



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125104/33

Biogen Idec, Inc.
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 update the Indications and Usage, Dosage and Administration, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, and Clinical Studies 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 inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α , submitted under section 351 of the Public Health Service Act.

We have completed our review of your supplement dated December 14, 2006, including all amendments to this supplement received through January 14, 2008. 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™ Prescribing Program Risk Minimization Action Plan (RiskMAP) for Crohn's disease (CD) patients referred to as the CD TOUCH™ Prescribing Program.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted January 14, 2008, the Medication Guide submitted January 14, 2008, and carton and container labels submitted December 14, 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, distribution of TYSABRI® is limited as described below and in the attached detailed TOUCH™ Prescribing Program. The primary goals of the TOUCH™ Prescribing Program are to assess the risk of progressive multifocal leukoencephalopathy (PML) associated with 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 for Crohn's disease patients is an important part of the postmarketing risk management for TYSABRI®, and must include each of the following components:

1. Enrollment in the TOUCH™ Prescribing Program of prescribers, infusion centers, and pharmacies associated with infusion centers, and patients who agree to specific responsibilities in order to prescribe, dispense, infuse, and use 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™ Prescribing 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, other serious opportunistic infections, malignancies and compliance with restrictions for safe use under the TOUCH™ Prescribing Program.

The TYSABRI® Risk Minimization Action Plan, submitted on January 7, 2008, 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™ Prescribing Program that may be identified following approval of this application.

Pediatric Studies:

All applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 to 5 years because the necessary studies are impossible or highly impracticable because the number of pediatric Crohn's disease patients in this age group is so small. We are deferring submission of your pediatric studies for ages 6 to 17 years for this application because pediatric studies should be delayed until additional safety data have been collected.

Your deferred pediatric studies required by section 505B(a) of the Food, Drug, and Cosmetic Act are required postmarketing study commitments. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Food, Drug, and Cosmetic Act. These commitment(s) are listed below.

1. Assess data anticipated from adults in protocol "TYSABRI Observational Study in Safety in CD (Crohn's disease)" (Postmarketing Commitment Number 4, below) and establish a pediatric study plan that incorporates these new data. These data must be analyzed, to include an assessment of safety, before the required pediatric studies are initiated. The due date for submitting this assessment and pediatric study plan is June 30, 2012.
2. Unless FDA agrees, based on your completion of Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 12 to 17 years, conduct a pediatric study in pediatric patients age 12 to 17 years for the treatment of Crohn's disease.

This pediatric study will enroll pediatric patients age 12 to 17 years into four study arms (placebo, 3 mg/kg, 4.5 mg/kg, and 6 mg/kg of TYSABRI administered intravenously every 4 weeks), and evaluate safety, efficacy, and pharmacokinetics of natalizumab.

Study Start Date: December 31, 2012

Study Completion Date: April 30, 2014

Final Report Submission: September 30, 2014

3. Unless FDA agrees, based on your completion of Postmarketing Commitment Number 1 above, that it is not appropriate to conduct a pediatric study in pediatric patients age 6 to 11 years, after completing the study described in Postmarketing Commitment Number 2, conduct a pediatric study in pediatric patients age 6 to 11 years for the treatment of Crohn's disease.

This second pediatric study will enroll pediatric patients age 6 to 11 years in a single, open-label arm (dose of TYSABRI will be selected based on results in older pediatric patients), and evaluate safety, pharmacokinetics, and response/remission rates.

Study Start Date: January 31, 2015

Study Completion Date: December 31, 2016

Final Report Submission: June 30, 2017

Submit final study reports to this BLA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

We acknowledge your written commitment, as described in your letter of January 9, 2008, and as agreed upon during our teleconference of January 8, 2008, to conduct the postmarketing commitment outlined below:

Postmarketing Observational Study subject to reporting requirements of 21 CFR 601.70.

4. To conduct a prospective, observational study in at least 2000 subjects with Crohn's disease who are receiving TYSABRI, with each subject followed for at least five years, by completing protocol, "TYSABRI Observational Study in Safety in CD (Crohn's disease)." You will ensure having at least 1000 patients with two years of TYSABRI treatment, and will increase the total number of patients enrolled beyond 2000 if necessary to achieve this. The final protocol will be submitted by March 31, 2008.

Study Start Date: June 30, 2008

Study Patient Accrual Completion Date: June 30, 2012

Study Completion Date: June 30, 2017

Final Report Submission: March 31, 2018

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. Postmarketing commitment number 1 agreed to in the approval of STN BL 125104/15 and described in the June 5, 2006, approval letter is also 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 previously determined that this product posed 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 continues to be necessary for safe and effective use of this product and FDA hereby approves the revised Medication Guide you submitted January 14, 2008. Please note your continued requirement to adhere to *General Requirements for a Medication Guide* specified in 21 CFR 208 Subpart B.

As part of the approval and 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.

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).

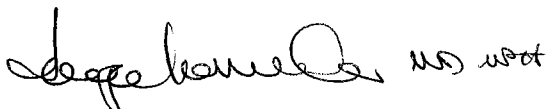
Please refer to <http://www.fda.gov/cder/biologics/default.htm> for important information regarding therapeutic biological products, including the addresses for submissions.

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,

A handwritten signature in dark ink, appearing to read "Joyce Korvick", followed by the initials "MS" and "not".

1/14/08

Joyce A. Korvick, M.D., M.P.H.
Deputy Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachments:

Tysabri BLA STN 125104/33 Final Label
Tysabri® Risk Minimization Action Plan: SUMMARY OF TOUCH

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYSABRI safely and effectively. See full prescribing information for TYSABRI.

TYSABRI (natalizumab) injection for intravenous use
Initial U.S. Approval: 2004

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning

- TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability (5.1)
- Monitor patients, and withhold TYSABRI immediately at the first sign or symptom suggestive of PML (4, 5.1)
- TYSABRI is available only through a special restricted distribution program called the TOUCH™ Prescribing Program and must be administered only to patients enrolled in this program (5.1, 5.2)

RECENT MAJOR CHANGES

Indications and Usage

Crohn's Disease (1.2) 1/2008

Dosage and Administration

Crohn's Disease (2.2) 1/2008

Warnings and Precautions

Progressive Multifocal Leukoencephalopathy (5.1) 1/2008

Distribution Program for TYSABRI (5.2) 1/2008

Immunosuppression/Infections (5.4) 1/2008

Hepatotoxicity (5.5) 1/2008

INDICATIONS AND USAGE

TYSABRI is an integrin receptor antagonist indicated for treatment of:

Multiple Sclerosis (MS) (1.1)

- As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies.

Crohn's Disease (CD) (1.2)

- Inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate conventional CD therapies and inhibitors of TNF- α .

Important Limitations:

- In CD, TYSABRI should not be used in combination with immunosuppressants or inhibitors of TNF- α .

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*Sections or subsections omitted from the Full Prescribing Information are not listed.

DOSAGE AND ADMINISTRATION

- 300 mg infused intravenously over approximately one hour, every four weeks. Do not give as an intravenous push or bolus (2.1, 2.2).
- TYSABRI solution must be administered within 8 hours of preparation (2.3).
- Observe patients during the infusion and for one hour after the infusion is complete (2.4).
- In CD, discontinue in patients that have not experienced therapeutic benefit by 12 weeks of induction therapy, and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy (2.2).

DOSAGE FORMS AND STRENGTH

- Solution [300 mg per 15 mL vial] for dilution prior to infusion (2.2, 3).

CONTRAINDICATIONS

- Patients who have or have had PML (4).
- Patients who have had a hypersensitivity reaction to TYSABRI (4).

WARNINGS AND PRECAUTIONS

- Progressive Multifocal Leukoencephalopathy (PML): Has occurred in 3 patients who received TYSABRI. Patients who have significantly compromised immune system function should not ordinarily be treated with TYSABRI. Obtain an MRI scan in MS patients prior to initiating TYSABRI. Monitor MS and CD patients and withhold TYSABRI at the first sign or symptom suggestive of PML (5.1).
- Hypersensitivity reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred. Permanently discontinue TYSABRI if such a reaction occurs (5.3).
- Immunosuppression/Infections: TYSABRI may increase the risk for certain infections. Monitor patients for development of infections due to increased risk with use of TYSABRI (5.4).
- Hepatotoxicity: Clinically significant liver injury has occurred. Discontinue TYSABRI in patients with jaundice or evidence of liver injury (5.5).

ADVERSE REACTIONS

The most common adverse reactions (incidence $\geq 10\%$) in MS were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash; and in CD were headache, upper respiratory tract infections, nausea, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Biogen Idec or Elan at 1-800-456-2255 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to enroll pregnant patients in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255 (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2008

TYSABRI® (natalizumab) Injection
FULL PRESCRIBING INFORMATION

WARNING: PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Although the cases of PML were limited to patients with recent or concomitant exposure to immunomodulators or immunosuppressants, there were too few cases to rule out the possibility that PML may occur with TYSABRI monotherapy [see *Warnings and Precautions* (5.1)].

- **Because of the risk of PML, TYSABRI is available only through a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program [see *Warnings and Precautions* (5.1, 5.2)].**
- **Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom that may be suggestive of PML. TYSABRI dosing should be withheld immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation that includes a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended [see *Contraindications* (4), *Warnings and Precautions* (5.1)].**

1 INDICATIONS AND USAGE

1.1 Multiple Sclerosis (MS)

TYSABRI is indicated as monotherapy for the treatment of patients with relapsing forms of multiple sclerosis to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. The safety and efficacy of TYSABRI beyond two years are unknown.

