# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125104**

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE
Food and Drug Administration

# Memorandum

Center for Drug Evaluation and Research
1451 Rockville Pike
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**Office of Drug Evaluation VI**
**HFD-106**

**Date:** **November 23, 2004**

**From:** **David Ross, M.D., Ph.D.; Deputy Director, ODE 6**

**Subject:** **Deputy Office Director Review of BLA/STN 125104/0**
**Natalizumab for relapsing-remitting multiple sclerosis**

**To:** **BLA 125104/0 File**
**Karen Weiss, M.D.; Director, ODE 6**

## Identifying information

| | |
|---|---|
| BLA/STN#: | 125104 |
| Applicant: | Biogen Idec |
| Biologic name: | Natalizumab |
| Proposed trade name: | Tsyabri |
| Submission date: | May 24, 2004 |
| Stamp date: | May 24, 2004 |
| PDUFA goal date: | November 23, 2004 |
| Formulation: | 300 mg natalizumab in sterile, single use vials for injection |
| Proposed indication: | Treatment of relapsing forms of multiple sclerosis |
| Proposed regimen: | 300 mg intravenous infusion every 4 weeks |

**Recommended regulatory action**: Accelerated approval under 21 CFR 601 Subpart E

The primary reviewers, the statistical team leader, and director of the reviewing division have done an excellent job in their respective reviews of analyzing the data in this application, discussing the relevant issues, and drawing scientifically sound conclusions supporting their regulatory recommendations. In this memorandum, I will summarize the review issues presented by this application and address the major issues arising in the review of this application. In summary, I concur with the primary reviewers, statistical team leader, and division director that this application should be granted accelerated approval under the provisions of 21 CFR 601 Subpart E.

## Clinical Background

Multiple sclerosis (MS) is a chronic, frequently progressive disorder of the central nervous system (CNS) that represents a major cause of disability. Its current prevalence in the United States has been estimated to be at least 350,000 cases (Anderson *et al.* 1992). Disease onset generally occurs in the second to third decade of life and follows a variable course, most often with intermittent relapses (exacerbations) with relative clinical stability between relapses (relapsing-remitting MS). In some patients, symptoms will progress between relapses (secondary progressive MS).

The etiology of MS is poorly understood, but is thought to result from immune-mediated CNS demyelination in genetically susceptible individuals (Noseworthy *et al.* 2000). Autoreactive T cells cross the blood-brain barrier (BBB) via interactions with adhesion molecules, particularly α4-integrins. These T cells, along with anti-myelin antibodies, are thought to cause a complex cascade of events that result in destruction of myelin sheaths and scar formation. Affected patients develop hypocellular demyelinated plaques with axonal preservation, particularly in the areas around the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter. Areas of active demyelination appear on magnetic resonance imaging (MRI) as gadolinium-enhancing lesions. Diagnosis is classically based on clinically apparent lesions "disseminated in time and space"; standardized criteria (McDonald *et al.* 2001) have been devised for MS diagnosis that now also encourage diagnosis based upon one clinical lesion and MRI evaluations to complete the evidence for dissemination in space and time.

Demyelination in MS prevents saltatory conduction via the nodes of Ranvier, leading to inefficient transmission of action potentials. Clinical manifestations are protean and include sensory disturbances (e.g., paresthesias), ophthalmologic symptoms (e.g., ophthalmoplegia and diplopia due to brainstem involvement), motor disturbances (which may progress to quadriplegia), and cerebral signs and symptoms (e.g., dementia, depression, and seizures).

Available therapies for MS include corticosteroids for acute exacerbations, and interferon-beta or glatiramer acetate for prevention of relapses or progression of disability in the relapsing forms of MS. Although the latter group of agents is safe and effective, a number of randomized, placebo-controlled trials in patients with relapsing-remitting MS have consistently shown that these therapies reduce the relative risk of relapse by about one-third at most. In addition, although the risk-benefit assessment of these agents supports their use, they are associated with potentially serious toxicities. Thus, new therapies for this potentially disabling disease are needed.

## Regulatory Background

Natalizumab is a recombinant humanized IgG4κ monoclonal antibody that binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). It is hypothesized that by interfering with leukocyte migration, natalizumab inhibits the migration of activated T cells across the blood-brain barrier, decreasing recruitment of these cells to inflamed parenchyma.

For a full history of significant pre-BLA submission activities, the reader is referred to the various primary reviews. The IND for natalizumab for treatment of relapsing-remitting MS

was originally submitted on October 23, 1996. Protocols for pivotal Phase 3 trials were submitted in mid-2001. A pediatric waiver was granted on August 2, 2002. A pre-BLA meeting was held with the Applicant on February 17, 2004, at which the Agency agreed to consider an application for accelerated approval. The application was submitted in eCTD format on May 24, 2004, and accepted for filing on July 23, 2004.

## Chemistry, manufacturing, and controls issues

The reader is referred to the CMC review by Drs. Elena Gubina, Joseph Kutza, and Lei Zhang of the Division of Monoclonal Antibodies. I concur with their conclusion that the manufacture of natalizumab is well controlled, and leads to a product that is pure and potent. Natalizumab is the first IgG4 monoclonal antibody intended for chronic administration. This raises a novel chemistry issue. Some IgG4 molecules have heavy chains that are held together by noncovalent interactions. In the case of natalizumab, — of the molecules have heavy chains linked together in this fashion. Thus, natalizumab has the potential to recombine *in vivo* with IgG4 molecules of different specificity and form bispecific antibodies (Aalberse and Schuurman 2002). Because of the potential effects of such "scrambling" on the safety and efficacy of natalizumab, I concur with the need for a post-marketing commitment to develop and validate bispecific natalizumab IgG4 antibodies in human serum samples. Other issues identified include problems with the current assay used to identify and quantify anti-natalizumab antibodies. However, I concur that these and other CMC issues do not preclude approval and can be addressed via the post-marketing commitments agreed to by the Applicant. The manufacturing facility was found to be in compliance with cGMPs and capable of manufacturing natalizumab drug substance in a consistent manner using validated processes.

## Pre-clinical pharmacology and toxicology issues

The reader is referred to the pre-clinical pharmacology review by Dr. Anne Pilaro and the pre-clinical toxicology review by Dr. Barbara Wilcox. In pre-clinical studies, the natalizumab administration was generally well tolerated; in single and multiple-dose studies, natalizumab was associated with a reversible increase in circulating leukocytes, an expected effect given the pharmacologic activity of this agent and one seen in clinical studies, as described below under Safety. Natalizumab-associated effects that were seen less consistently included dose-dependent increases in reticulocytes and/or nucleated red blood cells (nRBCs), increased spleen weight, mild to moderate follicular hypertrophy in spleen and lymph node, and minimal to mild focal leukocyte infiltrates in the liver. Mild to moderate glomerulonephritis was seen in one chronic administration study in monkeys along with circulating immune complexes; however, this phenomenon was not seen in another monkey study, and glomerulonephritis was not seen in clinical studies.

In guinea pigs with experimental allergic encephalomyelitis (EAE), a demyelinating disorder used as a pre-clinical model for MS, administration of natalizumab was associated with reduction or reversal in clinical signs of illness. In the guinea pig EAE model, natalizumab treatment was also associated with histopathologic reduction in inflammation and radiologic improvement in demyelinated plaques.

The epidemiology of MS shows a 2:1 female predominance; as mentioned above, disease onset occurs early in adulthood. In addition, embryogenesis could, in theory, be affected by agents such as natalizumab that bind to adhesion molecules such as integrins. Thus, the

reproductive toxicity of natalizumab represents an important issue in the evaluation of this agent. Non-clinical reproductive toxicology studies demonstrated that treatment with natalizumab has the potential to reduce fertility through impairment of embryonic implantation. In monkeys and guinea pigs a small tendency toward post-implantation loss and decreased fetal survival was noted. In monkeys and guinea pigs, natalizumab was found to undergo transport across the placenta and fetal drug levels were roughly 30% of maternal levels. Infants exposed to natalizumab before birth were born with hematologic findings characteristic of natalizumab exposure (increased WBC, nRBC, increased circulating lymphocytes). However, no teratogenic effects of natalizumab treatment were noted for either guinea pigs or monkeys. Given that the benefits of natalizumab in pregnant women may be acceptable despite its potential risks, and given the lack of human data on the risks of natalizumab treatment during pregnancy, I concur with Dr. Wilcox's recommendation that product labeling indicate natalizumab as being in Pregnancy Category C. The Applicant has agreed to obtain additional data via a registry of pregnant women treated with natalizumab.

