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TYSABRI® (natalizumab)

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. 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.

- 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, Progressive Multifocal Leukoencephalopathy; and WARNINGS, Prescribing, Distribution, and Administration Program for TYSABRI®**).
- 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 and WARNINGS, Progressive Multifocal Leukoencephalopathy**).

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 (IV) 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.

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CLINICAL PHARMACOLOGY

General

TYSABRI® binds to the $\alpha 4$ -subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the $\alpha 4$ -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*, TYSABRI® 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 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.

Pharmacokinetics

Following the repeat intravenous administration of a 300 mg dose of natalizumab to patients with multiple sclerosis, the mean 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 4 weeks of dosing. The mean 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. 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, Immunogenicity**). Age (18 to 62 years) and gender did not influence natalizumab pharmacokinetics.

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Pharmacokinetics of TYSABRI® in pediatric patients with multiple sclerosis or patients with renal or hepatic insufficiency have not been studied.

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 number of circulating neutrophils (see **PRECAUTIONS, Laboratory Tests**).

CLINICAL STUDIES

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.

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 1 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 IV infusion (n=627) or placebo (n=315) every 4 weeks for up to 28 months (30 infusions).

Study 2 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®.

Results for each study are shown in Tables 1 and 2. Median time on study drug was 120 weeks in each study. Safety and efficacy of treatment with TYSABRI® beyond two years are not known.

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 1 (Figure 1) and 2. The proportion of patients

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with increased disability and the annualized relapse rate were also lower in TYSABRI[®]-treated patients than in placebo-treated patients in Studies 1 and 2 (Tables 1 and 2).

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.

Table 1. Clinical and MRI Endpoints in Study 1 (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 2. Clinical and MRI Endpoints in Study 2 (Add-On Study) at 2 Years

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	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%

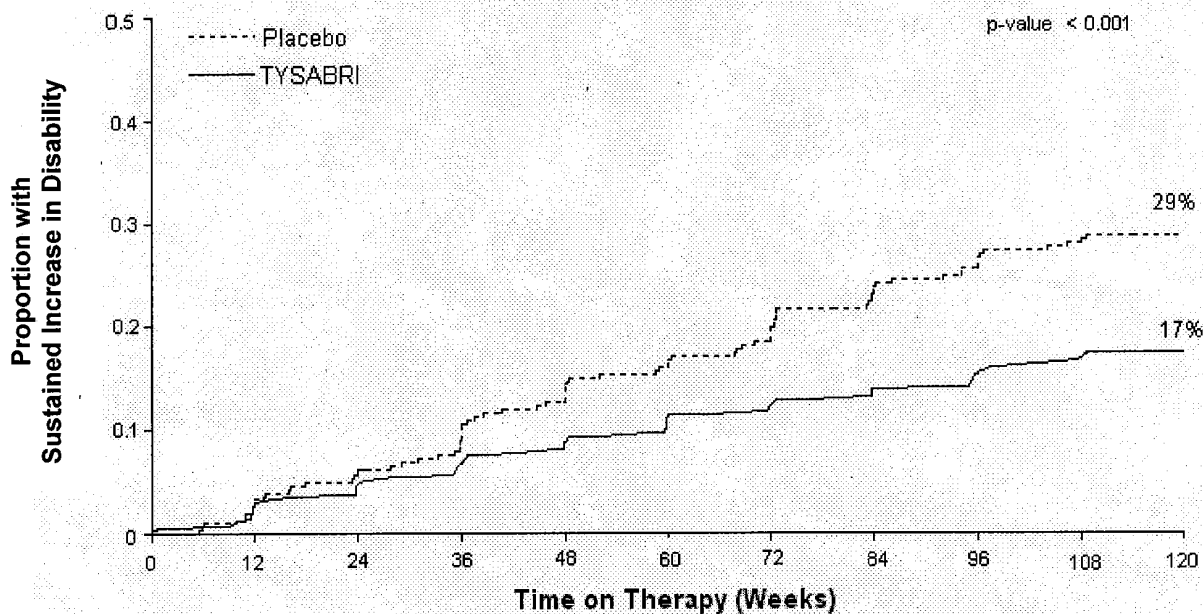
All analyses were intent-to-treat. For disability accumulation p=0.024, for all other endpoints, p<0.001. Determination of p-values: Increase in disability by Cox proportional hazards model adjusted for baseline EDSS; relapse rate by Poisson regression adjusting for baseline relapse rate, EDSS, presence 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.

