DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/15

JUN 5 2006

Biogen Idec, Incorporated
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Dr. Cohen:

Please refer to your supplement to your biologics license application for TYSABRI® (Natalizumab), to add a Boxed Warning and update the Clinical Pharmacology, Clinical Studies, Indication and Usage, Contraindications, Warnings, Precautions, and Adverse Reactions sections of the package insert with safety and efficacy data, submitted under section 351 of the Public Health Service Act.

This supplement, considered for approval under 21 CFR 601.42 (Subpart E), at your request, provides for the use of TYSABRI® for the treatment of patients with relapsing forms of multiple sclerosis (MS) to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations.

We have completed our review of your supplement dated September 26, 2005, including all amendments received through June 2, 2006. This supplement is approved under the provisions of 21 CFR 601.42 (Subpart E), effective on the date of this letter, for use as recommended in the agreed upon labeling text, required patient labeling, and the components of the TOUCH™ Risk Minimization Action Plan (RiskMAP).

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted May 23, 2006, the Medication Guide submitted May 23, 2006, and carton and container labels submitted May 12, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Under 21 CFR 601.42 (Subpart E), distribution of Natalizumab (TYSABRI®) is limited as described below and in the attached detailed TOUCH™ program. The primary goals of the TOUCH™ program are to assess the risk of progressive multifocal leukoencephalopathy (PML) associated with Natalizumab (TYSABRI®), minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding TYSABRI® use.

TYSABRI® RiskMAP:

We remind you that your TYSABRI® RiskMAP (called TOUCH™) is an important part of the postmarketing risk management for TYSABRI®, and must include each of the following components:

1. Registration in the TOUCH™ program of prescribers, infusion centers, and pharmacies associated with infusion centers who agree to specific responsibilities in order to distribute, prescribe, dispense, or infuse TYSABRI®.

2. Implementation of a program and distribution of materials to educate prescribers, pharmacies, nurses, and patients about the risks and benefits of TYSABRI®, including materials that describe the roles of the TOUCH program participants.

3. Implementation of a reporting and data collection system for safety surveillance.

4. Implementation of a plan to monitor, evaluate, and determine the incidence and risk factors for PML and other serious opportunistic infections and compliance with restrictions for safe use under the TOUCH™ program.

The TYSABRI® Risk Minimization Action Plan, submitted on June 2, 2006 and as described in the attached document, adequately addresses each of these requirements. This plan includes ongoing assessment and periodic reporting to FDA of the operation of the program and needed revisions, if any. Any change to the program must be discussed with FDA prior to its institution and is subject to FDA's determination that the required components are still present. We expect your continued cooperation to resolve any problems regarding the TOUCH™ program that may be identified following approval of this application.

Our approval of this supplement also represents our conclusion that you have fulfilled your commitments made under 21 CFR 601.41 as stated in commitment number 1 of the November 23, 2004 approval letter as stated below:

1. To verify that the clinical benefit of reduction in exacerbations is sustained with continued Natalizumab administration by completing the ongoing Protocols C-1801 and C-1802, "A Randomized, Double-blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects with Relapsing-Remitting Multiple Sclerosis" and "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab, When Added to Avonex® (Interferon beta-1a) in Subjects with Relapsing-Remitting Multiple Sclerosis" through the planned two years and to submit the results along with the appropriate label changes.

In addition, you have fulfilled your commitment number 2 of the November 23, 2004 approval letter as stated below:

2. To further evaluate the safety of Natalizumab and the efficacy of Natalizumab on physical disability by completing the ongoing Protocols C-1801 and C-1802, "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab in Subjects with Relapsing-Remitting Multiple Sclerosis" and "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Natalizumab, When Added to Avonex® (Interferon beta-1a) in Subjects with Relapsing-Remitting Multiple Sclerosis" through the planned two years and to submit the results along with the appropriate label changes.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the full waiver granted on August 2, 2002, for the pediatric study requirement for BL 125104/0 which is also applicable to this supplemental application, in accordance with 21 CFR 601.27(c)(2)(ii).

We acknowledge your written commitment, as described in your letter of June 2, 2006, to conduct the postmarketing commitment outlined below:

Postmarketing Study subject to reporting requirements of 21 CFR 601.70.

1. To conduct a prospective, observational study in at least 5000 subjects with multiple sclerosis who are receiving Natalizumab, with each subject followed for at least 5 years, by completing protocol 101-MS-402, "TYGRIS: TYSABRI® Global Observation Program in Safety." Biogen Idec will ensure having at least 3000 patients with 4 years of Natalizumab treatment, and will increase the total subject number beyond 5000 if necessary to achieve this. The final protocol will be submitted by June 30, 2006, the study will be initiated by July 31, 2006, patient accrual will be completed by January 31, 2009, the study will be completed by January 31, 2014 and the final study report will be submitted by September 30, 2014.

In addition, postmarketing commitments numbers 3 through 16 agreed to in the approval of STN BL 125104/0 and described in the November 23, 2004 approval letter that are not yet fulfilled are still in effect.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application (BLA), STN BL 125104. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

Under 21 CFR Part 208, we have determined that this product poses a serious and significant public health concern requiring the distribution of a Medication Guide. Natalizumab is a product for which patient labeling could help prevent serious adverse effects and inform the patient of serious risks relative to benefit that could affect their decisions to use, or continue to use, the product. Therefore, a Medication Guide is necessary for safe and effective use of this product and FDA hereby approves the draft Medication Guide you submitted May 23, 2006. Please note that:

- this Medication Guide must be reprinted at the end of the package insert [21 CFR 201.57(f)(2)];

- you are responsible for ensuring that this Medication Guide is available for distribution to every patient who is dispensed a prescription for this product [21 CFR 208];

- the final printed Medication Guide distributed to patients must conform to all conditions described in 21 CFR 208.20, including a minimum of 10 point text; and

- you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided.

As part of the approval under Subpart E, we acknowledge that you have submitted to the Agency your promotional materials (both promotional labeling and advertisements) that are to be used within the first 120 days after approval. In addition, as required by 21 CFR 601.45, you must submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Upon approval, you have informed us that you will be issuing a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter). We request that you submit a copy of the letter to this BLA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

This information will be included in your biologics license application file.

Sincerely,

6/5/06

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research