## Clinical Pharmacology issues

The reader is referred to the clinical pharmacology review by Dr. Iftekhar Mahmood. The available data adequately characterize the pharmacokinetics and pharmacodynamics of natalizumab, and support a dosing regimen of 300 mg given intravenously every 4 weeks. In particular, the data submitted support a fixed dose regimen, as opposed to a weight-based dose regimen, for the following reasons. First, a Phase 2, randomized, placebo-controlled multiple-dose study (Study 231) of natalizumab at doses of 3 mg/kg and 6 mg/kg in patients with relapsing-remitting MS showed similar reductions in relapse risk between treatment arms. Second, as discussed below, the pivotal clinical trials (Studies 1801 and 1802) did not show a relationship between patient weight and clinical outcome. Finally, in Study 231, 90% of patients in both dosage arms had serum natalizumab concentrations in excess of 2.5 μg/mL 4 weeks after infusion, a level sufficient to achieve at least 80% α4-integrin saturation.

Other relevant clinical pharmacology issues include interactions of natalizumab with Avonex (interferon-beta) and glatiramer acetate. Avonex appears to decrease clearance of natalizumab by 30%; however, given the similarity in adverse event profiles between populations receiving natalizumab alone (in Study 1801) and those receiving natalizumab in combination with Avonex (in Study 1802), I agree that dosage modification is not indicated in the latter circumstance. Characterization of the interaction between natalizumab and glatiramer acetate is inconclusive, and the Applicant has agreed to a post-marketing commitment to resolve this issue.

## Clinical/statistical issues

### *Efficacy*

For full details, please see the clinical review by Dr. Wilson Bryan and the statistical review by Dr. Kallappa Koti and the statistical team leader review by Dr. Boguang Zhen. The Phase 3 program consisted primarily of two on-going double-blind, randomized controlled trials, one comparing natalizumab to placebo (Study 1801), the other comparing natalizumab in combination with Avonex (a marketed brand of an interferon-beta) to Avonex plus placebo (Study 1802). Both trials were designed and powered to demonstrate superiority of the

natalizumab treatment arm to the comparator arm. For full details of study design and conduct, the reader is referred to the primary review by Dr. Bryan.

Study 1801 randomized patients in a 2:1 ratio to natalizumab, 300 mg every 4 weeks, versus placebo The patients consisted of adults aged 18-50 who met standardized (McDonald) criteria for the diagnosis of relapsing-remitting MS who had had at least one relapse in the 12 months prior to study entry (with resolution at least 50 days prior to study entry), had brain lesions on MRI consistent with MS, and who had a Kurtzke Extended Disability Status Scale (EDSS) score of 0.0 to 5.0. Patients were assessed every 12 weeks and during suspected relapses; the definition of relapses excluded pseudo-exacerbations. The primary endpoint for the one year analysis was the annualized relapse rate,

Study 1801 enrolled 627 patients in the natalizumab arm and 315 in the placebo arm. Patients in the two treatment arms were comparable with respect to demographic characteristics, disease stage and duration, relapse frequency, degree of disability, and number of lesions on MRI. The discontinuation rate was comparable in both arms.

Study 1802 randomized patients in a 1:1 ratio to natalizumab, 300 mg every 4 weeks in combination with Avonex, or to Avonex (plus placebo to maintain the double-blind design). The entry criteria were similar, except that patients had to have previously been receiving Avonex for the 12 months prior to study entry; the 1 year and 2 year endpoints were the same as Study 1801.

Study 1802 randomized 594 patients to natalizumab + Avonex and 602 to Avonex + placebo. Because of exclusion of data from a single site that was closed early, the primary analysis included 582 patients randomized to natalizumab + Avonex and 589 randomized to Avonex + placebo; sensitivity analyses did not show any effect of this exclusion on the overall results. As in Study 1801, patients in the two treatment arms were comparable with respect to demographic characteristics, McDonald criteria class, disease duration, relapse frequency, degree of disability, and number of lesions on MRI. The discontinuation rate was comparable in both arms.

The median patient time on study was 13 months for both Studies 1801 and 1802. Dr. Koti has raised the question as to whether it is valid to describe the results in product labeling with the term "one year data." This is in large part a terminological issue that does not significantly affect interpretation of the data. As outlined by Dr. Bryan, the original protocols pre-specified an analysis after patients had undergone an average of one year of observation, with subsequent amendment of the protocols to include a pre-specified cut-off date that achieved that criterion. Study 1801 included data on 988 patient-years of observation, while Study 1802 had data on 1268 patient-years of observation; both thus averaged 13 months of observations per patient, and this is reflected in the clinical studies section of the final version of product labeling, which has been agreed to by the Applicant. I concur that this is an accurate description of the nature of these data.

Efficacy results for studies C-1801 and C-1802 are shown in Table 1 for the primary endpoint.

**Table 1. Annualized Relapse Rate, All Subjects**

| | Study 1801 | | Study 1802 | |
|---|---|---|---|---|
| | Placebo N = 315 | Natalizumab N = 627 | Placebo + Avonex N = 582 | Natalizumab + Avonex N = 589 |
| Mean | 0.735 | 0.250 | 0.780 | 0.357 |
| Standard Deviation | 1.126 | 0.533 | 1.002 | 0.620 |
| Median | 0 | 0 | 0.685 | 0 |
| Range | | | | |

In study 1801, natalizumab-treated patients had a 66.0% relative reduction in the risk of relapse compared to placebo-treated patients. In study 1802, natalizumab-treated patients had a 54.2% relative risk reduction. This treatment effect of natalizumab was consistent when analyses were stratified by demographic subgroup, weight, geographic location, baseline disability score, baseline relapse rate, McDonald criteria class, baseline number of lesions on MRI, or treatment history. In addition, sensitivity analyses examining the effect of missing data showed a consistent treatment effect in natalizumab-treated patients.

Phase 1 and 2 studies of natalizumab employed a weight-based dosing regimen, while the submitted Phase 3 studies used a fixed dose regimen of 300 mg given every 4 weeks. Dr. Bryan's analyses of the effect of weight on the primary endpoint do not show a consistent relationship between patient weight and relapse frequency in any treatment group; if there were in fact such a relationship, natalizumab should consistently show a lesser treatment effect in heavier patients because of inadequate dosing. Thus, the available data support the proposed fixed dose of 300 mg. However, in Studies 1801 and 1802, natalizumab was administered every 4 weeks, rather than monthly as proposed in the Applicant's draft labeling. Since the clinical results were obtained with this administration schedule, I concur with Dr. Bryan's conclusion that the recommended dosage regimen should be 300 mg given intravenously every 4 weeks, which is reflected in the final version of product labeling and has been agreed to by the Applicant.

Dr. Koti's review raises the issue of whether p values may be appropriately used in product labeling, given complex statistical issues with the Poisson model employed by the Applicant and previously agreed to by the Agency. I concur with Dr. Zhen's statistical team leader review, in which he concludes that use of p values in product labeling is supported by the study design and conduct. Of note, the study design was extensively discussed with Agency clinical and statistical reviewers, including Dr. Koti, prior to study initiation and the Agency agreed that the study design as implemented would support approval. In this regard, I do not agree with Dr. Koti's unsupported assertion that the study design was suboptimal, for the following reasons: a) the study design employed randomization by site as a bias minimization feature; b) for the reasons outlined in Dr. Zhen's review, use of study sites with small numbers of patients is valid, and in fact, exclusion of such sites would have prevented any such study from being performed; and c) Dr. Koti's analysis of five arbitrarily selected sites represents a *post hoc* analysis that does not support his conclusions. Of note, in Dr. Bryan's analysis, when sites with 20 or more enrolled patients were individually examined, a consistent treatment effect was seen

in natalizumab-treated patients, although there was some variability because of the small number of patients at any given site.

Tables 2 and 3 show results for two of the secondary endpoints; results for other secondary endpoints were consistent with the results in these tables.