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



INDICATIONS AND USAGE

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 (see **BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**), TYSABRI[®] is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate multiple sclerosis therapies.

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

CONTRAINDICATIONS

TYSABRI[®] should not be administered to patients with known hypersensitivity to TYSABRI[®] or any of its components.

TYSABRI[®] is contraindicated in patients who have or have had progressive multifocal leukoencephalopathy (PML) (see **BOXED WARNING and WARNINGS**).

WARNINGS

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Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy, an opportunistic infection caused by the JC virus that typically occurs in patients that are immunocompromised, has occurred in 3 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 8 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 2 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.

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. Healthcare professionals should monitor patients on TYSABRI® for any new sign or symptom suggestive of PML. TYSABRI® dosing should be withheld 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.

Prescribing, Distribution, and Administration 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. In addition, TYSABRI® must be administered only to patients who are enrolled in and meet all the conditions of the TOUCH™ Prescribing Program (see BOXED WARNING and/or contact the TOUCH™ Prescribing Program at 1-800-456-2255).

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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:

- Diagnose and manage opportunistic infections and PML, or be prepared to refer patients to specialists with these abilities.
- Educate patients on the benefits and risks of treatment with TYSABRI®, provide them with 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 at 1-800-456-2255 and to the Food and Drug Administration's MedWatch Program at 1-800-FDA-1088.
- Evaluate the patient 3 months after the first infusion, 6 months after the first infusion, and every 6 months thereafter.
- Determine every 6 months whether patients should continue on treatment and if so reauthorize treatment every 6 months.
- Submit to Biogen Idec the TYSABRI® Patient Status Report and Reauthorization Questionnaire 6 months after initiating treatment and every 6 months thereafter.

Information for Patients

Patients should be fully counseled on and 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.

PATIENTS WHO ARE PRESCRIBED TYSABRI® SHOULD BE INSTRUCTED TO:

- Read the Medication Guide before starting TYSABRI® and before each TYSABRI® infusion.
- Promptly report any continuously worsening symptoms that persist over several days to their prescriber (**see BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**).
- Inform all of their physicians that they are receiving TYSABRI®.
- Plan to see their prescriber 3 months after the first infusion, 6 months after the first infusion, and at least as frequently as every 6 months thereafter.

If patients experience symptoms consistent with a hypersensitivity reaction (e.g., urticaria with or without associated symptoms) during or following an infusion of TYSABRI®, they should report these symptoms to their prescriber immediately (**see WARNINGS, Hypersensitivity**).

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Hypersensitivity

TYSABRI® has been associated with hypersensitivity reactions, including serious systemic reactions (e.g., anaphylaxis) which occurred at an incidence of <1%. These reactions usually occur within 2 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 (see **ADVERSE REACTIONS, Infusion-related Reactions**). Patients who experience a hypersensitivity reaction should not be re-treated with TYSABRI®. The possibility of antibodies to TYSABRI® should be considered in patients who have hypersensitivity reactions (see **ADVERSE REACTIONS, Immunogenicity**).

Immunosuppression

The immune system effects of TYSABRI® may increase the risk for infections. In Study 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, Progressive Multifocal Leukoencephalopathy (PML); and ADVERSE REACTIONS, General and Infections**). One opportunistic infection, a cryptosporidial gastroenteritis with a prolonged course, was observed in a patient who received TYSABRI® in Study 1.

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, Progressive Multifocal Leukoencephalopathy; and ADVERSE REACTIONS, Infections**). The safety and efficacy of TYSABRI® in combination with antineoplastic, immunosuppressant, or immunomodulating agents have not been established.