Because TYSABRI increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability, TYSABRI is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies [see *Boxed Warning, Warnings and Precautions* (5.1)].

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

1.2 Crohn's Disease (CD)

TYSABRI is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and

inhibitors of TNF- α . TYSABRI should not be used in combination with immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α [see *Boxed Warning, Warnings and Precautions (5.1)*].

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Sclerosis (MS)

Only prescribers registered in the MS TOUCH™ Prescribing Program may prescribe TYSABRI for multiple sclerosis [see *Boxed Warning, Warnings and Precautions (5.2)*]. The recommended dose of TYSABRI for multiple sclerosis is 300 mg intravenous infusion over one hour every four weeks.

2.2 Crohn's Disease (CD)

Only prescribers registered in the CD TOUCH™ Prescribing Program may prescribe TYSABRI for Crohn's disease [see *Boxed Warning, Warnings and Precautions (5.1)*].

The recommended dose of TYSABRI for Crohn's disease is 300 mg intravenous infusion over one hour every four weeks. TYSABRI should not be used with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or concomitant inhibitors of TNF- α . Aminosalicylates may be continued during treatment with TYSABRI.

If the patient with Crohn's disease has not experienced therapeutic benefit by 12 weeks of induction therapy, discontinue TYSABRI. For patients with Crohn's disease that start TYSABRI while on chronic oral corticosteroids, commence steroid tapering as soon as a therapeutic benefit of TYSABRI has occurred; if the patient with Crohn's disease cannot be tapered off of oral corticosteroids within six months of starting TYSABRI, discontinue TYSABRI. Other than the initial six-month taper, prescribers should consider discontinuing TYSABRI for patients who require additional steroid use that exceeds three months in a calendar year to control their Crohn's disease.

2.3 Dilution Instructions

- (1) Use aseptic technique when preparing TYSABRI solution for intravenous infusion. Each vial is intended for single use only.
- (2) TYSABRI is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI vial for particulate material and discoloration prior to dilution and administration. If visible particulates are observed and/or the liquid in the vial is discolored, the vial must not be used.
- (3) To prepare the solution, withdraw 15 mL of TYSABRI concentrate from the vial using a sterile needle and syringe. Inject the concentrate into 100 mL 0.9% Sodium Chloride Injection, USP. No other IV diluents may be used to prepare the TYSABRI solution.
- (4) Gently invert the TYSABRI solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.
- (5) The final dosage solution has a concentration of 2.6 mg/mL.
- (6) Following dilution, infuse TYSABRI solution immediately, or refrigerate solution at 2 to 8°C, and use within 8 hours. If stored at 2 to 8°C, allow the solution to warm to room temperature prior to infusion. DO NOT FREEZE.

2.4 Administration Instructions

- Infuse TYSABRI 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP, over approximately one hour (infusion rate approximately 5 mg per minute). Do not administer TYSABRI as an intravenous push or bolus injection. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.
- Observe patients during the infusion and for one hour after the infusion is complete. Promptly discontinue the infusion upon the first observation of any signs or symptoms consistent with a hypersensitivity-type reaction [see *Warnings and Precautions* (5.3)].
- Use of filtration devices during administration has not been evaluated. Other medications should not be injected into infusion set side ports or mixed with TYSABRI.

3 DOSAGE FORMS AND STRENGTHS

TYSABRI is a concentrated solution that must be diluted prior to intravenous infusion. TYSABRI injection is supplied as 300 mg natalizumab in 15 mL (20 mg/mL) in a sterile, single-use vial free of preservatives.

4 CONTRAINDICATIONS

- TYSABRI is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) [see *Boxed Warning, Warnings and Precautions* (5.1)].
- TYSABRI should not be administered to a patient who has had a hypersensitivity reaction to TYSABRI. Observed reactions range from urticaria to anaphylaxis [see *Warnings and Precautions* (5.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus, and which typically only occurs in patients that are immunocompromised, has occurred in three patients who received TYSABRI in clinical trials [see *Boxed Warning*]. Two cases of PML were observed in 1869 patients with multiple sclerosis treated for a median of 120 weeks. The third case occurred among 1043 patients with Crohn's disease after the patient received eight doses. The absolute risk for PML in patients treated with TYSABRI cannot be precisely estimated, and factors that might increase an individual patient's risk for PML have not been identified. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will mitigate the disease. There is limited experience beyond two years of treatment. The relationship between the risk of PML and the duration of treatment is unknown.

All three cases of PML occurred in patients who were concomitantly exposed to immunomodulators (interferon beta in the patients with multiple sclerosis) or were immunocompromised due to recent treatment with immunosuppressants (e.g., azathioprine in the patient with Crohn's disease). Ordinarily, therefore, patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not be treated with TYSABRI. However, the number of cases is too few and the number of patients treated too small to reliably conclude that the risk of

PML is lower in patients treated with TYSABRI alone than in patients who are receiving other drugs that decrease immune function or who are otherwise immunocompromised.

Because of the risk of PML, TYSABRI is available only under a special restricted distribution program, the TOUCH™ Prescribing Program.

In multiple sclerosis patients, an MRI scan should be obtained prior to initiating therapy with TYSABRI. This MRI may be helpful in differentiating subsequent multiple sclerosis symptoms from PML.

In Crohn's disease patients, a baseline brain MRI may also be helpful to distinguish pre-existent lesions from newly developed lesions, but brain lesions at baseline that could cause diagnostic difficulty while on TYSABRI therapy are uncommon.

Healthcare professionals should monitor patients on TYSABRI for any new sign or symptom suggestive of PML. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. Withhold TYSABRI dosing immediately at the first sign or symptom suggestive of PML. For diagnosis, an evaluation including a gadolinium-enhanced MRI scan of the brain and, when indicated, cerebrospinal fluid analysis for JC viral DNA are recommended.

5.2 Distribution Program for TYSABRI

TYSABRI is available only under a special restricted distribution program called the TOUCH™ Prescribing Program. Under the TOUCH™ Prescribing Program, only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. For prescribers and patients, the TOUCH™ Prescribing Program has two components: MS TOUCH™ (for patients with multiple sclerosis) and CD TOUCH™ (for patients with Crohn's disease). TYSABRI must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH™ Prescribing Program. Contact the TOUCH™ Prescribing Program at 1-800-456-2255 [see *Boxed Warning*].

To enroll in the TOUCH™ Prescribing Program, prescribers and patients are required to understand the risks of treatment with TYSABRI, including PML and other opportunistic infections. Prescribers are required to understand the information in the Prescribing Information and to be able to:

- Educate patients on the benefits and risks of treatment with TYSABRI, ensure that the patient receives the Medication Guide, instruct them to read it, and encourage them to ask questions when considering TYSABRI. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the TOUCH™ Prescriber/Patient Enrollment form for TYSABRI with the patient and answer all questions.
- As part of the initial prescription process for TYSABRI, obtain the patient's signature and initials on the TOUCH™ program enrollment form, sign it, place the original signed form in the patient's medical record, send a copy to Biogen Idec, and give a copy to the patient.
- Report serious opportunistic and atypical infections with TYSABRI to Biogen Idec or Elan at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Evaluate the patient three months after the first infusion, six months after the first

infusion, and every six months thereafter.

- Determine every six months whether patients should continue on treatment and if so reauthorize treatment every six months.
- Submit to Biogen Idec the TYSABRI Patient Status Report and Reauthorization Questionnaire six months after initiating treatment and every six months thereafter.

5.3 Hypersensitivity/Antibody Formation

Hypersensitivity reactions have occurred in patients receiving TYSABRI, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within two hours of the start of the infusion. Symptoms associated with these reactions can include urticaria, dizziness, fever, rash, rigors, pruritus, nausea, flushing, hypotension, dyspnea, and chest pain. Generally, these reactions are associated with antibodies to TYSABRI.

If a hypersensitivity reaction occurs, discontinue administration of TYSABRI and initiate appropriate therapy. Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI. Hypersensitivity reactions were more frequent in patients with antibodies to TYSABRI compared to patients who did not develop antibodies to TYSABRI in both MS and CD studies. Therefore, the possibility of antibodies to TYSABRI should be considered in patients who have hypersensitivity reactions [see *Adverse Reactions* (6.2)].

Antibody testing: If the presence of persistent antibodies is suspected, antibody testing should be performed. Antibodies may be detected and confirmed with sequential serum antibody tests. Antibodies detected early in the treatment course (e.g., within the first six months) may be transient and disappear with continued dosing. Repeat testing at three months after the initial positive result is recommended in patients in whom antibodies are detected to confirm that antibodies are persistent. Prescribers should consider the overall benefits and risks of TYSABRI in a patient with persistent antibodies.

Experience with monoclonal antibodies, including TYSABRI, suggests that patients who receive therapeutic monoclonal antibodies after an extended period without treatment may be at higher risk of hypersensitivity reactions than patients who received regularly scheduled treatment. Given that patients with persistent antibodies to TYSABRI experience reduced efficacy, and that hypersensitivity reactions are more common in such patients, consideration should be given to testing for the presence of antibodies in patients who wish to recommence therapy following a dose interruption. Following a period of dose interruption, patients testing negative for antibodies prior to re-dosing have a risk of antibody development with re-treatment that is similar to TYSABRI naïve patients [see *Adverse Reactions* (6.2)].

