70 points in the score on the Crohn's Disease Activity Index). The highest remission rate was 44 percent and the highest response rate was 71 percent (at week 6 in the group given two infusions of 3 mg per kilogram). Overall, the two infusions of 6 mg of natalizumab per kilogram and of 3 mg per kilogram had
similar effects. The quality of life improved in all natalizumab groups; C-reactive protein levels improved in groups receiving two infusions of natalizumab. The rates of adverse events were similar in all four groups.

Based on a review of current trials of natalizumab in Crohn’s Disease, a Cochrane review has determined pooled data from the four included studies suggest that natalizumab (300 mg or 3 to 4 mg/kg) is effective for induction of clinical response and remission in patients with moderately to severely active Crohn's disease. This benefit is statistically significant for one, two and three infusion treatments. Additionally, natalizumab appears to provide greater benefit for patient subgroups characterized by objective confirmation of active inflammation or chronically active disease despite conventional therapies. Currently, the manufacturer of natalizumab has a supplement undergoing FDA review for an indication in the treatment of Crohn’s Disease.

**Adverse Events (Safety Data)**

The most frequently reported serious adverse reactions associated with natalizumab treatment include infections (3.2%), hypersensitivity reactions (1.1%), depression (1%) and cholelithiasis (0.8%). Other reported adverse reactions include headache, fatigue and arthralgias. Frequently reported adverse reactions that resulted in discontinuation of therapy were urticaria and associated hypersensitivity reactions. The majority of the patients that showed infusion-related reactions did so within two hours of the start of the infusion. Anaphylaxis, or severe hypersensitivity associated with antibodies, was seen in less than 1% of patients. In the phase III clinical trials, antibodies to natalizumab were detected in approximately 9% of patients at least once during treatment; with persistent antibody-positivity in 6%. Patients who become persistently positive for the presence of natalizumab antibodies are more likely to develop infusion-related reactions. Twenty-four percent of patients receiving natalizumab developed infusion-related reactions compared to 18% of placebo-treated patients. Infusion-related reactions most often associated with persistent antibody-positivity include urticaria, rigors, nausea, vomiting, headache, flushing, dizziness, pruritus, tremor, feeling cold and pyrexia. In addition, the presence of antibodies and the subsequent reduction in serum natalizumab levels is associated with a substantial decrease in efficacy with natalizumab.

**Deaths and Other Serious Adverse Events**

**Progressive Multifocal Leukoencephalopathy (PML)**

PML is a serious, progressive neurologic disorder caused by infection of the central nervous system by JC virus, a member of the papovavirus family. JC virus is carried in a latent form by 70-75% of the general population but generally does not cause symptoms. PML is rare, but when it occurs it frequently results in irreversible neurologic deterioration and death, and there is no known effective treatment for the disease. Two patients with MS and one with Crohn’s disease treated with natalizumab were reported to have developed PML.

Natalizumab was temporarily withdrawn in 2005 because of the occurrence of three cases of progressive multifocal leukoencephalopathy (PML). PML is a demyelinating disease of the CNS caused by the JC polyoma virus, which is mainly seen in immunocompromised patients. Two of the three cases occurred in patients in the SENTINEL study involving MS patients and the third case of PML occurred in a patient receiving natalizumab for Crohn's disease. The reason for developing PML with natalizumab is still unknown. No additional cases of PML in patients receiving natalizumab have been reported. In an extensive evaluation of 3116 patients who had received natalizumab while participating in clinical trials, clinical history and examinations,
Natalizumab (Tysabri®) Monograph

MRIs, and testing of CSF for JC virus DNA were performed.\textsuperscript{20} Based on these evaluations, the investigators found that the estimated incidence of PML associated with exposure to natalizumab (with a mean exposures of 17.9 months) was 1.0 case per 1000 patients (95\% CI, 0.2-2.8 per 1000).

An evaluation of all patients who had received natalizumab in clinical trials or via compassionate use criteria or after FDA approval (n=3417) was undertaken. Of this group, 3389 patients were followed up, using neurological exam, brain MRI, and cerebrospinal fluid samples. 44 patients (1.3\%) had findings of possible PML. Data were then examined by an expert panel; 43 potential cases were ruled out, and one patient refused further follow-up. The authors then estimate the incidence of PML at 1.0 per 1000 treated patients (95\% CI 0.2 to 2.8 per 1000) based on the 3 original cases. Because these 3 patients had also been receiving immunomodulators or immunosuppressants, it is recommended that natalizumab be used only as monotherapy.

**Precautions/Contraindications\textsuperscript{1-4, 21,22}**

**Precautions**

MS and PML are both focal, CNS demyelinating conditions which begin with localized neurologic symptoms. Thus, patients must be aware that they should promptly report any new neurologic symptoms which the physician must then carefully consider to differentiate an MS relapse from the onset of PML. The MRI lesion characteristics typical of PML and MS are somewhat different and have been published and also contained in the TOUCH program materials. Nevertheless, with the onset of new symptoms, patients should be carefully examined for new neurologic signs and probably should have an immediate enhanced MRI with a follow-up MRI, perhaps 1 month later. Because the demyelinating lesions of PML produce either irreversible neurologic disability or death, the only useful response is to eliminate the immunosuppression induced by natalizumab. It must be withdrawn at once, if a diagnosis of PML is seriously considered or confirmed.

**Look-alike / Sound-alike (LA / SA) Error Risk Potential**

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for Tysabri
Ticar 30 gram vial, Tygacil 50 gram vial, tobramycin 300 mg vial and ticarcillin 30 gram vial

LA/SA for Natalizumab
Natamycin ophthalmic suspension, nateglinide 120 mg tablet, naglazyme 1 mg IV solution and almetuzamab 30 mg vial.

