MEMORANDUM

DATE: June 4, 2006

FROM: Director
Division of Neurology Products/HFD-120

TO: File, BLA 125104/15

SUBJECT: Action Memo for BLA 125104/15, for the use of Tysabri (natalizumab) in patients with Multiple Sclerosis (MS)

BLA 125104/15, for the use of Tysabri (natalizumab) in patients with Multiple Sclerosis (MS), was submitted by Biogen Idec, Incorporated, on 9/26/05.

The original BLA was submitted by Biogen Idec on 5/24/04. At that time, the application contained the one year results of two randomized placebo controlled trials, Study 1801 (use of Tysabri as monotherapy) and Study 1802 (use of Tysabri as adjunctive treatment to Avonex), both in patients with relapsing remitting MS, each of which was to run for two years. The results on annualized relapse rate in both studies at one year (a planned analysis) were sufficiently impressive that the drug was approved under Subpart E of the BLA regulations on 11/23/04. Under the terms of the approval, the sponsor was required to continue the studies to completion to document that the effect on relapse rate persisted during the second year. Under the study protocol, the primary endpoint at two years was a comparison of the time to sustained disability between the treatment groups.

In February, 2005, the company informed the Agency of the occurrence of two cases of Progressive Multifocal Leukoencephalopathy (PML), a typically fatal opportunistic infection of the brain, caused by the JC virus. Both cases occurred in patients in Study 1802, in which Tysabri was given in conjunction with Avonex. As a result, the sponsor voluntarily withdrew the drug from the market on 2/28/05. At that time, about 7000 patients had received at least one dose of marketed Tysabri, the vast majority having received one or two doses (the drug is given intravenously every four weeks).

Subsequent to withdrawal of the drug from the market, the company undertook an extensive review of all patients in their controlled trials to determine if there were any additional cases of PML (the drug had been studied in patients with Crohn's Disease and Rheumatoid Arthritis). An additional case of PML was detected in a patient with Crohn's Disease. In total, there were 3 cases (2 MS, 1 Crohn's Disease), in a total of about 3000 patients exposed.

The current supplement was submitted on 9/26/05, and contained the results of the required two year data for the two controlled trials. In addition, the

submission contained the detailed results of the sponsor's search of their controlled trial database to detect any additional cases of PML; there were no additional cases beyond the three described above. The application also contained a description of a Risk Minimization Action Plan (RiskMAP) that the sponsor proposed that was designed to monitor patients for the occurrence of PML, should the drug be permitted to be re-marketed.

This supplement has been reviewed by Drs. Susan McDermott and Alice Hughes, medical officers in DNP, Dr. Sharon Yan, statistician, and various members of the Office of Surveillance and Epidemiology (OSE; then the Office of Drug Safety) and the Division of Drug Marketing and Advertising (DDMAC).

This application was discussed at a meeting of the Peripheral and Central Nervous Systems (PCNS) Drugs Advisory Committee on 3/7,8/06.

The review of Drs. McDermott and Hughes describes in detail the effectiveness and safety data. As they note, the effects on relapse rate and accumulation of disability were clearly significant at two years, as were effects on various MRI measures. Regarding safety, a few comments are worth noting.

PML

As noted, a total of three cases of PML have occurred. In MS, there were two cases in a total of 1869 patients treated for a median duration of 120 weeks. One patient was a 46 year old woman who had received 37 infusions and who died. The second patient was a 46 year old man who had received a total of 28 infusions. Although he did not die, he remains severely disabled. As noted earlier, both patients were receiving concomitant Avonex.

In Crohn's Disease, there was one case in 1043 patients treated. This patient was a 60 year old man who had received 8 infusions; he first received three infusions in conjunction with azothiaprine, then azothiaprine alone for an additional 6 months, and then five infusions of Tysabri alone beginning 3 months after discontinuing the azothiaprine. This patient died.