5.4 Immunosuppression/Infections

The immune system effects of TYSABRI may increase the risk for infections. In Study MS1 [see *Clinical Studies* (14.1)], certain types of infections, including pneumonias and urinary tract infections (including serious cases), gastroenteritis, vaginal infections, tooth infections, tonsillitis, and herpes infections, occurred more often in TYSABRI-treated patients than in placebo-treated patients [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1)]. One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI in Study MS1.

In Studies MS1 and MS2, an increase in infections was seen in patients concurrently receiving short courses of corticosteroids. However, the increase in infections in TYSABRI-

treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.

In CD clinical studies, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants [see *Boxed Warning, Warnings and Precautions* (5.1, 5.4), *Adverse Reactions* (6.1)].

In Studies CD1 and CD2, an increase in infections was seen in patients concurrently receiving corticosteroids. However, the increase in infections was similar in placebo-treated and TYSABRI-treated patients who received steroids.

Concurrent use of antineoplastic, immunosuppressant, or immunomodulating agents may further increase the risk of infections, including PML and other opportunistic infections, over the risk observed with use of TYSABRI alone [see *Boxed Warning, Warnings and Precautions* (5.1), *Adverse Reactions* (6.1)]. The safety and efficacy of TYSABRI in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established. Patients receiving chronic immunosuppressant or immunomodulatory therapy or who have systemic medical conditions resulting in significantly compromised immune system function should not ordinarily be treated with TYSABRI.

For patients with Crohn's disease who start TYSABRI while on chronic corticosteroids, commence steroid withdrawal as soon as a therapeutic benefit has occurred. If the patient cannot discontinue systemic corticosteroids within six months, discontinue TYSABRI.

5.5 Hepatotoxicity

Clinically significant liver injury has been reported in patients treated with TYSABRI in the postmarketing setting. Signs of liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, occurred as early as six days after the first dose; signs of liver injury have also been reported for the first time after multiple doses. In some patients, liver injury recurred upon rechallenge, providing evidence that TYSABRI caused the injury. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients.

TYSABRI should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

5.6 Laboratory Test Abnormalities

TYSABRI induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persist during TYSABRI exposure, but are reversible, returning to baseline levels usually within 16 weeks after the last dose. Elevations of neutrophils are not observed. TYSABRI induces mild decreases in hemoglobin levels that are frequently transient.

5.7 Immunizations

No data are available on the effects of vaccination in patients receiving TYSABRI. No data are available on the secondary transmission of infection by live vaccines in patients receiving TYSABRI.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

The most serious adverse reactions were [see *Warnings and Precautions* (5)]:

- Progressive Multifocal Leukoencephalopathy (PML)
- Hypersensitivity
- Immunosuppression/Infections

The most common adverse reactions (incidence $\geq 10\%$) were headache and fatigue in both the multiple sclerosis (MS) and Crohn's disease (CD) studies. Other common adverse reactions (incidence $\geq 10\%$) in the MS population were arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea NOS, and rash. Other common adverse reactions (incidence $\geq 10\%$) in the CD population were upper respiratory tract infections and nausea.

The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI), in the MS studies were urticaria (1%) and other hypersensitivity reactions (1%), and in the CD studies (Studies CD1 and CD2) were the exacerbation of Crohn's disease (4.2%) and acute hypersensitivity reactions (1.5%) [see *Warnings and Precautions* (5.3)].

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI, with a median duration of exposure of 28 months. A total of 1563 patients received TYSABRI in all CD studies for a median exposure of 5 months; of these patients, 33% (n=518) received at least one year of treatment and 19% (n=297) received at least two years of treatment.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of TYSABRI cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. The adverse reaction information does, however, provide a basis for identifying the adverse events that appear to be related to drug use and a basis for approximating rates.

Multiple Sclerosis Clinical Studies

The most frequently reported serious adverse reactions in Study MS1 [see *Clinical Studies* (14.1)] with TYSABRI were infections (3.2% versus 2.6% in placebo, including urinary tract infection [0.8% versus 0.3%] and pneumonia [0.6% versus 0%]), acute hypersensitivity reactions (1.1% versus 0.3%, including anaphylaxis/anaphylactoid reaction [0.8% versus 0%]), depression (1.0% versus 1.0%, including suicidal ideation or attempt [0.6% versus 0.3%]), and cholelithiasis (1.0% versus 0.3%). In Study MS2, serious adverse reactions of appendicitis were also more common in patients who received TYSABRI (0.8% versus 0.2% in placebo) [see *Warnings and Precautions* (5.4), *Adverse Reactions - Infections*].

Table 1 enumerates adverse reactions and selected laboratory abnormalities that occurred in Study MS1 at an incidence of at least 1 percentage point higher in TYSABRI-treated patients than was observed in placebo-treated patients.

Table 1. Adverse Reactions in Study MS1 (Monotherapy Study)

Adverse Reactions (Preferred Term)	TYSABRI n=627 Percentage	Placebo n=312 Percentage
General		
Headache	38%	33%
Fatigue	27%	21%
Arthralgia	19%	14%
Chest discomfort	5%	3%
Acute hypersensitivity reactions**	4%	<1%
Other hypersensitivity reactions**	5%	2%
Seasonal allergy	3%	2%
Rigors	3%	<1%
Weight increased	2%	<1%
Weight decreased	2%	<1%
Infection		
Urinary tract infection	21%	17%
Lower respiratory tract infection	17%	16%
Gastroenteritis	11%	9%
Vaginitis*	10%	6%
Tooth infections	9%	7%
Herpes	8%	7%
Tonsillitis	7%	5%
Psychiatric		
Depression	19%	16%
Musculoskeletal/Connective Tissue Disorders		
Pain in extremity	16%	14%
Muscle cramp	5%	3%
Joint swelling	2%	1%
Gastrointestinal		
Abdominal discomfort	11%	10%
Diarrhea NOS	10%	9%
Abnormal liver function test	5%	4%
Skin		
Rash	12%	9%
Dermatitis	7%	4%
Pruritus	4%	2%
Night sweats	1%	0%

Adverse Reactions (Preferred Term)	TYSABRI n=627 Percentage	Placebo n=312 Percentage
Menstrual Disorders*		
Irregular menstruation	5%	4%
Dysmenorrhea	3%	<1%
Amenorrhea	2%	1%
Ovarian cyst	2%	<1%
Neurologic Disorders		
Somnolence	2%	<1%
Vertigo	6%	5%
Renal and Urinary Disorders		
Urinary incontinence	4%	3%
Urinary urgency/frequency	9%	7%
Injury		
Limb injury NOS	3%	2%
Skin laceration	2%	<1%
Thermal burn	1%	<1%

*Percentage based on female patients only.

** Acute versus other hypersensitivity reactions are defined as occurring within 2 hours post-infusion versus more than 2 hours.

In Study MS2, peripheral edema was more common in patients who received TYSABRI (5% versus 1% in placebo).

Crohn's Disease Clinical Studies

The following serious adverse events in the induction Studies CD1 and CD2 [see *Clinical Studies (14.2)*] were reported more commonly with TYSABRI than placebo and occurred at an incidence of at least 0.3%: intestinal obstruction or stenosis (2% vs. 1% in placebo), acute hypersensitivity reactions (0.5% vs. 0%), abdominal adhesions (0.3% vs. 0%), and cholelithiasis (0.3% vs. 0%). Similar serious adverse events were seen in the maintenance Study CD3. Table 2 enumerates adverse drug reactions that occurred in Studies CD1 and CD2 (median exposure of 2.8 months). Table 3 enumerates adverse drug reactions that occurred in Study CD3 (median exposure of 11.0 months).

**Table 2. Adverse Reactions in Studies CD1 and CD2
(Induction Studies)**

Adverse Reactions*	TYSABRI n=983 Percentage	Placebo n=431 Percentage
General		
Headache	32%	23%
Fatigue	10%	8%
Arthralgia	8%	6%
Influenza-like illness	5%	4%
Acute hypersensitivity reactions	2%	<1%
Tremor	1%	<1%
Infection		
Upper respiratory tract infection	22%	16%
Vaginal infections **	4%	2%
Viral infection	3%	2%
Urinary tract infection	3%	1%
Respiratory		
Pharyngolaryngeal pain	6%	4%
Cough	3%	<1%
Gastrointestinal		
Nausea	17%	15%
Dyspepsia	5%	3%
Constipation	4%	2%
Flatulence	3%	2%
Aphthous stomatitis	2%	<1%
Skin		
Rash	6%	4%
Dry skin	1%	0%
Menstrual Disorder		
Dysmenorrhea **	2%	<1%

* Occurred at an incidence of at least 1% higher in TYSABRI-treated patients than placebo-treated patients.

** Percentage based on female patients only.

**Table 3. Adverse Reactions in Study CD3
(Maintenance Study)**

Adverse Reactions*	TYSABRI n=214 Percentage	Placebo n=214 Percentage
General		
Headache	37%	31%
Influenza-like illness	11%	6%
Toothache	4%	<1%
Peripheral edema	6%	3%
Infection		
Influenza	12%	5%
Sinusitis	8%	4%
Viral infection	7%	3%
Vaginal infections **	8%	<1%
Respiratory		
Cough	7%	5%
Gastrointestinal		
Lower abdominal pain	4%	2%
Musculoskeletal and Connective Tissue		
Back pain	12%	8%
Menstrual disorder		
Dysmenorrhea **	6%	3%

* Occurred at an incidence of at least 2% higher in TYSABRI-treated patients than placebo-treated patients.