**Table 2. Number of New or Newly-Enlarging T2 Hyperintense Lesions on Year 1 MRI**

| | Study 1801 | | Study 1802 | |
|---|---|---|---|---|
| | Placebo N = 293 | Natalizumab N = 600 | Placebo N = 485 | Natalizumab N = 505 |
| 0 | 70 (24%) | 376 (63%) | 230 (47%) | 392 (78%) |
| 1 | 41 (14%) | 112 (19%) | 70 (14%) | 69 (14%) |
| 2 | 23 (8%) | 40 (7%) | 61 (13%) | 24 (5%) |
| 3 | 24 (8%) | 30 (5%) | 39 (8%) | 10 (2%) |
| 4-9 | 71 (24%) | 34 (6%) | 55 (11%) | 8 (2%) |
| 10-98 | 64 (22%) | 8 (1%) | 30 (6%) | 2 (<1%) |

**Table 3. Proportion of Subjects Relapse-Free**

| | Study 1801 | | | Study 1802 | | |
|---|---|---|---|---|---|---|
| | Placebo N = 315 | Natalizumab N = 627 | Relative risk* (95% CI) | Placebo + Avonex N = 582 | Natalizumab + Avonex N = 589 | Relative risk* (95% CI) |
| Number relapse – free | 166 (53%) | 474 (76%) | 1.43 (1.28, 1.61) | 265 (46%) | 392 (67%) | 1.46 (1.32, 1.62) |

* Relative risk of being relapse-free, comparing natalizumab group to placebo group

Efficacy conclusions

The primary and secondary endpoint results, along with the subgroup and sensitivity analyses performed by the primary reviewers, support the efficacy of natalizumab in decreasing the relapse rate at one year, whether administered as monotherapy or in combination with Avonex. Dr. Walton, in his division director's memorandum, clear and convincingly articulates why this endpoint is reasonably likely to predict clinical benefit over a longer time period and support accelerated approval. I fully concur with his analysis and recommendation.

I will briefly recapitulate the rationale for accelerated approval for this application,. One year data is not sufficient to support traditional approval for this indication, given the chronic nature of relapsing-remitting MS, and the potential for lack of durability of the treatment effect. However, accelerated approval under 21 CFR 601 Subpart E is supported by the serious nature of relapsing-remitting MS; the magnitude of the observed treatment effect of natalizumab; the consequent reasonable likelihood that the one year data predicts longer-term clinical benefit; and the potential of natalizumab to represent a meaningful therapeutic benefit to patients over existing treatments. I agree with Dr. Walton's description of the reasons why an early time point can serve as a reasonable predictor of results at a later time point; his analogy with the regulatory basis for accelerated approval of anti-retroviral agents is particularly persuasive, given the durability of benefit issues with that group of therapeutic agents.

Conventional approval will depend on verifying the clinical benefit of natalizumab by demonstrating clinical efficacy at two years. Studies 1801 and 1802, which are currently

ongoing, were designed to study the effects of two years of treatment. The Applicant has committed to complete these studies and submit study reports on them, along with revised labeling reflecting the results.

## *Safety*

### Extent of exposure

The reader is referred to Dr. Bryan's review for full details of the safety analysis. The safety database from placebo-controlled trials for natalizumab includes 2,539 patients; duration of exposure and patient populations exposed are shown in Table 4. The majority of the multiple sclerosis patients were exposed at the proposed recommended regimen. The safety analysis focused on MS patients treated with natalizumab for prolonged periods; other populations, such as Crohn's disease patients or healthy volunteers, were small in size and treated for short durations, and except for serious clinical or laboratory adverse events are unlikely to contribute significantly to understanding of the toxicity profile of natalizumab. The size of the patient population exposed to natalizumab for one year or more is sufficient to detect, with 95% confidence, adverse events occurring at a rate of 0.3% or greater. Given the potential population exposure to natalizumab, this database appears adequately powered to evaluate the safety of natalizumab for purposes of licensure.

**Table 4. Total Exposure to Natalizumab in Placebo-Controlled Trials**

| | Multiple Sclerosis | | | Crohn's disease | | |
|---|---|---|---|---|---|---|
| | Total | Natalizumab | Placebo | Total | Natalizumab | Placebo |
| Total N | 2752 | 1617 | 1135 | 1178 | 922 | 256 |
| Duration of Exposure (weeks) | | | | | | |
| 1 to <12 | 376 | 247 | 129 | 1178 | 922 | 256 |
| 12 to <24 | 114 | 63 | 51 | 0 | 0 | 0 |
| 24 to <52 | 331 | 184 | 147 | 0 | 0 | 0 |
| 52 to <116 | 1924 | 1119 | 805 | 0 | 0 | 0 |
| ≥ 116 | 7 | 4 | 3 | 0 | 0 | 0 |

### Deaths

There have been nine deaths in the natalizumab studies conducted to date; three in placebo-treated MS patients, four in natalizumab-treated MS patients, and two in natalizumab-treated Crohn's disease patients. In two of these cases (one malignancy and one infection), there was a possible relationship between natalizumab treatment and a fatal outcome; a third fatal outcome in a natalizumab-treated patient may have represented a suicide, which is of concern given the association between suicide in MS patients receiving interferon. However, I concur with Dr. Bryan's assessment that these cases do not represent a clear safety signal, given the presence of confounding factors (e.g., the association of these events with the underlying disease itself), lack of data (for example, the case of possible suicide may have in fact been a homicide) and the lack of a substantial difference in mortality rates between natalizumab and placebo-treated subjects (0.2% vs. 0.2%), although the size of the placebo-treated population precludes meaningful statistical analysis. However, continued evaluation of these issues via examination of post-marketing surveillance data is warranted.

## Nonfatal clinical serious adverse events (SAEs)

Rates of nonfatal SAEs are shown in Table 5. I concur with Dr. Bryan's conclusion that there is a signal with regard to hypersensitivity and anaphylactoid events in natalizumab-treated patients. Furthermore, analysis of infections in studies C-1801 and 1802 showed a higher incidence of infections in natalizumab-treated patients (2.1% natalizumab vs. 1.3% placebo in study 1801 and 1.8% natalizumab vs. 1.2% placebo in study 1802); given the mechanism of action of natalizumab, this may reflect immunosuppression in these patients. The events reported do not appear to represent infections due to opportunistic pathogens; however, given the mechanism of action of natalizumab, this issue deserves continued scrutiny, both via post-marketing surveillance and via post-marketing commitments agreed to by the Applicant to more fully characterize the effect of natalizumab on the immune system.

**Table 5. Percent of Subjects with Serious Adverse Events in Placebo-Controlled Trials; Includes All Serious Adverse Events With Incidence ≥ 1% In Natalizumab Group, And Selected Serious Adverse Events of Interest (From Applicant's Analysis)**

| | Multiple Sclerosis* | | Crohn's Disease** | |
|---|---|---|---|---|
| | Natalizumab N = 1617 | Placebo N = 1135 | Natalizumab N = 922 | Placebo N = 256 |
| Any serious adverse event | 12.5 | 15.2 | 17.4 | 17.2 |
| Infections and Infestations | 1.8 | 1.6 | 2.8 | 3.1 |
| Neoplasms | 0.6 | 1.2 | 0.9 | 0.4 |
| Hypersensitivity / Anaphylactoid | 0.7 | 0.2 | 0.5 | 0.4 |
| Depression / Suicide attempt | 0.6 | 0.7 | 0.2 | 0.8 |
| Cardiac disorders | <0.1 | 0.4 | 0.5 | 0 |

Dr. Bryan performed additional, treatment-blinded categorization-analyses of non-fatal SAEs occurring in Studies 1801 and 1802 at a rate of 0.5% or more that were more frequent in natalizumab-treated patients, pooling AEs in related groups (e.g., lobar pneumonia, atypical pneumonia) to increase the sensitivity of the analysis. He found that events that were more frequent in natalizumab-treated patients in these studies included infection (including pneumonia and urinary tract infection), allergic reaction, anaphylaxis, and cholelithiasis.

## Dropouts and treatment discontinuations

Dropouts were less frequent in natalizumab treatment arms in both Studies 1801 and 1802 (1801: 3% natalizumab vs. 6% placebo; 1802: 5% natalizumab vs. 7% placebo). Treatment discontinuations were also less frequent in natalizumab-treated patients (1801: 7% natalizumab vs. 9% placebo; 1802: 10% natalizumab vs. 12% placebo). The majority of natalizumab-treated patients who withdrew did so for adverse events, and the majority of these represented urticaria, anaphylaxis, and hypersensitivity reactions, depression or suicidal ideation, and infection, AEs that were more common overall in natalizumab-treated patients.