Infections

The rate of infections, both serious and not, was similar in Tysabri and placebo-treated patients. There was one opportunistic infection, a case of cryptosporidial gastroenteritis with a prolonged course, in a patient with MS. In patients with Crohn's Disease, there were additional opportunistic infections, including pneumocystis carinii pneumonia and several others. In controlled trials, there were two cases of serious non-bacterial meningitides in Tysabri, and none in Placebo, treated patients. In post-marketing experience, there was a report of a patient with herpes encephalitis, who died, and another case of a patient with herpes meningitis, who recovered.

Hypersensitivity reactions

In Study 1801, the incidence of acute hypersensitivity reactions in Tysabri patients was 4% compared to <1% in placebo patients. The overall rate of severe hypersensitivity reactions was <1%. These reactions consist of urticaria, dizziness, fever, rash, nausea, dyspnea, flushing, chest pain, and other symptoms.

Immunogenicity

About 9% of patients in Study 1801 developed detectable antibodies at least once during their course of treatment. A total of 6% of patients developed persistent antibodies, defined as the presence of antibodies on more than one occasion at least 12 weeks apart. About 80% of patients with persistent antibodies developed these antibodies by 12 weeks of treatment. Anti-natalizumab antibodies were neutralizing in *in vitro* tests. In general, patients who developed anti-natalizumab antibodies experienced decreased effectiveness and an increased risk of developing a hypersensitivity reaction to an infusion.

Advisory Committee Synopsis

As noted above, the application was discussed at a meeting of the PCNS Drugs AC on March 7 and 8, 2006. The main conclusions are described below:

The committee voted unanimously to permit the re-marketing of Tysabri. However, they voted unanimously to permit the marketing only to patients with relapsing disease. They also voted unanimously to permit marketing only to patients who are not taking other approved agents to treat their MS (recall that the only two MS cases of PML occurred in conjunction with Avonex), although they acknowledged that there was no certainty that the risk of PML was actually greater in these patients compared to patients who might receive Tysabri alone.

The one important question on which the committee did not reach a clear consensus was the question of whether or not Tysabri should be indicated as first line therapy (that is, whether the indication should be restricted to patients who had failed, or were intolerant of, other available treatments for MS). Seven committee members voted to permit first line therapy and 5 voted against permitting such use in labeling. The committee also discussed, and voted on, several components of the RiskMAP. The major elements of the agreed-upon RiskMAP are described below.

Risk Minimization Action Plan (RiskMAP)

As noted, the sponsor proposed an RMP designed to monitor for, and detect, as rapidly as possible, additional cases of PML and other serious opportunistic infections. The main elements of this plan are as follows:

1) Only physicians, patients, pharmacies, and infusion centers that agree to participate in, and comply with the requirements of, this program (called TOUCH) will receive Tysabri. The sponsor will educate physicians and infusion centers about the appropriate use of Tysabri, and only those prescribers and infusions centers certified by the sponsor will be permitted to administer Tysabri.
2) Physicians will enroll patients only with relapsing forms of MS.
3) Physicians will counsel patients about the risks and benefits of Tysabri treatment.
4) Physicians will assert that they are capable of diagnosing and managing opportunistic infections and PML, or are prepared to refer patients to a physician who is so capable.
5) Physicians will complete a detailed patient enrollment form and fax it to Biogen Idec before treatment can begin.
6) Physicians will evaluate patients at 3 and 6 months after treatment initiation, and at least every 6 months thereafter.
7) Physicians will determine every 6 months if a patient is still eligible to receive Tysabri.
8) Physicians will report to Biogen any case of PML, any death, or hospitalization for an opportunistic infection as soon as possible.
9) Patients will understand the risks and benefits and read a Medication Guide before each infusion.
10) Patients must inform their physician of any new relevant symptoms that last more than a few days.
11) Patients must inform the infusion center staff of other medications and treatments they are receiving.
12) Infusion center staff will verify, prior to each infusion, that the patient is still authorized to receive Tysabri treatment.
13) Infusion center staff will question the patient, prior to each infusion, about their use of certain immunomodulator treatments and concomitant illnesses. If a patient reports taking a drug on this list or a medical condition that might put the patient at risk for PML, the staff must confirm with the prescriber that the patient may still receive Tysabri treatment.
14) Infusion staff will fax to the sponsor the completed patient questionnaire. The sponsor will follow-up all cases in which a questionnaire is not received at an expected time.