** Percentage based on female patients only.

Infections

Progressive Multifocal Leukoencephalopathy (PML) has occurred in three patients who received TYSABRI in clinical trials [see *Boxed Warning, Warnings and Precautions (5.1)*]. Two cases of PML were observed in the 1869 patients with multiple sclerosis who were treated for a median of 120 weeks. These two patients had received TYSABRI in addition to interferon beta-1a [see *Boxed Warning, Warnings and Precautions (5.1)*]. The third case occurred after eight doses in one of the 1043 patients with Crohn's disease who were evaluated for PML.

In Studies MS1 and MS2 [see *Clinical Studies (14.1)*], the rate of any type of infection was approximately 1.5 per patient-year in both TYSABRI-treated patients and placebo-treated patients. The infections were predominately upper respiratory tract infections, influenza, and urinary tract infections. In Study MS1, the incidence of serious infection was approximately 3% in TYSABRI-treated patients and placebo-treated patients. Most patients did not interrupt treatment with TYSABRI during infections. The only opportunistic infection in the multiple sclerosis clinical trials was a case of cryptosporidial gastroenteritis with a prolonged course.

In Studies CD1 and CD2 [see *Clinical Studies (14.2)*], the rate of any type of infection was 1.7 per patient-year in TYSABRI-treated patients and 1.4 per patient-year in placebo-treated patients. In Study CD3, the incidence of any type of infection was 1.7 per patient-year in TYSABRI-treated patients and was similar in placebo-treated patients. The most common infections were nasopharyngitis, upper respiratory tract infection, and influenza. The majority of patients did not interrupt TYSABRI therapy during infections and recovery occurred with appropriate treatment. Concurrent use of TYSABRI in CD clinical trials with chronic steroids and/or methotrexate, 6-MP, and azathioprine did not result in an increase in overall infections compared to TYSABRI alone; however, the concomitant use of such agents could lead to an increased risk of serious infections.

In Studies CD1 and CD2, the incidence of serious infection was approximately 2.1% in both TYSABRI-treated patients and placebo-treated patients. In Study CD3, the incidence of serious infection was approximately 3.3% in TYSABRI-treated patients and approximately 2.8% in placebo-treated patients.

In clinical studies for CD, opportunistic infections (pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been observed in <1% of TYSABRI-treated patients; some of these patients were receiving concurrent immunosuppressants [see *Warnings and Precautions (5.4)*]. Two serious non-bacterial meningitides occurred in TYSABRI-treated patients compared to none in placebo-treated patients.

Infusion-related Reactions

An infusion-related reaction was defined in clinical trials as any adverse event occurring within two hours of the start of an infusion. In MS clinical trials, approximately 24% of TYSABRI-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. In the controlled CD clinical trials, infusion-related reactions occurred in approximately 11% of patients treated with TYSABRI compared to 7% of placebo-treated patients. Reactions more common in the TYSABRI-treated MS patients compared to the placebo-treated MS patients included headache, dizziness, fatigue, urticaria, pruritus, and rigors. Acute urticaria was observed in approximately 2% of patients. Other hypersensitivity reactions were observed in 1% of patients receiving TYSABRI. Serious systemic hypersensitivity infusion reactions occurred in <1% of patients [see *Warnings and Precautions (5.3)*]. All patients recovered with treatment and/or discontinuation of the infusion.

Infusion-related reactions more common in CD patients receiving TYSABRI than those receiving placebo included headache, nausea, urticaria, pruritus, and flushing. Serious infusion reactions occurred in Studies CD1, CD2, and CD3 at an incidence of <1% in TYSABRI-treated patients.

MS and CD patients who became persistently positive for antibodies to TYSABRI were more likely to have an infusion-related reaction than those who were antibody-negative.

6.2 Immunogenicity

Patients in Study MS1 [see *Clinical Studies (14.1)*] were tested for antibodies to natalizumab every 12 weeks. The assays used were unable to detect low to moderate levels of antibodies to natalizumab. Approximately 9% of patients receiving TYSABRI developed detectable antibodies at least once during treatment. Approximately 6% of patients had positive antibodies on more than one occasion. Approximately 82% of patients who became persistently antibody-positive developed detectable antibodies by 12 weeks. Anti-natalizumab antibodies were neutralizing *in vitro*.

The presence of anti-natalizumab antibodies was correlated with a reduction in serum natalizumab levels. In Study MS1, the Week 12 pre-infusion mean natalizumab serum concentration in antibody-negative patients was 15 mcg/mL compared to 1.3 mcg/mL in antibody-positive patients. Persistent antibody-positivity resulted in a substantial decrease in the effectiveness of TYSABRI. The risk of increased disability and the annualized relapse rate were similar in persistently antibody-positive TYSABRI-treated patients and patients who received placebo. A similar phenomenon was also observed in Study MS2.

Infusion-related reactions most often associated with persistent antibody-positivity included urticaria, rigors, nausea, vomiting, headache, flushing, dizziness, pruritus, tremor, feeling cold, and pyrexia. Additional adverse reactions more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

Patients in CD studies [see *Clinical Studies (14.2)*] were first tested for antibodies at Week 12, and in a substantial proportion of patients, this was the only test performed given the 12-week duration of placebo-controlled studies. Approximately 10% of patients were found to have anti-natalizumab antibodies on at least one occasion. Five percent (5%) of patients had positive antibodies on more than one occasion. Persistent antibodies resulted in reduced efficacy and an increase in infusion-related reactions with symptoms that include urticaria, pruritus, nausea, flushing, and dyspnea.

The long-term immunogenicity of TYSABRI and the effects of low to moderate levels of antibody to natalizumab are unknown [see *Warnings and Precautions (5.3)*, *Adverse Reactions (6.1)*].

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody-positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to TYSABRI with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TYSABRI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

In post-marketing experience, one MS patient who received TYSABRI developed herpes encephalitis and died; a second MS patient developed herpes meningitis and recovered with appropriate treatment.

7 DRUG INTERACTIONS

Because of the potential for increased risk of PML and other infections, Crohn's disease patients receiving TYSABRI should not be treated with concomitant immunosuppressants (e.g., 6-mercaptopurine, azathioprine, cyclosporine, or methotrexate) or inhibitors of TNF- α , and corticosteroids should be tapered in those patients with Crohn's disease who are on chronic corticosteroids when they start TYSABRI therapy [see *Boxed Warning, Indications and Usage (1.2)*, *Warnings and Precautions (5.1, 5.4)*]. Ordinarily, MS patients receiving chronic immunosuppressant or immunomodulatory therapy should not be treated with TYSABRI [see *Boxed Warning, Indications and Usage (1.1)*, *Warnings and Precautions (5.1, 5.4)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. TYSABRI has been shown to reduce pup survival in guinea pigs when given in doses 7 times the human dose, and has been shown to have hematologic effects on the fetus in monkeys when given in doses 2.3 times the human dose [see *Nonclinical Toxicology* (13.2)]. There are no adequate and well-controlled studies in pregnant women. TYSABRI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If a woman becomes pregnant while taking TYSABRI, consider enrolling her in the TYSABRI Pregnancy Exposure Registry by calling 1-800-456-2255.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TYSABRI, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of TYSABRI in pediatric patients with multiple sclerosis or Crohn's disease below the age of 18 years have not been established. TYSABRI is not indicated for use in pediatric patients.

8.5 Geriatric Use

Clinical studies of TYSABRI did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

10 OVERDOSAGE

Safety of doses higher than 300 mg has not been adequately evaluated. The maximum amount of TYSABRI that can be safely administered has not been determined.

11 DESCRIPTION

TYSABRI (natalizumab) is a recombinant humanized IgG4 κ monoclonal antibody produced in murine myeloma cells. Natalizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to α 4-integrin. The molecular weight of natalizumab is 149 kilodaltons. TYSABRI is supplied as a sterile, colorless, and clear to slightly opalescent concentrate for intravenous infusion.

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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Natalizumab binds to the α 4-subunit of α 4 β 1 and α 4 β 7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α 4-mediated adhesion of leukocytes to their

counter-receptor(s). The receptors for the $\alpha 4$ family of integrins include vascular cell adhesion molecule-1 (VCAM-1), which is expressed on activated vascular endothelium, and mucosal addressin cell adhesion molecule-1 (MAdCAM-1) present on vascular endothelial cells of the gastrointestinal tract. Disruption of these molecular interactions prevents transmigration of leukocytes across the endothelium into inflamed parenchymal tissue. *In vitro*, anti- $\alpha 4$ -integrin antibodies also block $\alpha 4$ -mediated cell binding to ligands such as osteopontin and an alternatively spliced domain of fibronectin, connecting segment-1 (CS-1). *In vivo*, natalizumab may further act to inhibit the interaction of $\alpha 4$ -expressing leukocytes with their ligand(s) in the extracellular matrix and on parenchymal cells, thereby inhibiting further recruitment and inflammatory activity of activated immune cells.

The specific mechanism(s) by which TYSABRI exerts its effects in multiple sclerosis and Crohn's disease have not been fully defined.

In multiple sclerosis, lesions are believed to occur when activated inflammatory cells, including T-lymphocytes, cross the blood-brain barrier (BBB). Leukocyte migration across the BBB involves interaction between adhesion molecules on inflammatory cells and their counter-receptors present on endothelial cells of the vessel wall. The clinical effect of natalizumab in multiple sclerosis may be secondary to blockade of the molecular interaction of $\alpha 4\beta 1$ -integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells, and with CS-1 and/or osteopontin expressed by parenchymal cells in the brain. Data from an experimental autoimmune encephalitis animal model of multiple sclerosis demonstrate reduction of leukocyte migration into brain parenchyma and reduction of plaque formation detected by magnetic resonance imaging (MRI) following repeated administration of natalizumab. The clinical significance of these animal data is unknown.