## Common clinical adverse events

Rates of common adverse events in Studies 1801 and 1802 are shown in Table 6.

| Table 6. Rates of common adverse events in Studies 1801 and 1802 | | | | |
|---|---|---|---|---|
| | Study 1801 | | Study 1802 | |
| | Natalizumab N=627 | Placebo N=315 | Natalizumab + Avonex N=601 | Placebo + Avonex N=595 |
| Infection | 424 (68%) | 200 (63%) | 241 (40%) | 251 (42%) |
| Headache | 229 (37%) | 97 (31%) | 163 (27%) | 153 (26%) |
| Fatigue or malaise | 226 (36%) | 87 (28%) | 189 (31%) | 206 (35%) |
| Depression | 122 (19%) | 49 (16%) | 84 (14%) | 74 (12%) |
| Arthritis/arthralgia | 107 (17%) | 42 (13%) | 98 (16%) | 85 (14%) |
| Urinary urgency | 65 (10%) | 26 (8%) | 67 (11%) | 69 (12%) |
| Urinary tract infection | 91 (15%) | 41 (13%) | 98 (16%) | 85 (14%) |
| Rhinitis, congestion, stuffiness | 85 (14%) | 37 (12%) | 59 (10%) | 44 (7%) |
| Abdominal discomfort | 71 (11%) | 31 (10%) | 42 (7%) | 37 (6%) |
| Rash | 58 (9%) | 22 (7%) | 38 (6%) | 41 (7%) |
| Gastroenteritis | 56 (9%) | 16 (5%) | 51 (8.5%) | 43 (7%) |
| Infection, viral | 32 (7%) | 9 (4%) | 20 (5%) | 28 (6%) |
| Vaginitis* | 32 (5%) | 10 (3%) | 1 (0.2%) | 3 (0.5%) |
| Elevated ALT/AST/GGT | 31 (7%) | 7 (3%) | 16 (4%) | 12 (3%) |
| Tonsillitis | 27 (4%) | 7 (2%) | 24 (4%) | 19 (3%) |
| Menstrual irregularities* | 27 (4%) | 7 (2%) | 18 (3%) | 26 (4%) |
| Pruritus | 27 (4%) | 9 (3%) | 25 (4%) | 13 (2%) |
| Chest discomfort | 26 (4%) | 9 (3%) | 28 (5%) | 23 (4%) |
| Dermatitis | 24 (4%) | 4 (1%) | 15 (2%) | 23 (4%) |
| Tremor | 18 (3%) | 3 (1%) | 16 (3%) | 2 (0.3%) |
| Miscellaneous allergic reaction | 17 (3%) | 4 (1%) | 11 (2%) | 1 (0.2%) |
| Rigors | 17 (3%) | 5 (2%) | 10 (2%) | 7 (1%) |
| Syncope | 13 (3%) | 1 (0.5%) | 9 (2%) | 17 (4%) |
| Bleeding | 9 (2%) | 0 | 1 (0.2%) | 4 (1%) |
| Dysmenorrhea* | 424 (68%) | 200 (63%) | 241 (40%) | 251 (42%) |
| Amenorrhea* | 229 (37%) | 97 (31%) | 163 (27%) | 153 (26%) |
| * percentage based on female N | | | | |

Among AEs rated as severe, infections occurred more frequently in natalizumab-treated patients than in the placebo group in Study 1801 (3.5% vs. 2.5%) and Study 1802 (5.8% vs. 4.9%). However, as noted by Dr. Bryan, the infections in natalizumab-treated patients resolved spontaneously or responded to appropriate anti-microbial therapy. In the two studies, there were 7 malignancies in natalizumab-treated patients and 5 in placebo-treated patients (0.5% vs. 0.7%); thus, the data did not demonstrate an association between natalizumab and malignancy, but given the immunomodulatory activities of this agent, continued evaluation of this issue via post-marketing surveillance is warranted.

Infusion-related reactions, an AE characteristic of monoclonal antibodies, occurred in both studies at higher rates in natalizumab-treated patients than in placebo-treated patients (1801: natalizumab 20% vs. placebo 15%; 1802: natalizumab + Avonex 21% vs. placebo + Avonex 16%), with headache being the most common infusion-related reaction.

Analyses of disability progression did not show any adverse effect of natalizumab. In addition, data from a Phase 2 study (Study 231) involving treatment of patients with natalizumab for 6 months followed by at least 3 months of follow-up did not show evidence for rebound after

withdrawal from natalizumab; relapse rates during follow-up were 35% in placebo-treated patients and 33% in natalizumab-treated patients.

## Laboratory analyses

Because of the mechanism of action of natalizumab, Dr. Bryan performed an extensive series of analyses of hematologic parameters, including measures of central tendency, shifts in laboratory values, and outlier analyses. These showed increases in mean values for all leukocytes, except neutrophils, which do not express α4β1-integrin. In addition, subjects showed, on average, an increase in the percentage of peripheral nucleated red blood cells, which may reflect alterations in retention of these cells in the marrow.

There was minimal evidence for hepatotoxicity when natalizumab is administered alone; there was a slightly higher incidence in shift to abnormal transaminase and bilirubin levels in patients receiving natalizumab in combination with Avonex. However, outlier analysis showed similar numbers of severe elevations in liver function test values in Study 1802 (1 patient in the natalizumab + Avonex group, and 2 patients in the placebo + Avonex-treated group).

## Immunogenicity

As with any immunogenic agent, development of antibodies against natalizumab was of concern because of the potential for effects on efficacy and safety. Results of immunogenicity testing for development of antibodies to natalizumab are shown in Table 7.

**Table 7. Development of antibodies to natalizumab**

| | Study 1801 | C-1802 |
|---|---|---|
| | Natalizumab | Natalizumab + Avonex |
| Subjects randomized | 627 | 589 |
| Subjects evaluated | 625 (99.7%) | 585 (99.3%) |
| Antibody negative | 568 (91%) | 516 (88%) |
| Any positive antibody | 57 (9%) | 69 (12%) |
| Transient antibody positive | 20 (3%) | 31 (5%) |
| Persistent antibody positive | 37 (6%) | 38 (6%) |
| Time to antibody positive = 0-13 weeks | 47 (82%) | 66 (96%) |
| Time to antibody positive = 13 – 26 weeks | 7 (12%) | 3 (4%) |
| Time to antibody positive = > 26 weeks | 3 (5%) | 0 (0%) |
| Anti-Avonex antibody at Week 24 | - | 18 (3%) |

These data show that 9% of patients receiving natalizumab in Study 1801 and 12% in Study 1802 developed antibodies to this agent, either transiently or persistently. Dr. Bryan analyzed the incidence of AEs according to development of anti-natalizumab antibodies, and found a clear relationship between an immunogenic response and infusion reactions, with the incidence of such reactions higher in those patients with persistent seropositivity (18% for antibody-negative patients, 27% for transiently seropositive patients, and 77% for persistently seropositive patients). Allergic reactions also showed an association with seropositivity, while other common AEs did not.

In addition, antibody development was correlated with a decrease in treatment effect, with the loss being greatest in those patients who were persistently positive for anti-natalizumab

antibodies. These data underscore the need to obtain long-term data (i.e., 2 year data) to evaluate the durability of response to natalizumab and further characterize its toxicity profile.

### Safety conclusions

The safety data in this application and Dr. Bryan's analyses, in combination with the efficacy data described above, support the conclusion that natalizumab has an acceptable benefit-risk ratio, warranting accelerated approval. However, further description of the clinical benefit of natalizumab, via collection of two year data, is necessary to fully characterize the toxicity profile of this agent and to support full approval.

## Regulatory conclusions

In summary, the data in this application support approval under 21 CFR 601 Subpart E for treatment of relapsing-remitting multiple sclerosis at a dosage regimen of 300 mg intravenously every 4 weeks, and provide a basis for construction of product labeling that contains the essential scientific information needed for the safe and effective use of natalizumab. The product labeling should indicate the lack of information about safety and efficacy beyond one year, and contain appropriate warnings regarding the risk of infusion reactions and immunosuppression. The Applicant has agreed to appropriate post-marketing commitments, including collection of two year data to verify the clinical benefit of natalizumab in relapsing-remitting MS

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**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Public Health Service**
**Food and Drug Administration**
**Center for Drugs Evaluation and Research**

# Memorandum

**DATE:** **November 23, 2004**

**FROM:** **Beverly A. Conner, Pharm.D.**
Regulatory Project Manager, DRMP
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research, HFD-109

**TO:** **STN 125104/0**

**SUBJECT:** **SBA Equivalent for**

- **Product:** TYSABRI®, **Natalizumab**
- **Manufacturer: Biogen, Inc.**
- **License Number: 1697**

**Product: TYSABRI®** (natalizumab) is a recombinant humanized IgG4κ monoclonal antibody produced in murine myeloma cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α4-integrin. The molecular weight of natalizumab is 149 kilodaltons. TYSABRI® is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous (IV) infusion

**Indications and Usage**

TYSABRI® is indicated for the treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. This indication is based on results achieved after approximately one year of treatment in ongoing controlled trials of two years in duration. The safety and efficacy of TYSABRI® beyond one year are unknown.

Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

**Dosage Form, Route of Administration, and Recommended Dosage**

- Natalizumab, (TYSABRI®) concentrate is supplied as 300 mg/15 mL (20 mg/mL) in a sterile, single-use vial free of preservatives. Each package contains a single-use vial.
- The TYSABRI® concentrate comes in a 300 mg/15 mL and is diluted in 100 mL 0.9% Sodium Chloride Injection, USP, and is intended to be infused over approximately one hour. TYSABRI® is not intended to be used as an IV push or bolus injection.
- The recommended dose of TYSABRI® is 300 mg IV infusion every four weeks

- Each 15 mL dose contains 300 mg natalizumab; 123 mg sodium chloride, USP; 17.0 mg sodium phosphate, monobasic, monohydrate, USP; 7.24 mg sodium phosphate, dibasic, heptahydrate, USP; 3.0 mg polysorbate 80, USP/NF, in water for injection, USP at pH 6.1.

**Basis for Approval**
The following reviews, filed in the CBER correspondence section of the license file for STN 125104/0 comprise the SBA equivalent for this application/supplement:

| Discipline | Reviewer Name | Date |
|---|---|---|
| CMC, Product | Elena Gubina, Ph.D.<br>Lei Zhang, Ph.D.<br>Joseph Kutza, Ph.D. | November 18, 2004 |
| CMC, Facility | Calvin Koerner | October 29, 2004 |
| Clinical (Safety and Efficacy) | Wilson Bryan, M.D. | November 23, 2004 |
| Pharmacology/Toxicology | Barbara Wilcox, Ph.D. | November 3, 2004 |
| Clinical Pharmacology | Ifterhar Mahmood, Ph.D. | November 1, 2004 |
| Non-clinical Pharmacology | Anne Pilaro, Ph.D. | November 17, 2004 |
| Statistical Review | Kallapa Koti, Ph.D. | October 25, 2004 |
| Secondary Statistical Review | Bo-Guang Zhen, Ph.D. | November 22, 2004 |
| Bioresearch Monitoring | J. Lloyd Johnson, R.Ph. | November 18, 2004 |
| DMETS Consult Review | Charles Hoppes, R.Ph., M.P.H. | November 17, 2004 |
| Secondary Clinical Review | Marc Walton, M.D., Ph.D. | November 22, 2004 |
| Tertiary Clinical Review | David Ross, M.D., Ph.D. | November 23, 2004 |

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
Food and Drug Administration
Center for Drug Evaluation and Research
1451 Rockville Pike
Rockville, MD 20852

# Memorandum

Division of Therapeutic Biological Internal Medicine Products
HFD-108

Date: November 22, 2004

From: M Walton, Director, DTBIMP/ODE6

Subject: Recommendations regarding action for BLA 125104 / 0
Natalizumab for the treatment of multiple sclerosis
Submitted by Biogen-Idec, Inc.

To: BLA 124104 / 0 File
K. Weiss, Director, ODE6

This memorandum addresses Biogen-Idec's request that FDA grant accelerated approval for their product natalizumab for the treatment of multiple sclerosis. This memorandum is not intended to be a comprehensive overview of the totality of the data regarding this product (please refer to the memorandum from Dr. D. Ross) or a detailed examination of the data submitted by the applicant (please refer to the individual discipline reviews).

## Summary and Recommendation

Two independent clinical studies have provided robust evidence that natalizumab treatment of patients with relapsing multiple sclerosis leads to a reduction in relapses over a 1 year period. However the evidence from only 1-year of treatment is insufficient to support a definitive conclusion regarding reduction in relapses for this chronic disease, as discussed in this memorandum. Therefore, conventional marketing approval for natalizumab at this time is not warranted. Consideration of accelerated approval is worthwhile in this circumstance. While it is uncertain whether the treatment effect observed in these studies will be durable, the observed treatment effect is of very substantial size and is reasonably likely to persist, at least in part, during the second year of study treatment. Furthermore, one of the two studies (Study 1802) has shown natalizumab provides a meaningful benefit beyond that from Avonex treatment alone. Other applicable available marketed therapies for multiple sclerosis provide somewhat similar treatment effect size to Avonex (and several are of the same class as Avonex), and thus it is likely that natalizumab provides a meaningful benefit beyond the other existing therapies as well.

In summary, a natalizumab-associated treatment effect has been shown in robust, adequate, and well-controlled trials, this effect can be regarded as reasonably likely to predict a durable benefit in the reduction of relapses, and natalizumab can be regarded as an important advance to the treatment of multiple sclerosis, beyond that seen with available therapies alone.

Therefore, I recommend granting of marketing approval under 21CFR601.42 (accelerated approval) for natalizumab for the reduction of relapses in patients with relapsing forms of multiple sclerosis. Marketing approval should be contingent upon Biogen-Idec committing to verify the expected benefit of a durable reduction in relapses through a full two years of treatment. This can be accomplished by continuing studies 1801 and 1802 to their intended completion (when the mean time on-study in each study will be two years)

**Available Evidence of Efficacy and Safety**

Biogen-Idec has submitted a marketing application for natalizumab describing two independent clinical studies in multiple sclerosis patients. These two studies have demonstrated an effect of natalizumab upon relapse rate through approximately 13 months of treatment. In Study 1801, the monotherapy study, annualized relapse rates were 0.74 in the placebo group, 0.25 in the natalizumab group, representing a 66% relative reduction in relapse rate. In the add-on to Avonex study (Study 1802) the annualized relapse rates were 0.78 placebo, 0.36 natalizumab, a 54% relative reduction. As detailed by Dr Bryan in his review, these findings were robust to exploration of the data. MRI evaluations were performed in these studies, and both Gd-enhancing lesion counts and T2 lesion counts were also substantially reduced in the natalizumab treated group compared to the placebo group.

The safety profile of natalizumab was adequately evaluated in these studies, and safety risks are acceptable for this disorder and expected benefit. As described by Dr. Bryan, while some adverse events appear to be associated with natalizumab exposure, most are not of a serious nature, nor of a high enough frequency to render the risk-benefit unfavorable (when considering the benefit as durable).

**Existing efficacy evidence is insufficient to permit a definitive conclusion**

While relapses are a meaningful event for patients with multiple sclerosis, the nature of the disease is a chronic one, unlike the transient individual relapses. Natalizumab, like most treatments for MS, is not intended as an acute treatment of an ongoing relapse. Natalizumab is intended as a chronically administered treatment, potentially for as long a duration as the disease course, that is for several decades. Thus, only a product that provides a sufficiently durable treatment effect should be considered a worthwhile treatment for this disorder.

Demonstration of durability of effect was addressed in the data that supported approval of the five existing approved products for multiple sclerosis. The marketing applications for all five products included evidence of treatment effect for two years duration in placebo controlled studies, and this evidence was available at the time of initial approval of the product.

The immune system is a highly dynamic system, comprised of a large number of interacting processes. The pathologic immune system underlying a clinical disorder may have the ability to

"break free" of an immunosuppressant therapy over time. If such occurs, benefit from a treatment initially efficacious may wane over time. This would be particularly problematic for multiple sclerosis therapies. Once a patient begins treatment with one of the approved products, the intent is to continue treatment indefinitely. There are no ongoing clinical signs and symptoms, or laboratory parameters of the acute, active inflammatory process that can be evaluated to assess the effectiveness of the treatment in an individual patient. It is not possible to determine whether the treatment continues to provide a durable benefit in a particular patient. If waning of effect occurs to a substantial degree, there is ongoing exposure with ongoing safety risks, but without counterbalancing benefit. Consequently, it is important to have evidence that the treatment-associated benefit is durable and does not substantially wane with time.