Concurrent use of short courses of corticosteroids was associated with an increase in infections in Studies 1 and 2. However, the increase in infections in TYSABRI®-treated patients who received steroids was similar to the increase in placebo-treated patients who received steroids.

PRECAUTIONS

Information for Patients

See **WARNINGS, Information for Patients**

Laboratory Tests

TYSABRI® induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed changes persist during TYSABRI® exposure, but are

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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.

Drug Interactions

See **BOXED WARNING** and **WARNINGS, Immunosuppression**.

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 α 4-integrin positive human tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude mice with two α 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 66-72% in the other groups. Natalizumab did not affect male fertility at doses up to 7-fold the clinical dose.

Pregnancy (Category C)

There are no adequate and well-controlled studies of TYSABRI[®] therapy in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. If a woman becomes pregnant while taking TYSABRI[®], discontinuation of TYSABRI[®] should be considered.

If a woman becomes pregnant while taking TYSABRI[®], consider enrolling her in the TYSABRI[®] Pregnancy Exposure Registry by calling 1-800-456-2255.

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

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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.

Nursing Mothers

It is not known whether TYSABRI[®] is excreted in human milk. Because many drugs and immunoglobulins are excreted in human milk, and because the potential for serious adverse reactions is unknown, discontinuation of TYSABRI[®] or alternatives to nursing should be considered.

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.

Pediatric Use

Safety and effectiveness of TYSABRI[®] in pediatric patients with multiple sclerosis below the age of 18 have not been studied. TYSABRI[®] is not indicated for use in pediatric patients.

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[®].

ADVERSE REACTIONS

General

The most frequently reported serious adverse events in Study 1 (see **CLINICAL STUDIES**) 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 2, serious adverse events of appendicitis were also more common in patients who received TYSABRI[®] (0.8% versus 0.2% in placebo) (see **WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infections**).

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The most frequently reported adverse reactions resulting in clinical intervention (i.e., discontinuation of TYSABRI®), were urticaria (1%) and other hypersensitivity reactions (1%) (see **WARNINGS, Hypersensitivity**).

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.

A total of 1617 multiple sclerosis patients in controlled studies received TYSABRI®, with a median duration of exposure of 28 months.

Table 3 enumerates adverse events and selected laboratory abnormalities that occurred in Study 1 at an incidence of at least 1 percentage point higher in TYSABRI®-treated patients than was observed in placebo-treated patients.

Table 3. Adverse Reactions in Study 1 (Monotherapy Study)

Adverse Events (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%

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Adverse Events (Preferred Term)	TYSABRI® n=627 Percentage	Placebo n=312 Percentage
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%
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 2, peripheral edema was more common in patients who received TYSABRI® (5% versus 1% in placebo).

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Infections

Progressive Multifocal Leukoencephalopathy (PML) has occurred in 3 patients who received TYSABRI® in clinical trials (see **BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**). Two cases of PML were observed in the 1869 patients with multiple sclerosis who were treated for a median of 120 weeks. These 2 patients had received TYSABRI in addition to interferon beta-1a (see **BOXED WARNING and WARNINGS, Progressive Multifocal Leukoencephalopathy**). The third case occurred after 8 doses in one of the 1043 patients with Crohn's disease who were evaluated for PML.

In Studies 1 and 2, 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 1, 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 clinical studies for indications other than multiple sclerosis, opportunistic infections (e.g., pneumocystis carinii pneumonia, pulmonary mycobacterium avium intracellulare, bronchopulmonary aspergillosis, and burkholderia cepacia) have been uncommonly observed in TYSABRI®-treated patients; some of these patients were receiving concurrent immunosuppressants (see **WARNINGS, Immunosuppression**). Two serious non-bacterial meningitides occurred in TYSABRI®-treated patients compared to none in placebo-treated patients.

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

Infusion-related Reactions (see **WARNINGS, Hypersensitivity**)

An infusion-related reaction was defined in clinical trials as any adverse event occurring within 2 hours of the start of an infusion. Approximately 24% of TYSABRI®-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 18% of placebo-treated patients. Events more common in the TYSABRI®-treated 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. All patients recovered with treatment and/or discontinuation of the infusion.