**Drug Interactions\textsuperscript{1}**

Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may increase the risk of infections, including PML and other opportunistic infections. The safety and efficacy of natalizumab in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established. Concurrent use of short courses of corticosteroids was associated with an increase in infections in clinical trials; however, the increase in infections in
natalizumab-treated patients who received corticosteroids was similar to the increase in placebo-treated patients who received corticosteroids. In addition, no data are available on the effects of vaccination with either attenuated or live virus vaccines.

**Acquisition Costs**

**Table 4: Acquisition costs of disease modifying therapies for MS***

<table>
<thead>
<tr>
<th>Name</th>
<th>Frequency/Route of Delivery/Usual Dose</th>
<th>Monthly cost based on a 70 kg patient (FSS pricing as of 10/30/07)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta – 1b</td>
<td>Every other day, Subcutaneous injection, 0.25 mg</td>
<td>16 injections per month $943.52</td>
</tr>
<tr>
<td>Interferon beta – 1a</td>
<td>Once a week, Intramuscular injection, 30 mcg.</td>
<td>4 injections per month $757.80</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Every day, subcutaneous injection, 20 mg.</td>
<td>31 injections per month $725.40</td>
</tr>
<tr>
<td>Interferon beta – 1a</td>
<td>3 times a week, subcutaneous injection, 44 mcg.</td>
<td>12 injections per month $848.16</td>
</tr>
<tr>
<td>natalizumab</td>
<td>300 mg given intravenously every 4 weeks</td>
<td>One injection per month $1,619.26</td>
</tr>
</tbody>
</table>

* cost is for drug procurement only- does not include infusion center costs

**Pharmacoeconomic Analysis**

There have been no published pharmacoeconomic analyses for natalizumab. Several considerations for this agent are the use of an infusion center, the increased monitoring required by the TOUCH program and additional training for practitioners who will be using the agent. These factors will increase the actual cost of the drug above the acquisition cost.

The manufacturer of natalizumab has developed a pharmacoeconomic model. The anticipated relative reduction in relapse rate over 2 years for natalizumab is 67%, and the total 2-year cost of therapy per patient for natalizumab is $66,917. This equates to a cost per relapse avoided for natalizumab of $52,511. Natalizumab is the most cost-effective agent for reducing relapses over a 2-year period, compared with interferon beta 1a (Avonex®) (cost per relapse avoided of $69,111), interferon beta 1b ($65,241), glatiramer acetate ($73,601), and interferon beta 1a [Rebif® 44 mcg] ($75,785). This model assumes the costs of managing an MS relapse may vary depending on the intensity of the relapse, the model takes into account a distribution of patients requiring low-intensity (40% of patients, $275 per relapse), medium-intensity (40% of patients, $2,091 per relapse), and high-intensity (20% of patients, $14,569 per relapse) medical management, for a weighted average of $3,860 per relapse. These costs include hospitalization, medication, additional physician visits, and other resource utilization necessary for treatment. For flexibility, the distribution and costs of managing a relapse can also be modified to better reflect a health plan’s own costs. Disability progression was not captured in this analysis because the challenges in appropriately comparing this efficacy measure across the...
immunomodulator agents were too great. The definition of disability progression used to assess clinical efficacy varied from an increase of one point in the EDSS score sustained for at least 3 months to an increase of one point sustained for at least 6 months. Additionally, the model has not been published or validated in the medical literature.

Conclusions

Natalizumab was approved by the FDA in November 2004 under the Accelerated Priority Review process on the basis of the preliminary results of two ongoing phase III clinical trials. When the requested preliminary results were presented, the cases of PML were found. Because of the therapeutic niche that natalizumab therapy offers, and after the development of a risk management program, the medication was re-released onto the market. Natalizumab decreases the annualized relapse rate by 68% as compared to other currently available therapy using interferon beta-1 or glatiramer, which achieve around 30%. The relapses lead to significant morbidity and mortality. Natalizumab has shown efficacy for the treatment of Crohn’s disease and is currently under FDA review for expanded indications.

Recommendations

Natalizumab is an effective treatment option for multiple sclerosis patients who have an inadequate response or intolerant to other MS therapies. Natalizumab has documented efficacy in the treatment of MS by decreasing the number of relapses, decreasing gadolinium enhancing lesions on MRI, and improving quality of life. In comparison to other disease modifying treatments available for MS, the absolute risk and resultant health benefits of natalizumab in comparison to the interferon products (based on PRISMS data) are similar. However, while the patient populations in these trials included RRMS and comparable EDSS scores, the trials used different inclusion criteria for previous drug therapy. Currently, natalizumab would not be considered first line therapy for MS. Natalizumab remains investigational in the treatment of Crohn’s Disease, however current clinical data demonstrates efficacy in terms of inducing a clinical response and remission.

Natalizumab has been associated with the development of PML a serious, life threatening condition. The benefit of natalizumab therapy must be weighed against potential patient risk. The use of the TOUCH program for distribution and administration as well as other surveillance data (FDA MedWatch) will continue to track and/or identify any other issues with natalizumab use.

References:

4. Special Handling Drugs: Tysabri® (natalizumab) Pharmacy benefits Management Service http://vaww.national.cmop.va.gov/PBM/Special%20Handling%20Drugs/Forms/AllItems.aspx?RootFolder=%2fPBM%2fSpecial%20Handling%20Drugs%2fTYSABRI%20%28Natalizumab%29&View=%7b0B1484F5%2d1A23%2d4573%2d9AE6%2d8677021828CB%7d


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