In Crohn's disease, the interaction of the $\alpha 4\beta 7$ integrin with the endothelial receptor MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of the disease. MAdCAM-1 is mainly expressed on gut endothelial cells and plays a critical role in the homing of T lymphocytes to gut lymph tissue found in Peyer's patches. MAdCAM-1 expression has been found to be increased at active sites of inflammation in patients with CD, which suggests it may play a role in the recruitment of leukocytes to the mucosa and contribute to the inflammatory response characteristic of CD. The clinical effect of natalizumab in CD may therefore be secondary to blockade of the molecular interaction of the $\alpha 4\beta 7$ -integrin receptor with MAdCAM-1 expressed on the venular endothelium at inflammatory foci. VCAM-1 expression has been found to be upregulated on colonic endothelial cells in a mouse model of IBD and appears to play a role in leukocyte recruitment to sites of inflammation. The role of VCAM-1 in CD, however, is not clear.

12.2 Pharmacodynamics

TYSABRI administration increases the number of circulating leukocytes (including lymphocytes, monocytes, basophils, and eosinophils) due to inhibition of transmigration out of the vascular space. TYSABRI does not affect the absolute count of circulating neutrophils [see *Warnings and Precautions* (5.6)].

12.3 Pharmacokinetics

Multiple Sclerosis (MS) Patients:

In patients with MS, following the repeat intravenous administration of a 300 mg dose of TYSABRI, the mean $\pm$ SD maximum observed serum concentration was 110 ± 52 mcg/mL. Mean average steady-state trough concentrations ranged from 23 mcg/mL to 29 mcg/mL. The

observed time to steady-state was approximately 24 weeks after every four weeks of dosing. The mean $\pm$ SD half-life, volume of distribution, and clearance of natalizumab were 11 ± 4 days, 5.7 ± 1.9 L, and 16 ± 5 mL/hour, respectively.

The effects of covariates such as body weight, age, gender, and presence of anti-natalizumab antibodies on natalizumab pharmacokinetics were investigated in a population pharmacokinetic study (n=2195). Natalizumab clearance increased with body weight in a less than proportional manner such that a 43% increase in body weight resulted in a 32% increase in clearance. The presence of persistent anti-natalizumab antibodies increased natalizumab clearance approximately 3-fold [see *Adverse Reactions* (6.2)].

Crohn's Disease (CD) Patients:

In patients with CD, following the repeat intravenous administration of a 300 mg dose of TYSABRI, the mean $\pm$ SD maximum observed serum concentration was 101 ± 34 mcg/mL. The mean $\pm$ SD average steady-state trough concentration was 10 ± 9 mcg/mL. The estimated time to steady-state was approximately 16 to 24 weeks after every four weeks of dosing. The mean $\pm$ SD half-life, volume of distribution, and clearance of natalizumab were 10 ± 7 days, 5.2 ± 2.8 L, and 22 ± 22 mL/hour, respectively.

The effects of total body weight, age, gender, race, selected hematology and serum chemistry measures, co-administered medications (infliximab, immunosuppressants, or steroids), and the presence of anti-natalizumab antibodies were investigated in a population pharmacokinetic analysis (n=1156). The presence of anti-natalizumab antibodies was observed to increase natalizumab clearance [see *Adverse Reactions* (6.2)].

Pharmacokinetics of natalizumab in patients with renal or hepatic insufficiency have not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

No clastogenic or mutagenic effects of natalizumab were observed in the Ames test or *in vitro* chromosomal aberration assay in human lymphocytes. Natalizumab showed no effects in *in vitro* assays of $\alpha 4$ -integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two $\alpha 4$ -integrin positive human tumor lines (leukemia, melanoma) demonstrated no increase in tumor growth rates or metastasis resulting from natalizumab treatment.

Reductions in female guinea pig fertility were observed in one study at dose levels of 30 mg/kg, but not at the 10 mg/kg dose level (2.3-fold the clinical dose). A 47% reduction in pregnancy rate was observed in guinea pigs receiving 30 mg/kg relative to control. Implantations were seen in only 36% of animals having corpora lutea in the 30 mg/kg group versus 66 to 72% in the other groups. Natalizumab did not affect male fertility at doses up to 7-fold the clinical dose.

13.2 Animal Toxicology and/or Pharmacology

In reproductive studies in monkeys and guinea pigs, there was no evidence of teratogenic effects at doses up to 30 mg/kg (7 times the human clinical dose based on a body weight comparison). In one study where female guinea pigs were exposed to natalizumab during the second half of pregnancy, a small reduction in pup survival was noted at post-natal day 14 with respect to control (3 pups/litter for the group treated with 30 mg/kg natalizumab and 4.3 pups/litter for the control group). In one of five studies that exposed monkeys or guinea pigs during pregnancy, the number of abortions in treated (30 mg/kg) monkeys was 33% versus 17% in

controls. No effects on abortion rates were noted in any other study. TYSABRI underwent trans-placental transfer and produced *in utero* exposure in developing guinea pigs and cynomolgus monkeys. When pregnant dams were exposed to natalizumab at approximately 7-fold the clinical dose, serum levels in fetal animals at delivery were approximately 35% of maternal serum natalizumab levels. A study in pregnant cynomolgus monkeys treated at 2.3-fold the clinical dose demonstrated natalizumab-related changes in the fetus. These changes included mild anemia, reduced platelet count, increased spleen weights, and reduced liver and thymus weights associated with increased splenic extramedullary hematopoiesis, thymic atrophy, and decreased hepatic hematopoiesis. In offspring born to mothers treated with natalizumab at 7-fold the clinical dose, platelet counts were also reduced. This effect was reversed upon clearance of natalizumab. There was no evidence of anemia in these offspring. Offspring exposed *in utero* and via breast milk had no natalizumab-related changes in the lymphoid organs and had normal immune response to challenge with a T-cell dependent antigen.

14 CLINICAL STUDIES

14.1 Multiple Sclerosis

TYSABRI was evaluated in two randomized, double-blind, placebo-controlled trials in patients with multiple sclerosis. Both studies enrolled patients who experienced at least one clinical relapse during the prior year and had a Kurtzke Expanded Disability Status Scale (EDSS) score between 0 and 5.0. Results for each study are shown in Tables 4 and 5. Median time on study drug was 120 weeks in each study. In both studies, neurological evaluations were performed every 12 weeks and at times of suspected relapse. Magnetic resonance imaging evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually.

Study MS1 enrolled patients who had not received any interferon-beta or glatiramer acetate for at least the previous 6 months; approximately 94% had never been treated with these agents. Median age was 37, with a median disease duration of 5 years. Patients were randomized in a 2:1 ratio to receive TYSABRI 300 mg intravenous infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study MS2 enrolled patients who had experienced one or more relapses while on treatment with AVONEX® (Interferon beta-1a) 30 mcg intramuscularly (IM) once weekly during the year prior to study entry. Median age was 39, with a median disease duration of 7 years. Patients were evenly randomized to receive TYSABRI 300 mg (n=589) or placebo (n=582) every 4 weeks for up to 28 months (30 infusions). All patients continued to receive AVONEX 30 mcg IM once weekly. The efficacy of TYSABRI alone was not compared with the efficacy of TYSABRI plus AVONEX.

The primary endpoint at 2 years was time to onset of sustained increase in disability, defined as an increase of at least 1 point on the EDSS from baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or at least a 1.5 point increase on the EDSS from baseline EDSS=0 that was sustained for 12 weeks. Time to onset of sustained increase in disability was longer in TYSABRI-treated patients than in placebo-treated patients in Studies MS1 (Figure 1) and MS2. The proportion of patients with increased disability and the annualized relapse rate were also lower in TYSABRI-treated patients than in placebo-treated patients in Studies MS1 and MS2 (Tables 4 and 5).

Table 4. Clinical and MRI Endpoints in Study MS1 (Monotherapy Study) at 2 Years

	TYSABRI n=627	Placebo n=315
Clinical Endpoints		
Percentage with sustained increase in disability	17%	29%
Relative Risk Reduction	42% (95% CI 23%, 57%)	
Annualized relapse rate	0.22	0.67
Relative reduction (percentage)	67%	
Percentage of patients remaining relapse-free	67%	41%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	5.0
Percentage of patients with*:		
0 lesions	57%	15%
1 lesion	17%	10%
2 lesions	8%	8%
3 or more lesions	18%	68%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	97%	72%
1 lesion	2%	12%
2 or more lesions	1%	16%

All analyses were intent-to-treat. For each endpoint, $p < 0.001$. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS and age; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