The sponsor has also proposed a post-marketing safety study, called TYGRIS. This study will enroll 5000 patients who will be followed for 5 years, with a total of at least 3000 treated for a minimum of 4 years. This study will collect detailed information on these patients, and is primarily designed to examine the incidence

of other serious infections, hypersensitivity reactions, and malignancies (no malignancies reasonably considered to be related to treatment were detected in the clinical trial database).

COMMENTS

The sponsor has completed its Phase 4 commitments, as described in the 11/23/04 Approval letter, to document the persistent effects of Tysabri at 2 years in Studies 1801 and 1802 (there are numerous other Phase 4 commitments described in that Approval letter that are still outstanding). Further, the sponsor has fulfilled its commitment to fully and adequately investigate the clinical trial database for additional cases of PML; as noted above, there remain only three cases of PML detected.

In addition, the sponsor has proposed a RiskMAP. The elements of this plan have been the subject of intensive internal Agency discussions, and the sponsor's original plan has been extensively revised to provide adequate mechanisms to ensure that 1) physicians and patients are adequately informed about the risks and benefits of treatment with Tysabri, 2) only appropriate patients receive treatment with Tysabri, and 3) information is obtained, rapidly and in real-time, about all patients receiving Tysabri who might have developed PML or other serious opportunistic infections, or who have discontinued treatment. This RiskMAP clearly meets the requirements discussed and recommended by the PCNS Advisory Committee.

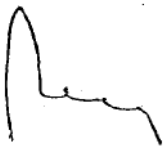
Based on the review of the effectiveness and safety data, and on the elements of the RiskMAP, the review team has concluded that Tysabri can be returned to the market. I completely agree. Although there is much still unknown about the potential risk for PML (in particular, we do not know whether the risk is lower in patients not receiving concomitant immunomodulators or immunosuppressants, nor do we have adequate information about whether the risk increases with increasing duration of treatment, especially beyond 2 years of treatment), there is general agreement (including, as described earlier, the unanimous vote of the AC), that, in the face of the potential risks, the benefit of treatment with Tysabri clearly justifies its re-introduction into the market, at this time, given appropriate conditions of use, including labeling and the RiskMAP as it is currently constructed, and that physicians and patients should be given the opportunity to decide if this treatment is appropriate in any given case.

Specifically with regard to labeling, we believe (and we and the sponsor have agreed) that labeling should contain a boxed warning describing the risks of PML, as well as additional prominent language throughout the label (including a Medication Guide) describing what is known (and unknown) about these risks. In particular, we have concluded that Tysabri will be indicated as monotherapy for patients with relapsing forms of MS (although, as noted, we cannot be confident that the risk of PML in the monotherapy setting is less than when Tysabri is used

concomitantly with other treatments for MS, because there are only 2 cases in patients with MS, it seems prudent to restrict the indication to monotherapy at this time). Also, because of the risk of PML, the labeling will state that treatment with Tysabri is generally recommended for patients who have not responded adequately to, or are intolerant of, other available MS treatments.

We have also agreed with the sponsor on a final, detailed RiskMAP that we are confident will meet, to the extent possible, the goals described above.

For these reasons, then, I will issue the attached Approval letter, to which is attached the agreed upon product label and Medication Guide, as well as a detailed summary of the critical elements of the RiskMAP. Because of the restricted distribution plan, Tysabri will be approved under the provisions of 21 CFR 601.42 (Subpart E).



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