A potential for waning of effect is not purely theoretical. The three year, randomized, placebo controlled trial of sulfasalazine (Noseworthy JH, et al, 1998) clearly illustrates this phenomenon. The study enrolled patients who, while not identical to the population studied with natalizumab, were substantially similar. Patients with either relapsing-remitting or progressive MS patients were enrolled. Approximately three-fourths were categorized as relapsing-remitting, and at least some of the "progressive MS" patients of this study would have qualified as a "relapsing form" of MS under the eligibility criteria of the natalizumab, as well as other recent studies in multiple sclerosis patients. For the secondary endpoint of relapses in the sulfasalzine, the annualized relapse rate was 1.0 in the placebo group, 0.8 in the sulfasalazine group (20% reduction in relapse rate). However, the authors state that the treatment-associated effect on relapse frequency was not continued after month 18; during the second 18 months of the study (month 18 to 36) the mean relapse rates were 1.15 in the placebo group and 1.11 in the sulfasalazine group. Thus, the majority of the reduction in relapses occurred during the first 18 months of treatment and largely waned thereafter.

Another important aspect to the treatments for multiple sclerosis is that there are no established methods for physicians to identify patients likely to respond to treatment from among the general relapsing-remitting MS population. As noted, there are no ongoing signs and symptoms of the acute inflammatory process that permit assessment of the effectiveness of the product in the individual patient. Thus, a brief "trial of treatment" approach to select which patients with multiple sclerosis are likely to respond is not feasible. It is important to have confidence in the wide-spread nature of the benefit across the treated population to ensure that the product's risk-benefit comparison is likely to remain favorable in clinical practice.

Studies of relapse rates from one-year-only trials are generally not suitable to establish the breadth of the treatment effect. In the studies submitted in support of natalizumab's efficacy, the fraction of patients in the control groups who had no relapses during the study period was approximately half (53% in study 1801, 46% in study 1802). Thus, half of the patients in the natalizumab group would have had the same, entirely good outcome of no relapses irrespective of their treatment assignment. Yet these patients will likely experience relapses sometime in the future. There is no adequate explanation for why some patients experience clinical relapses of at a greater or lesser frequency. Intrinsic difference in their disease may possibly account for this clinical variability. If that is the case, then there may be less confidence that the patients with a disease "nature" who would not experience a relapse in that first year of treatment would benefit from the drug treatment when their disease does shift to the process leading to a relapse. Since patients characterized by more as well as fewer relapses will be treated in clinical practice, it is important to ensure that the

range of patient phenotypes within the indicated population are all reasonably well evaluated for the effects of the product. This permits that the study results can reasonably be generalized to the entire indicated population. Studies of only 1 year duration are insufficient to support conclusions regarding efficacy because a substantial fraction of patients (who would be in the indicated population) have not had the opportunity to benefit (or show no benefit) from the product. Thus, a comprehensive risk-benefit assessment is unfeasible, and the generalizability of the observed data to the proposed indicated population is uncertain. Therefore, studies of only 1 year duration are insufficient for approval based on the endpoint of relapse rate

Two years of controlled study will allow the great majority of patients in the control groups to have experienced at least one relapse, and thus to have had at least one opportunity to contribute to the demonstration of a benefit being associated with the product. This will better serve to ensure that the observed benefit is applicable to the broad population and not some small subset of the population studied.

The concerns discussed above indicate why, for any product for this disorder, one year data on relapses is not sufficient to support conclusions regarding efficacy as would be necessary to support conventional marketing approval. An uneasiness to accept short-term assessments as a definitive efficacy demonstration has also been expressed by some members the clinical community (e.g., Rudge P, 1999). Natalizumab and similar large protein products raise an additional concern that militates to caution when considering shorter term data.

Exogenous proteins have the potential to elicit an antibody response against the product, which can potentially alter the efficacy of the product. This might occur either through antibodies that directly neutralize the protein's physiologic activity, or antibodies that alter the pharmacokinetic profile of the product by causing it to be removed from the circulation more rapidly, lowering the effective exposure to the drug. Antibodies are known to form in response to the interferon beta products. There does not appear to be an overwhelming clinical problem from these antibodies during longer term use, but antibodies may still be an important limitation to the effectiveness of these products in some patients. The time course of antibody formation may be different for the different interferon products, and frequency of antibody formation may differ as well. With each of the three interferon beta products there is data suggesting that at least higher titers of the antibodies may diminish the effectiveness of the product.

Current data from the clinical studies indicate that natalizumab does elicit antibody responses in at least some patients, but the available data may incompletely reflect the true frequency of antibody formation because a) the assay has limited sensitivity while circulating natalizumab is present, and b) the duration of observation is limited. The present results do indicate that antibodies form in some patients, and leave the question of antibody incidence during the second year of treatment unaddressed.

Dr. Bryan's exploration of the data suggests that for patients who develop an antibodies response the treatment effect is reduced or eliminated. This issue again raises the durability of benefit issue discussed above. If a substantial fraction of patients develop persistent antibodies against natalizumab during the second year of treatment, the efficacy of the product may wane. The value of natalizumab in the treatment of multiple sclerosis would then be in question. This issue provides

additional caution regarding reliance on 1 year clinical results as definitive evidence of efficacy for products to treat multiple sclerosis.

**Accelerated approval**

The regulations followed by FDA have recognized that there may be data regarding a new product that appears to provide important benefits to patients who may have inadequate or no therapy for a serious disease, but that the available evidence of effect is not sufficient to provide conventional marketing approval. Nonetheless, it can be in the interest of the public health to make the product available commercially under certain conditions.

The accelerated approval regulations provide a means to permit, under specific circumstances, marketing of a product for which there is not substantial evidence of efficacy. This is applicable to "...products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments ..." (21CFR601.40). For the circumstance relevant here, the regulations further state "FDA may grant marketing approval for a biological product on the basis of adequate and well controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, ..., to predict clinical benefit...." and "Approval under this section will be subject to the requirement that the applicant study the biological product further to verify and describe its clinical benefit..." (21CFR601.41).

The FDA Guidance for Industry: Fast Track Drug Development Programs – Designation, Development, and Application Review (Revision 1, July 2004) provides further discussion on accelerated approval. The guidance illustrates by some examples circumstances in which accelerated approval could be appropriate. The examples include "clinical benefits measuring short-term benefit in a chronic condition where short-term benefit per se does not outweigh risk and where durability of benefit is uncertain but expected"

The essential aspects of this program are that it is focused upon disorders that are serious or life-threatening and that the new product appears to provide important benefits to patients that are beyond what is obtained with the existing treatments (if any) for the disorder. If there are data that establish, through adequate, well-controlled clinical trials, a drug-associated effect upon a surrogate (or an intermediate endpoint), but that endpoint is not a suitable clinical efficacy endpoint, or is inadequate to establish the durability of the benefit, and that endpoint is regarded as reasonably likely to predict the desired ultimate clinical outcome, then accelerated approval can be applied.

Multiple sclerosis is clearly a serious disease, with repeated episodes of transient disability (relapses) a prominent feature, along with accumulation of irreversible disability over time. Secondly, the existing multiple sclerosis therapies are valuable, but are not fully sufficient treatments.

The approved therapies for multiple sclerosis are interferon beta-1b (Betaseron), two forms of interferon-beta-1a (Avonex and Rebif), glatiramer acetate (Copaxone), and mitoxantrone

(Novantrone). The interferons and glatiramer acetate are indicated for relapsing forms of MS or relapsing-remitting multiple sclerosis, largely the same population that BiogenIdec is requesting for natalizumab. None of these four therapies completely abrogate relapses. Many patients will continue to have relapses while on one of these therapies. Mitoxantrone is also not fully effective, and in addition it is not indicated for the broad relapsing-remitting patient population. Consequently, new therapies for multiple sclerosis are needed. If data derived from appropriate studies meet the spirit of this regulation, and all other criteria are satisfied, then new therapies can be made available sooner than under the conventional approval mechanism.

**Reasonably likely to predict**

Do the available data constitute evidence of an effect on an endpoint which is reasonably likely to predict a definitive clinical outcome? The evidence supplied to-date describes the effect on relapses through approximately 13 months of treatment. These data were obtained in adequate and well-controlled clinical studies, and the results were robust to exploratory analyses. As described above these data do not constitute definitive evidence of efficacy. There remains uncertainty as to the durability of observed effect. However, it is likely that in this case, due to the substantial size of the treatment effect seen through 1 year, that some portion of effect will continue over the longer term. Had the data described a 1 year effect size that was smaller than this, this conclusion might not be well founded. The large magnitude of the effect seen in these studies is essential to provide a basis for concluding that the 1 year observations are reasonably likely to predict durability of benefit.

In this approach, relapse rate at 1 year is regarded as an insufficient endpoint for approval, but is used to predict the outcome at 2 yrs on the same parameter, which is regarded as a definitive clinical efficacy endpoint. Guidance and Agency precedent support accelerated approval based on an endpoint at an intermediate time used to predict a finding on the same endpoint at a later time.