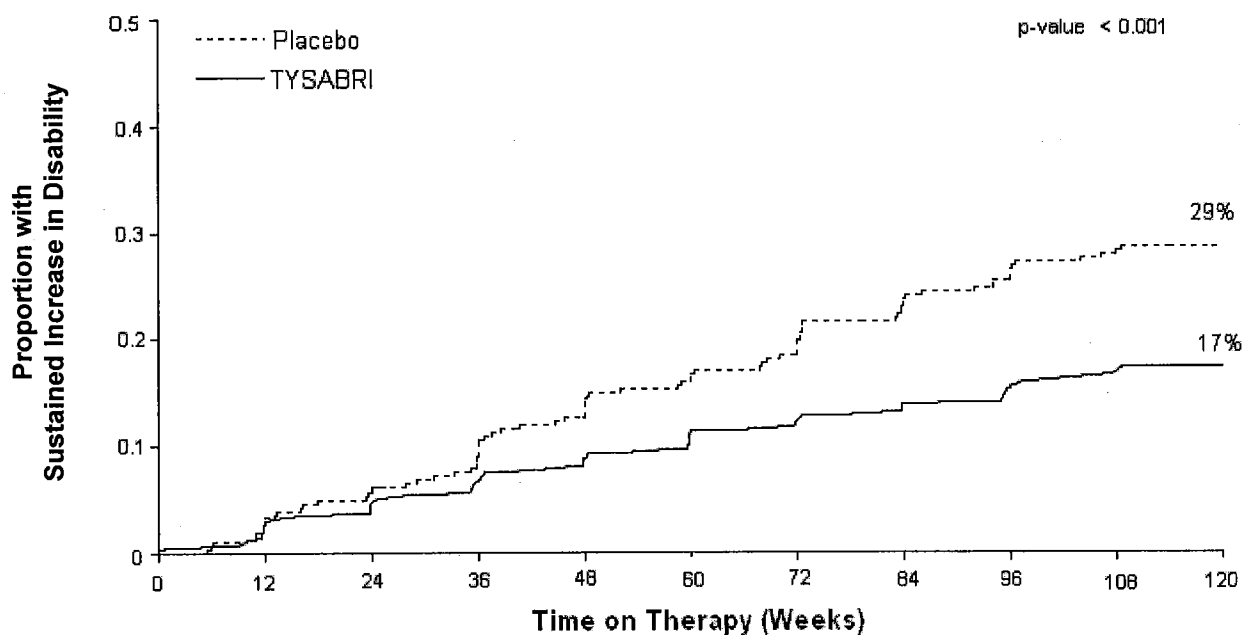
Table 5. Clinical and MRI Endpoints in Study MS2 (Add-On Study) at 2 Years

	TYSABRI plus AVONEX n=589	Placebo plus AVONEX n=582
Clinical Endpoints		
Percentage with sustained increase in disability	23%	29%
Relative Risk Reduction	24% (95% CI 4%, 39%)	
Annualized relapse rate	0.33	0.75
Relative reduction (percentage)	56%	
Percentage of patients remaining relapse-free	54%	32%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	3.0
Percentage of patients with*:		
0 lesions	67%	30%
1 lesion	13%	9%
2 lesions	7%	10%
3 or more lesions	14%	50%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with*:		
0 lesions	96%	75%
1 lesion	2%	12%
2 or more lesions	1%	14%

All analyses were intent-to-treat. For disability accumulation $p=0.024$, for all other endpoints, $p<0.001$. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence of Gd-enhancing lesions, age; percentage relapse-free by logistic regression adjusting for baseline relapse rate; and lesion number by ordinal logistic regression adjusting for baseline lesion number.

Annualized relapse rate is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

*Values do not total 100% due to rounding.

Figure 1. Time to Increase in Disability Sustained for 12 Weeks in Study MS1

Changes in MRI findings often do not correlate with changes in the clinical status of patients (e.g., disability progression). The prognostic significance of the MRI findings in these studies has not been evaluated.

Safety and efficacy of treatment with TYSABRI beyond two years are not known.

14.2 Crohn's Disease

The safety and efficacy of TYSABRI were evaluated in three randomized, double-blind, placebo-controlled clinical trials in 1414 adult patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 450) [see *Reference (15)*]. Concomitant inhibitors of TNF- α were not permitted. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunosuppressants (e.g., 6-mercaptopurine, azathioprine, or methotrexate) were permitted, and 89% of patients continued to receive at least one of these medications. Although permitted in the clinical trials, combination therapy with immunosuppressants is not recommended. [see *Indications and Usage (1.2)*]. Overall, approximately two-thirds of patients were not taking concomitant immunosuppressants, and approximately one-third of patients were taking neither concomitant immunosuppressants nor concomitant corticosteroids.

Induction of clinical response (defined as ≥ 70 -point decrease in CDAI from baseline) was evaluated in two studies. In Study CD1, 896 patients were randomized 4:1 to receive three monthly infusions of either 300 mg TYSABRI or placebo. Clinical results were assessed at Week 10, and patients with incomplete information were considered as not having a clinical response. At Week 10, 56% of the 717 patients receiving TYSABRI were in response compared to 49% of the 179 patients receiving placebo (treatment effect: 7%; 95% confidence interval (CI): [-1%, 16%]; $p=0.067$). In a *post hoc* analysis of the subset of 653 patients with elevated

baseline C-reactive protein (CRP), indicative of active inflammation, 57% of TYSABRI patients were in response compared to 45% of those receiving placebo (treatment effect: 12%; 95% CI: [3%, 22%]; nominal $p=0.01$).

In the second induction trial, Study CD2, only patients with elevated serum C-reactive Protein (CRP) were studied. A total of 509 patients were randomized 1:1 to receive three monthly infusions of either 300 mg TYSABRI or placebo. In Study CD2, in contrast to Study CD1, clinical response and clinical remission (defined as CDAI score <150) were required to be met at both Weeks 8 and 12, rather than at a single time-point; patients with incomplete information were considered as not having a response (Table 6).

Table 6. Induction of Clinical Response and Remission in Study CD2

	TYSABRI n=259	Placebo n=250	Treatment Difference (95% CI)
Clinical Response at:			
Week 8	56%	40%	16% (8%, 26%)
Week 12	60%	44%	16% (7%, 25%)
Both Weeks 8 & 12*	48%	32%	16% (7%, 24%)
Clinical Remission at:			
Week 8	32%	21%	11% (3%, 19%)
Week 12	37%	25%	12% (4%, 21%)
Both Weeks 8 & 12*	26%	16%	10% (3%, 18%)

* $p < 0.005$

Response is defined as a ≥ 70 -point reduction in CDAI score from baseline.

Remission is defined as CDAI < 150 .

In studies CD1 and CD2, for subgroups defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF- α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF- α appeared to have lower clinical response and lower clinical remission in both the treatment and placebo groups. For patients in Study CD2 with an inadequate response to prior treatment with inhibitors of TNF- α , clinical response at both Weeks 8 and 12 was seen in 38% of those randomized to TYSABRI, and clinical remission at both Weeks 8 and 12 was seen in 17%.

Maintenance therapy was evaluated in Study CD3. In this study, 331 patients from Study CD1 that had had a clinical response to TYSABRI at both Weeks 10 and 12 were re-randomized 1:1 to treatment with continuing monthly infusions of either 300 mg TYSABRI or placebo.

Maintenance of response was assessed by the proportion of patients who did not lose clinical response at any study visit for an additional 6 and 12 months of treatment (i.e., Month 9 and Month 15 after initial treatment with TYSABRI). The study also assessed the proportion of patients who did not lose clinical remission at any study visit within the subset of those who were in remission at study entry. Requiring maintenance of response or remission at each visit, as opposed to just at Month 9 or Month 15, may result in lower proportions meeting endpoint criteria, and may make a comparison of these results with those of other products used to treat Crohn's disease misleading (Table 7).

Table 7. Maintenance of Clinical Response and Remission in Study CD3

	TYSABRI	Placebo	Treatment Difference (95% CI)
	n=164	n=167	
Clinical Response through:			
Month 9*	61%	29%	32% (21%, 43%)
Month 15	54%	20%	34% (23%, 44%)
	n=128[†]	n=118[†]	
Clinical Remission through:			
Month 9*	45%	26%	19% (6%, 31%)
Month 15	40%	15%	25% (13%, 36%)

*p<0.005

†Number of patients included for analysis of “through” Month 9 and Month 15 includes only those in remission upon entry into Study CD3.

Response is defined as CDAI <220 and a ≥70-point reduction in CDAI score compared to Baseline from Study CD1. Remission is defined as CDAI <150.

For subgroups in study CD3 defined by prior use of, or by inadequate response to prior therapies (i.e., corticosteroids, immunosuppressants, and inhibitors of TNF- α), the treatment effect was generally similar to that seen in the whole study population. In the subgroup of patients that were taking neither concomitant immunosuppressants nor concomitant corticosteroids, the treatment effect was generally similar to that seen in the whole study population. Patients with inadequate response to inhibitors of TNF- α appeared to have lower maintenance of clinical response and lower maintenance of clinical remission in both the treatment and placebo groups. For patients in study CD3 with an inadequate response to prior treatment with inhibitors of TNF- α , maintenance of clinical response through Month 9 was seen in 52% of those randomized to TYSABRI, and maintenance of clinical remission through Month 9 was seen in 30%.

Given the requirement to discontinue chronic steroids it is important to note that in the subgroup of patients (n=65) who were receiving corticosteroid medication at baseline, responded to TYSABRI in Study CD1, and were re-randomized to TYSABRI in Study CD3, approximately two-thirds were able to discontinue steroids within 10 weeks of initiating a steroid taper.

15 REFERENCES

- Best WR, Beckett JM, Singleton JW, Kern F: Development of a Crohn's Disease Activity Index, National Cooperative Crohn's Disease Study. *Gastroenterology* 1976; 70(3): 439-444.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 59075-730-15, TYSABRI injection is supplied as 300 mg natalizumab in 15 mL in a sterile, single-use vial free of preservatives. Each package contains a single-use vial. TYSABRI is a colorless and clear to slightly opalescent solution for dilution prior to intravenous infusion.

TYSABRI is available only through registered infusion centers participating in the TOUCH™ Prescribing Program. To locate these infusion centers, contact Biogen Idec at 1-800-456-2255.