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Patients who became persistently positive for antibodies to TYSABRI[®] were more likely to have an infusion-related reaction than those who were antibody-negative (see **ADVERSE REACTIONS, Immunogenicity**).

Immunogenicity

Patients in Study 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 1, the Week 12 pre-infusion mean natalizumab serum concentration in antibody-negative patients was 14.9 mcg/mL compared to 1.3 mcg/mL in antibody-positive patients. Persistent antibody-positivity was associated with 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 2.

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 events more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

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 6 months) may be transient and disappear with continued dosing. Repeat testing at 3 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.

The long-term immunogenicity of TYSABRI[®] and the effects of low to moderate levels of antibody to natalizumab are unknown. Experience with other monoclonal antibodies suggests that patients who receive therapeutic antibodies after an extended period without treatment may be at higher risk of hypersensitivity reactions than patients who received regularly scheduled treatment. It is not known if this will occur with TYSABRI[®] (see **WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infusion-related Reactions**).

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.

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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.

DOSAGE AND ADMINISTRATION

Only prescribers registered in the TOUCH[™] Prescribing Program may prescribe TYSABRI[®] (see **BOXED WARNING**).

The recommended dose of TYSABRI[®] is 300 mg IV infusion every four weeks. Dilute TYSABRI[®] concentrate 300 mg/15 mL in 100 mL 0.9% Sodium Chloride Injection, USP, and infuse over approximately one hour. Do not administer TYSABRI[®] as an IV push or bolus injection (see **Preparation Instructions**).

Observe patients during the infusion and for 1 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, Hypersensitivity**).

Preparation Instructions

Use aseptic technique when preparing TYSABRI[®] solution for IV infusion. Each vial is intended for single use only.

TYSABRI[®] is a colorless, clear to slightly opalescent concentrate. Inspect the TYSABRI[®] vial for particulate material 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. Do not use TYSABRI[®] beyond the expiration date stamped on the carton or vial.

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.

Gently invert the TYSABRI[®] solution to mix completely. Do not shake. Inspect the solution visually for particulate material prior to administration.

Following dilution, infuse TYSABRI[®] solution immediately, or refrigerate solution at 2-8°C, and use within 8 hours. If stored at 2-8°C, allow the solution to warm to room temperature prior to infusion. **DO NOT FREEZE.**

Administration Instructions

Infuse TYSABRI[®] 300 mg in 100 mL 0.9% Sodium Chloride Injection, USP over approximately one hour. After the infusion is complete, flush with 0.9% Sodium Chloride Injection, USP.

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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®.

HOW SUPPLIED

TYSABRI® concentrate is supplied as 300 mg natalizumab in a sterile, single-use vial free of preservatives. Each package contains a single-use vial. NDC 59075-730-15

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.

Storage

TYSABRI® single-use vials must be refrigerated between 2-8°C (36°-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 TYSABRI® solution for infusion at 2-8°C (36°-46°F). TYSABRI® solution for infusion must be administered within 8 hours of preparation.

I61061-2 Issue date [XXXX]

TYSABRI® (natalizumab)

Manufactured by:

Biogen Idec Inc.

14 Cambridge Center

Cambridge, MA 02142 USA

1-800-456-2255

Distributed by:

Elan Pharmaceuticals, Inc.

San Diego, CA 92121

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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

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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). PML 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 MS treatments.
- Even if you use **TYSABRI®** alone to treat your MS, 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**.

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- 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 patients with relapsing forms of 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 other treatments for MS.
- TYSABRI[®] does not cure MS.
- TYSABRI[®] has not been studied for use longer than 2 years. Also, TYSABRI[®] has not been studied in patients with chronic progressive MS, or in children. It is not known if patients older than 65 years have a different response to TYSABRI[®].

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[®]?

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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.

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- 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). PML 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
 - chills
 - rash
 - nausea
 - flushing of skin
 - low blood pressure

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- 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.

Other side effects with TYSABRI® include:

- headache
- urinary tract infection
- lung infection
- pain in your arm and legs
- vaginitis
- 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.