A similar case are the antiviral agents used for the treatment of HIV infection. Many of these products were studied for their effect on a laboratory assay of viral load. This parameter has served as both the unvalidated surrogate endpoint of the study for an interim analysis supporting an accelerated approval as well as the validated definitive outcome for the final analysis. Viral load is regarded as the most informative outcome measure for this disease. However, the viral load at 6 months is not regarded as definitive. Only a durable reduction in viral load is considered to be validated (i.e., predictive of a longer term clinical outcome), and the early timepoint analysis occurs prior to the demonstration of durability. The 1 year timepoint is regarded as sufficient to assess durability of the treatment effect. Therefore, it is suitable as a basis for a conventional approval.

The Fast Track Guidance Document recognizes the concern that for chronic diseases there will need to be a demonstration of a chronic (i.e., durable) treatment effect to adequately justify chronic administration. Consequently, the use of a particular parameter at an early timepoint as a surrogate for a later, durability-demonstrating, timepoint on that same parameter is fully in keeping with the spirit of the accelerated approval program.

**Meaningful benefit over existing treatments**

As already noted, a number of approved treatments for multiple sclerosis exist. The three beta interferons and glatiramer acetate are all indicated broadly for relapsing remitting multiple sclerosis patients, essentially the same population as has been studied with natalizumab. Therefore it is important to consider whether natalizumab appears to provide a meaningful benefit over these treatments.

Mitoxantrone, the remaining product is indicated for secondary progressive MS patients, or relapsing patients who are having important disability progression either unrelated to relapses (progressive relapsing) or related to relapses ("worsening relapsing remitting"). This is a patient population that has a limited overlap with the population studied with natalizumab and requested by the applicant for approval as the indicated population for natalizumab. In addition, the concern with safety risks associated with mitoxantrone have limited its use to the more severely affected patients. Consequently, natalizumab has the potential to provide meaningful benefit to patients beyond mitoxantrone by providing benefit to patients for whom mitoxantrone is not appropriate.

No randomized studies have been conducted directly comparing natalizumab treatment to treatment with any of the other products approved for reduction of relapses. However, one adequate and well-controlled study demonstrated that natalizumab can provide additional benefit to patients who are already receiving one of the interferon betas (Avonex). These patients gained additional benefit over Avonex (alone) when natalizumab was added to their treatment regimen.

No similar efficacy studies were performed with the other two interferon betas or glatiramer acetate. However, there appears to be sufficient basis to extrapolate the general finding of Study 1802 (Avonex vs Avonex plus natalizumab) to the other three approved products.

All three products have been studied for an effect upon relapses in controlled studies, as summarized in Table 1:

**Table 1: Placebo Controlled Study Results on Relapses**

| Product | Study | Dose & Regimen | Annualized Relapse Rates | | |
|---|---|---|---|---|---|
| | | | Placebo | Drug | Relative Reduction |
| **Relapsing Remitting MS** | | | | | |
| Interferon beta-1b | Phase3 | 250 µg qod | 1.31 | 0.9 | 31% |
| Interferon beta-1a (Avonex) | MSCRG | 30 µg qwk | 0.82 | 0.67 | 18% |
| Interferon beta-1a (Rebif) | PRISMS | 44 µg tiw | 1.28 | 0.86 | 33% |
| Glatiramer Acetate | Phase3 | 20 mg qd | 0.84 | 0.6 | 29% |
| | Ph3 MRI focus | 20 mg qd | 1.21 | 0.81 | 33% |
| **Secondary Progressive MS** | | | | | |
| Interferon beta-1b | EU-SPMS | 250 µg qod | 0.63 | 0.42 | 33% |
| | NA-SPMS | 250 µg qod | 0.28 | 0.16 | 43% |
| | NA-SPMS | BSA adj | | 0.2 | 29% |
| Interferon beta-1a (Avonex) | IMPACT | 30 µg qwk | 0.3 | 0.2 | 33% |
| Interferon beta-1a (Rebif) | SPECTRIMS | 44 µg tiw | 0.71 | 0.5 | 30% |

Data sources: Approved package inserts, or published reports of the studies where the relapse result is not included in approved labeling (GA MRI focus study [Comi G 2001], IMPACT (Cohen JA 2002), SPECTRIMS [Spectrims study group 2001]). Relapse rates shown as annualized rates; when reported rates were over a specific period of time (not annualized), an "annualized" rate for this table was calculated as the reported rate divided by the number of years of observation (usually 2).

Among the notable features in this table is that most studies with each of these products have shown an effect upon relapses of a reduction in relapse rate by approximately 1/3. The two exceptions are the phase 3 MSCRG study of Avonex (relative reduction of 18%), and the interferon beta-1b North American Secondary Progressive MS Study (NA-SPMS; 43% relative reduction at the recommended dose of 250 μg qod).

In the case of the Avonex study, there was a disparity between those patients who had a full two years on study, and those who had less than 2 years on study. The 2-year patients had an annualized relapse rate that was reduced by 1/3 in the Avonex group compared to placebo, while the patients with less than 2 years on study had much less of a reduction in relapse incidence. This discrepancy could not be attributed to duration of treatment, as the 2 year patients had reduced numbers of relapses during both the first and second years of study participation. The disparity remains without explanation (see FDA Clinical Review for PLA 95-0979, Avonex for treatment of relapsing forms of MS, March 1996). However, the Avonex study in patients with secondary progressive MS a 33% relative relapse rate reduction was also observed. This suggests the 1/3 relative reduction may be a more appropriate estimate of Avonex treatment effect. In addition, there was a third placebo controlled Avonex study, conducted in early relapsing MS patients (see approved Avonex labeling). Due to study design, this study could not provide a relapse-rate result. However, examining the incidence of patients with at least 1-relapse over 2 years (39% placebo, 21% Avonex) in this study of very low frequency relapsing patients again suggests a treatment relative effect size greater than the 18% observed in the MSCRG study.

The interferon beta-1b NA-SPMS study suggests a larger effect on reduction of relapses, but closer examination of that study reveals the tenuous nature of that suggestion. The NA-SPMS study also incorporated a treatment group that received interferon on a body surface area adjusted regimen. That group's mean dose was actually slightly higher than in the fixed dose group. The relapse rate in the group dosed by body surface area was reduced 29% relative the control group. As the mean dosing was nearly the same in the two groups, it is unlikely that the 43% and 29% relapse rate reductions accurately represent a difference in treatment effect. The true treatment effect size may lie somewhere in-between those two numbers; i.e., near the 33% reduction observed in the European study (EU-SPMS).

Two randomized studies provide direct comparison between the interferon products. One study, EVIDENCE, compared Avonex to Rebif (data incorporated into Avonex labeling). This study indicated a modest superiority of Rebif over Avonex, with 62% of patients relapse-free at 1 year on Rebif, compared to 52% on Avonex. However, the difference in relapse-free incidence was larger on a relative-risk basis at 6 months than at 1 year (Panitch H et al. 2002), suggesting that the relative superiority may be of limited size in a timeframe of 2 years; the timeframe for the relapse rates that served as the bases for approval (Table 1 studies).

An additional study, INCOMIN (Durelli et al., 2002), compared interferon beta-1b to Avonex. The observed mean relapse rate was 0.7 in Avonex patients, 0.5 in interferon beta-1b patients (29% relative reduction). The data from the INCOMIN study have not been submitted in detail to FDA, prohibiting full assessment of the study or results. One published meta-analytic review (Vartanian 2003) has also examined the published information. This article expressed uncertainty regarding any conclusion of major differences in the efficacy of these products due to the inconsistency of the evidence supporting such a viewpoint.

These cross-study comparisons cannot be used to develop any precise or quantitative comparisons between products. However, there is a notable consistency observed across many placebo controlled studies with patient populations even broader than being considered under the natalizumab application. These comparisons can provide a useful qualitative assessment. Consequently, the general conclusion regarding the placebo controlled studies on the available approved products is that all four products provide generally similar benefit in reduction of relapses. If Avonex has a treatment effect that is less than the other products, it is unlikely to be much smaller.