TYSABRI single-use vials must be refrigerated between 2 to 8°C (36° to 46°F). Do not use beyond the expiration date stamped on the carton and vial label. DO NOT SHAKE OR FREEZE. Protect from light.

If not used immediately, store the diluted TYSABRI solution for infusion at 2 to 8°C (36° to 46°F). TYSABRI solution for infusion must be administered within 8 hours of preparation.

17 PATIENT COUNSELING INFORMATION

See Medication Guide (17.6)

17.1 General Counseling Information

Counsel patients to understand the risks and benefits of TYSABRI before an initial prescription is written. The patient may be educated by either the enrolled prescriber or a healthcare provider under that prescriber's direction. INSTRUCT PATIENTS USING TYSABRI TO:

- Read the Medication Guide before starting TYSABRI and before each TYSABRI infusion.
- Promptly report any new or continuously worsening symptoms that persist over several days to their prescriber [see *Boxed Warning, Warnings and Precautions (5.1)*].
- Inform all of their physicians that they are receiving TYSABRI.
- Plan to see their prescriber three months after the first infusion, six months after the first infusion, and at least as frequently as every six months thereafter.

17.2 Progressive Multifocal Leukoencephalopathy

Inform patients that Progressive Multifocal Leukoencephalopathy (PML) has occurred in three patients who received TYSABRI. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Instruct the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. Instruct the patient that the progression of deficits usually leads to death or severe disability over weeks or months [see *Warnings and Precautions (5.1)*].

17.3 Hypersensitivity Reactions

Instruct patients to report immediately if they experience symptoms consistent with a hypersensitivity reaction (e.g., urticaria with or without associated symptoms) during or following an infusion of TYSABRI [see *Warnings and Precautions (5.3)*].

17.4 Immunosuppression/Infections

Inform patients that TYSABRI may lower the ability of their immune system to fight infections. Instruct the patient of the importance of contacting their doctor if they develop any symptoms of infection [see *Warnings and Precautions (5.4)*].

17.5 Hepatotoxicity

Inform patients that TYSABRI may cause liver injury. Instruct the patient to contact their doctor if they develop symptoms of hepatotoxicity [see *Warnings and Precautions (5.5)*].

TYSABRI (natalizumab)

Manufactured by:

Biogen Idec Inc.
14 Cambridge Center
Cambridge, MA 02142 USA
1-800-456-2255

Distributed by:

Elan Pharmaceuticals, Inc.
South San Francisco, CA 94080

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AVONEX® is a registered trademark of Biogen Idec

TOUCH™ is a trademark of Elan Pharmaceuticals, Inc.

U.S. Patent Numbers: 5,840,299, 6,033,665, 6,602,503, 5,168,062, 5,385,839, 5,730,978

17.6 Medication Guide

MEDICATION GUIDE

TYSABRI® (tie-SA-bree) (natalizumab)

Read the Medication Guide given to you before you start TYSABRI and before each infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment. Ask your doctor or nurse if you have any questions.

What is the most important information I should know about TYSABRI?

- **TYSABRI increases your chance of getting a rare brain infection that usually causes death or severe disability. This infection is called progressive multifocal leukoencephalopathy (PML).** If PML happens, it usually happens in people with weakened immune systems.
- No one can predict who will get PML.
- There is no known treatment, prevention, or cure for PML.

- Your chance of getting PML may be higher if you are also being treated with other medicines that can weaken your immune system, including other treatments for Multiple Sclerosis (MS) and Crohn's disease (CD).
- Even if you use TYSABRI alone to treat your MS or CD, it is not known if your chance of getting PML will be lower. It is also not known if treatment for a long period of time with TYSABRI can increase your chance of getting PML.
- TYSABRI is available only through a restricted distribution program called the TOUCH™ Prescribing Program. In order to receive TYSABRI, you must talk to your doctor and understand the benefits and risks of TYSABRI and agree to all of the instructions in the TOUCH™ Prescribing Program.
- If you take TYSABRI, it is important that you call your doctor right away if you get any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, or strength or other problems) that have lasted over several days. Tell all of your doctors that you are getting treatment with TYSABRI.

Also, see **“What are the possible side effects with TYSABRI?”** for other serious side effects with TYSABRI.

What is TYSABRI?

TYSABRI is a prescription medicine approved for:

1. adult patients with relapsing forms of Multiple Sclerosis (MS) to:

- Slow the worsening of disability that is common in patients with MS and,
- Decrease the number of flare-ups (relapses)

Because of the chance of getting PML, TYSABRI is generally recommended for patients that have not been helped enough by, or cannot tolerate treatments for MS.

2. adult patients with moderate to severe Crohn's disease:

- To reduce signs and symptoms of Crohn's disease
 - In patients who have not been helped enough by, or cannot tolerate usual Crohn's disease medicines and medicines called tumor necrosis factor (TNF) inhibitors.
 - Patients should not be taking certain medicines that weaken the immune system at the same time they are taking TYSABRI. Ask your doctor if you have questions.
-
- TYSABRI does not cure MS or Crohn's disease.
 - TYSABRI has not been studied for use longer than 2 years. Also, TYSABRI has not been studied in patients with chronic progressive MS. It is not known if patients older than 65 years have a different response to TYSABRI.
 - TYSABRI is not approved for use in patients under age 18.

TYSABRI is only:

- prescribed by doctors who are enrolled in the TOUCH™ Prescribing Program
- infused at an infusion center that is enrolled in the TOUCH™ Prescribing Program
- given to patients who are enrolled in the TOUCH™ Prescribing Program

Who should not receive TYSABRI?

Do **not** receive TYSABRI if you:

- have PML
- are allergic to TYSABRI

TYSABRI is not recommended if you:

- have a medical condition that can weaken your immune system such as HIV infection or AIDS, leukemia or lymphoma, or an organ transplant, and others.
- are taking medicines that can weaken your immune system. Talk with your doctor about all of the medicines you take or have taken.

If you have questions about any of the above, talk to your doctor.

What should I tell my doctor and nurse before receiving each infusion of TYSABRI?

Tell your doctor and nurse about all of your medical conditions. Tell them if you:

- have any new or worsening medical problems (such as a new or sudden change in your thinking, eyesight, balance, or strength or other problems) that have lasted several days
- have had hives, itching or trouble breathing during or after an infusion of TYSABRI
- have a fever or infection (including shingles or any unusually long lasting infection)
- are pregnant or plan to become pregnant
- are breastfeeding

Tell your doctor and nurse about all of the medicines you are taking, including prescription and non-prescription medicines, vitamins and herbal supplements.

- Know the medicines you take. Keep a list of them with you to show your doctor and nurse. The nurse may ask to see this list before every TYSABRI infusion.

How do I receive TYSABRI?

- TYSABRI is given once every four weeks through a needle placed in a vein (IV infusion).
- You must follow all the instructions of the TOUCH™ Prescribing Program. Before you can begin to receive TYSABRI, your doctor or nurse will:
 - explain the TOUCH™ Prescribing Program to you
 - have you sign the TOUCH™ Prescriber/Patient Enrollment Form
- Before every TYSABRI infusion you will be asked a series of questions to confirm that TYSABRI is still right for you.
- Call your doctor who prescribes TYSABRI right away to report any medical problems that keep getting worse and last several days.

What are the possible side effects of TYSABRI?

TYSABRI increases your chance of getting a rare brain infection that usually causes death or severe disability. This infection is called progressive multifocal leukoencephalopathy (PML). If PML happens, it usually happens in people with weakened immune systems. (see “What is the most important information I should know about TYSABRI?”)

Other serious side effects with TYSABRI include:

- Allergic reactions including serious allergic reactions. Symptoms can include:
 - hives
 - itching
 - trouble breathing
 - chest pain
 - dizziness
 - wheezing
 - chills
 - rash
 - nausea
 - flushing of skin
 - low blood pressure
- Serious allergic reactions usually happen within 2 hours of the start of the infusion, but they can happen at any time after receiving TYSABRI.
- Tell your doctor or nurse right away if you have any symptom of an allergic reaction, even if it happens after you leave the infusion center. You may need treatment if you are having an allergic reaction.
- **Infections.** TYSABRI may increase your chance of getting an unusual or serious infection because TYSABRI can affect your immune system.
- **Liver damage.** TYSABRI may cause liver damage. Symptoms can include:

- yellowing of the skin and eyes (jaundice)
- nausea
- vomiting
- unusual darkening of the urine
- feeling tired or weak

Blood tests can be done to check for liver damage. Call your doctor right away if you have symptoms of liver damage.

Other side effects with TYSABRI include:

- headache
- urinary tract infection
- lung infection
- pain in your arm and legs
- vaginitis
- nose and throat infections
- feeling tired
- joint pain
- depression
- diarrhea
- rash
- stomach area pain

Tell your doctor about any side effect that bothers you or that does not go away.

These are not all the side effects with TYSABRI. Ask your doctor for more information.

General information about the safe and effective use of TYSABRI

This Medication Guide provides a summary of the most important information about TYSABRI. If you would like more information or have any questions, talk with your doctor or nurse. You can ask your doctor or nurse for information about TYSABRI that is written for healthcare professionals. You can also call 1-800-456-2255 or visit www.TYSABRI.com.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

What are the ingredients in TYSABRI?

Each dose of TYSABRI contains natalizumab; sodium chloride; sodium phosphate, monobasic, monohydrate; sodium phosphate, dibasic, heptahydrate; polysorbate 80; and water for injection.