The estimated treatment effect size of natalizumab is notably larger than any of the treatment effect sizes observed with any of the existing products in any well controlled study. This larger treatment effect size was also evident in the study of natalizumab as an add-on to Avonex. In that study, patients already receiving Avonex benefited by the addition of natalizumab, by a margin well greater than the generally observed 1/3 reduction in relapse rate that occurs with the existing products. Since the treatment effects of the other products are likely to be generally similar to that of Avonex, it is likely that natalizumab added onto any of the other products would also produce a notable incremental increase in efficacy. The accelerated approval provisions do not require that a new therapy be studied in every possible permutation of comparison with other existing therapies to be regarded as providing a meaningful benefit beyond existing therapies. Thus it can be concluded that natalizumab provides a meaningful advance beyond the existing multiple sclerosis treatments. Therefore, these data fulfill the requirements of 21 CFR 601.41 that the new product under consideration provide a meaningful advance over the existing treatments for the disorder.

**Suitability of Accelerated Approval and Verification Requirement**

In summary, multiple sclerosis is a suitable disorder for application of the approval mechanism under 21 CFR 601.41. The existing treatments, though worthwhile, are not ideal, and additional therapies for patients are desirable. Natalizumab has been studied in adequate and well-controlled trials. The results demonstrated an effect upon relapses during 1 year of treatment. This observation cannot be considered a definitive clinical endpoint for this disorder. However, in part because of the substantial magnitude of the observed effect it can be considered reasonably likely to predict a relapse reduction through two years of treatment, an endpoint considered to be a definitive clinical efficacy finding. In addition the efficacy observed in the Avonex-add-on study permits the conclusion that natalizumab has the potential to provide an important advance over the existing treatments. Consequently the criteria for granting accelerated approval appear to be satisfied for natalizumab.

The accelerated approval regulations stipulate that approval is contingent upon a commitment to further study the product to verify the actual clinical benefit that is expected to occur. In the case of natalizumab, the studies which provided the one-year data are planned as two year studies, and will continue through two years of blinded treatment. Approval should be made contingent upon a commitment from Biogen-Idec to complete these studies and submit the final study reports to FDA with labeling changes as appropriate based on the study results.

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**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**
**OFFICE OF DRUG SAFETY**
**(DMETS; HFD-420)**

| **DATE RECEIVED:** | **DESIRED COMPLETION DATE:** | **ODS CONSULT #:** 04-0278 |
|---|---|---|
| October 27, 2004 | November 20, 2004<br>**PDUFA DATE:** November 23, 2004 | |

**TO:** Earl Dye, Ph.D.
Acting Director, Division of Review Management and Policy
HFM-585

**THROUGH:** Beverly Conner, Pharm.D.
Project Manager
HFM-585

| **PRODUCT NAME:** | **BLA SPONSOR:** Elan Pharmaceuticals Inc. and Biogen Idec |
|---|---|
| **Tysabri** (Natalizumab) 300 mg/15 mL<br><br>BLA#: 125104 | |

**SAFETY EVALUATOR:** Charlie Hoppes, R.Ph., M.P.H.

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Tysabri. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in Section III. of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Tysabri acceptable from a promotional perspective.

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**Division of Medication Errors and Technical Support (DMETS)**
**Office of Drug Safety**
**HFD-420; PKLN Rm. 6-34**
**Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** November 8, 2004

**BLA#:** 125104

**NAME OF DRUG:** Tysabri (Natalizumab) 300 mg/15 mL

**BLA HOLDER:** Elan Pharmaceuticals Inc. and Biogen Idec

***NOTE: This review contains proprietary and confidential information that should not be released to the public.***

## I. INTRODUCTION:

This consult was written in response to a request from the Division of Review Management and Policy (HFM-585), for assessment of the proprietary name, "Tysabri", regarding potential name confusion with other proprietary or established drug names. The sponsor has submitted an independent analysis of the proposed proprietary name conducted by the ——— as well as expert opinions from ——— to DMETS in support of the proposed name. Container labels, carton and insert labeling were provided for review and comment.

This is the third proposed name for this application. DMETS previously did not recommend the use of the name Antegren due to concerns with potential confusion with the marketed products Antagon, Edecrin, Integrilin, and Ativan (See ODS Consult # 04-0041). The sponsor was notified of this decision and submitted additional information in support of the Antegren name, including a ——— study. DMETS continued to recommend against the name Antegren due to concerns with potential confusion with the marketed products Integrelin and Ativan (See ODS Consult #04-0041-1). The sponsor then proposed the name ——— but DMETS did not recommend the use of that name due to concerns with potential confusion with the marketed product Integrilin (See ODS Consult #04-0258).

PRODUCT INFORMATION

Tysabri is the proposed proprietary name for natalizumab, a recombinant humanized anti-α4 integren. Tysabri is the subject of application, BB-IND 6895, indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow the progression of disability and decrease the frequency and severity of clinical exacerbations. ———

——— DMETS is unaware of any plans for a separate proprietary name for the product with the latter indication. The usual recommended dosage for Tysabri is 300 mg, administered once a month as a slow (over 60 minutes) intravenous infusion. The drug is to be administered in a free-standing medical clinic, infusion center, or in an outpatient hospital setting and is not intended for administration in the home setting. The sponsor proposes to market Tysabri in 15 mL vials having a strength of 20 mg/mL. The drug is to be further diluted into preservative-free 0.9% sodium chloride to attain a total infusion volume of 100 mL. Tysabri should be stored at 2-8°C, and protected from light.

## II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Tysabri to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Tysabri. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Tysabri acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Tysabri. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

| Product Name | Dosage form(s), Established name | Usual adult dose* | Other** |
|---|---|---|---|
| **Tysabri** | **Natalizumab 300 mg/15 mL (20 mg/mL)** | **Administer 300 mg once every month by slow (over 60 minutes) intravenous infusion.** | |
| Tyrosine | L-Tyrosine Capsules, 500 mg | Take one capsule once or twice daily. | SA/LA |

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
***Name pending approval. Not FOI releasable.**

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

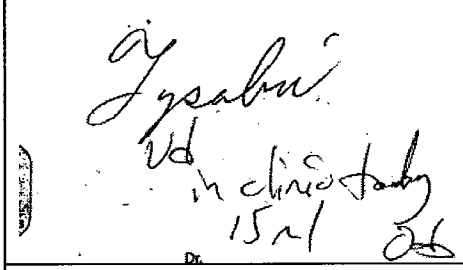
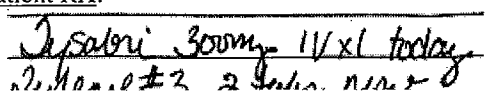
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. No additional names of concern were identified in POCA that were not discussed in EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Tysabri with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Tysabri (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|---|---|
| Outpatient RX:<br>  | Tysabri as directed in clinic today.<br>15 mL.<br>Dr. ODS |
| Inpatient RX:<br>  | |

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

In reviewing the proprietary name Tysabri, the primary concerns related to look-alike and sound-alike confusion with [redacted] and Tyrosine. Upon further review of the names gathered from EPD, the name Tyrosine was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Tysabri in addition to numerous differentiating product characteristics such as the dosage form, route of administration, indications for use, storage conditions, strengths, dosing intervals, and prescriptive status, (Rx vs. OTC).

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Tysabri.

[redacted]

***

E. INDEPENDENT NAME ANALYSIS

The [redacted] conducted a study entitled, "Nomenclature Safety Research: **TYSABRI™** Proposed Proprietary Name For Elan, Biogen Idec, dated, October 12, 2004. Additionally, expert opinions from [redacted] were submitted in support of the name, Tysabri. The analysis conducted by [redacted] discusses the following names that were not identified as potential sound or look-alike products by DMETS: Tiagabine, Ticlid, Tigan, Tussin, Tylenol, Tessalon, Tikosyn, Tyzine, Tiazac, Tilade, and Triphasil. The study identified medical term similarity between Tysabri and the following terms: Tympanic, Tympany, and Typhoid. Computer-assisted analysis identified the following additional sound-alike and look-alike names: Atabrine, Hexabrix, Sabin, Tabron, Tisit, Tisol, Tis-U-Sol, Tioxysalen, and Tussabid. Following review of the proprietary name analysis submitted by [redacted] DMETS concurs that none of the aforementioned names or medical terms poses a significant safety risk. Additionally, the [redacted] found no apparent safety issues with the name Tysabri, and did not identify any names with which Tysabri would be confused. We concur with the overall findings of these studies.

## III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton, and insert labeling of Tysabri, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABELS (300 mg)

1. [redacted]

2. [redacted]

   a.

   b. [redacted]

   c. [redacted]

__1__ Page(s) of Draft Labeling have been Withheld from this Portion of the Review.

## IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name Tysabri.
This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III. of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name Tysabri acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

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Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
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cc: BLA#: 125104
HFM 585: Beverly Conner, Pharm.D., Project Manager
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