Manufactured by Biogen Idec Inc.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

I61061-X

01/08

Manufactured by: Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142 USA

Distributed by: Elan Pharmaceuticals, Inc., South San Francisco, CA 94080

TYSABRI[®] is a registered trademark of Elan Pharmaceuticals, Inc.
TOUCH[™] is a trademark of Elan Pharmaceuticals, Inc.



TYSABRI® RISK MINIMIZATION ACTION PLAN: SUMMARY OF TOUCH™

The TOUCH™ (TYSABRI® Outreach: Unified Commitment to Health) Prescribing Program is a distribution program designed to assess the risk of progressive multifocal leukoencephalopathy (PML) associated with TYSABRI®, minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions regarding TYSABRI® use. The risks of TYSABRI® treatment are addressed through the distribution program, along with education of prescribers, pharmacists, infusion center staff, and patients about potential PML infection associated with TYSABRI® treatment.

The TOUCH Prescribing Program is being applied to both CD and MS patients. The versions differ slightly to address patient population (see below). The two versions of the TOUCH Prescribing Program are the MS-TOUCH program for the Multiple Sclerosis, and CD-TOUCH for the Crohn's Disease.

1. Prescribing Program

1.1 General Requirements

Biogen Idec, Inc. will ensure that the following requirements are addressed by its Risk Minimization Action Plan, the TOUCH™ Prescribing Program:

- TYSABRI® will only be available under a special restricted distribution program called the TOUCH™ Prescribing Program.
- Only prescribers enrolled in the TOUCH™ Prescribing Program and who agree to comply with the TOUCH™ program will be able to prescribe TYSABRI®.
- Only infusion sites enrolled in and authorized under the TOUCH™ Prescribing Program will be able to administer TYSABRI®.
- Only pharmacies enrolled in the TOUCH™ Prescribing Program will be able to dispense TYSABRI® to affiliated authorized infusion sites.
- Only patients enrolled in the TOUCH™ Prescribing Program and who agree to comply with the TOUCH™ Prescribing Program will be able to receive TYSABRI®.
- All TOUCH™ prescribers, pharmacies, infusion sites, and patients will be educated about the TOUCH™ Prescribing Program and the risks of TYSABRI® treatment.
- Safety surveillance, including monitoring and expedited reporting of PML infections, other serious opportunistic infections, malignancies, and deaths and systematic tracking of patients and drug disposition will be conducted.

1.2 Pharmacy and Infusion Site Requirements

Biogen Idec, Inc. will limit the distribution of TYSABRI® only to authorized infusion sites and their associated central pharmacies. The agreements between Biogen Idec and the central pharmacies and infusion sites require the following:

- All pharmacies and infusion sites will be enrolled in the TOUCH™ Prescribing Program, and agree to comply with the TOUCH™ Prescribing Program.
- Infusion sites and central pharmacies will obtain TYSABRI® directly from a single contract distributor or specialty pharmacy providers.
- All appropriate pharmacy and infusion site staff will be trained by Biogen Idec and/or Elan Pharmaceuticals about the TOUCH™ Prescribing Program and about the known risks, potential benefits, and appropriate use of TYSABRI®.
- All appropriate pharmacy and infusion site staff will be trained by Biogen Idec and/or Elan Pharmaceuticals in adverse experience reporting procedures, including 15 day reporting of PML infection, other serious opportunistic infections, malignancies (in CD patients) and deaths.
- Infusion site staff are to follow the infusion guidelines outlined below:
 - [cbk1] Only infuse patients who are enrolled and authorized in the TOUCH™ Prescribing Program.
 - Prior to infusing a patient, the infusion site will verify the patient is authorized to receive TYSABRI®.
 - TOUCH On-Line Infusion Sites: Patient Authorization Status must be “Authorized”
 - Paper-based Infusion Sites: Current Notice of Patient Authorization on file, and confirm that there is not a Notice of Discontinuation on file in the patient's medical record
 - Prior to infusing a patient, the infusion site will provide the patient the Tysabri Medication Guide and give the patient time to read it.
 - Prior to infusing a patient, the infusion site will complete the MS or CD Pre-Infusion Patient Checklist, as appropriate, and confirm prescriber clearance if needed.
 - Within one day of completing the Pre-Infusion Patient Checklist, the infusion site will submit the form to Biogen Idec via TOUCH On-Line or fax, regardless of whether the patient was infused TYSABRI®.
 - The infusion site will not infuse TYSABRI® if it is determined that the patient (or their prescriber) is not in conformance with the TOUCH™ Prescribing Program.
 - For Paper-based Infusion Sites, keep a record of the current Notice of Patient Authorization, the Pre-infusion Patient Checklist, and/or Notice of Patient Discontinuation for each corresponding patient. [cbk2]
- Central pharmacies are to follow the dispensing guidelines outlined below:
 - [cbk3] Dispense TYSABRI® only to affiliated authorized infusion sites.

- Complete the TYSABRI® Inventory Tracking Log for every dose/vial of TYSABRI® dispensed to authorized infusion sites. The Inventory Tracking Log will be kept for at least 5 years from the date of the final log entry.

1.3 Prescriber Requirements

Biogen Idec will accept registration of prescribers who agree to the following:

- To comply with the TOUCH™ program.
- Read and understand the full Prescribing Information for TYSABRI®.
- To understand that TYSABRI® increases the risk of progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the brain that usually leads to death or severe disability.
- To determine that a patient has a relapsing form of MS based on clinical and radiological evidence before prescribing TYSABRI® (MS Prescribers).
- To determine that a patient has moderately to severely active Crohn's disease with evidence of inflammation (CD Prescribers).
- [cbk4]To counsel all patients on the benefits and risks of TYSABRI® therapy, including the risks of PML, and to provide each patient with the TYSABRI® Medication Guide.
- To instruct all patients to promptly report any continuously worsening symptoms that persists over several days.
- To not prescribe TYSABRI® to any patient who is inappropriate for receiving the drug under the TOUCH™ program.
- To sign and complete the MS or CD Prescriber/Patient Enrollment form for each patient as appropriate, and to fax it to Biogen Idec before the patient can begin to receive infusions.
- To report to Biogen Idec, as soon as possible, any case of PML, any hospitalization due to opportunistic infection, malignancy and any death.
- To evaluate the patient 3 months after the first infusion, 6 months after the first infusion, every 6 months thereafter as long as the patient receives TYSABRI®, and 6 months after TYSABRI® has been discontinued.
- To evaluate the CD patient by 12 weeks of TYSABRI® therapy to determine if the patient has experienced a therapeutic benefit.
- To determine every 6 months whether each patient should continue on TYSABRI® therapy and fill out the Patient Status Report and Reauthorization Questionnaire.

1.4 Patient Requirements

Biogen Idec will accept registration for patients who meet the following conditions:

- Must be enrolled in the TOUCH™ Prescribing Program.
- Must understand the risks and benefits of TYSABRI® treatment, including that taking the drug increases the risk of getting PML.
- Must complete and sign the MS or CD Prescriber/Patient Enrollment Form, as appropriate, indicating the patient's understanding of the potential risks associated with TYSABRI® treatment.
- Must agree to contact their prescriber if new or worsening symptoms, especially nervous system symptoms develop.

- Must read the TYSABRI® Medication Guide.
- Must agree to notify the TOUCH™ Prescribing Program if they switch infusion sites and/or prescribers
- Must provide information about all medicines and treatments during the past month at each TYSABRI® infusion.

2. Educational Program

Biogen Idec, Inc. will provide prescribers, infusion site staff, pharmacists and patients with educational materials on the benefits and risks associated with TYSABRI® therapy, the increased risk of PML, and the requirements of the TOUCH™ Prescribing Program.

2.1 Healthcare Provider and Patient Educational Materials

Educational information about the drug will be distributed to prescribers, pharmacies, infusion sites, and patients.

The TOUCH™ Prescribing Program Educational Materials and forms include:

- The Patient Medication Guide and Package Insert (for patients and prescribers)
- TOUCH™ Prescribing Program Education Slide Set
- TYSABRI® and the TOUCH™ Prescribing Program Slide Set (for prescribers and patients)
- The TOUCH™ Prescribing Program Overview (general description)
- Prescriber/Patient Enrollment Form (MS and CD specific form to be signed by patients and prescribers)
- Infusion Site Enrollment Form (for infusion site enrollment)
- Central Pharmacy Enrollment Form (for central pharmacy enrollment)
- TYSABRI® Inventory Tracking Log (central pharmacies use to document dispensing of TYSABRI® to affiliated authorized infusion sites)
- Pre-infusion Patient Checklist (MS and CD specific forms to be completed by infusion site prior to each scheduled infusion)
- Patient Status Report and Reauthorization Questionnaire (MS and CD specific forms to be filled out ever 6 months by prescribers)
- [cbk5]TYSABRI® Patient Discontinuation Questionnaire (MS and CD specific forms for prescribers to complete at discontinuation and 6 months after the patient discontinues TYSABRI®)
- 12-Week Questionnaire for Crohn's Disease (CD specific form for prescribers to complete to determine if patient has experienced a therapeutic benefit)
- The TOUCH™ Prescribing Program Enrollment Kit (MS or CD specific folder for prospective prescribers -- contains above information and describes program)
- Dear Doctor and Dear Patient Letters
- Patient Getting Started Brochure (MS and CD specific versions with information for patients about the TOUCH™ Prescribing Program and TYSABRI®)
- Healthcare Professional Infusion Guide (for infusion sites)
- Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI® (for healthcare professionals caring for MS patients treated with Tysabri)