What are the ingredients in TYSABRI®?

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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.

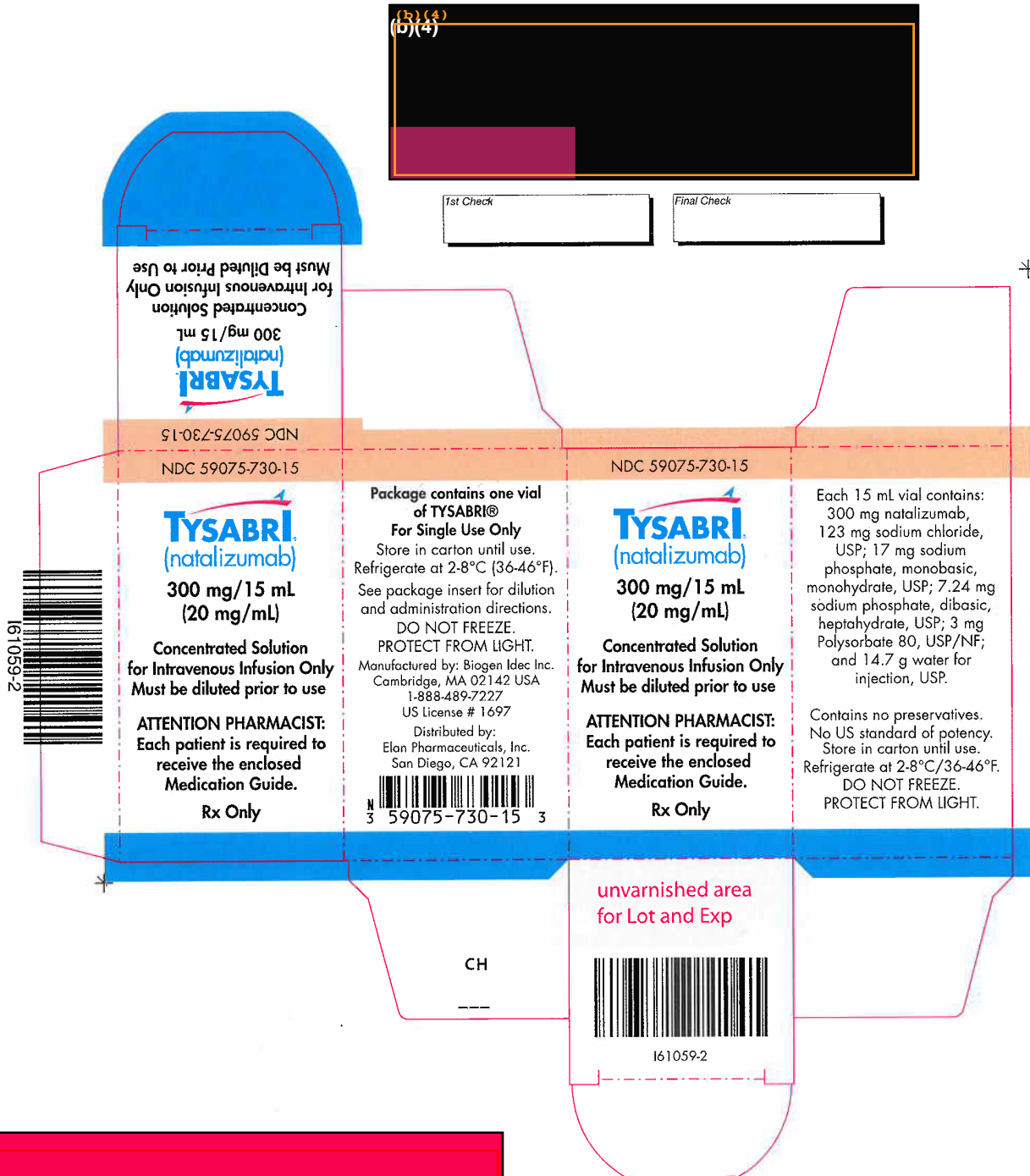
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Manufactured by: Biogen Idec Inc., 14 Cambridge Center, Cambridge, MA 02142 USA

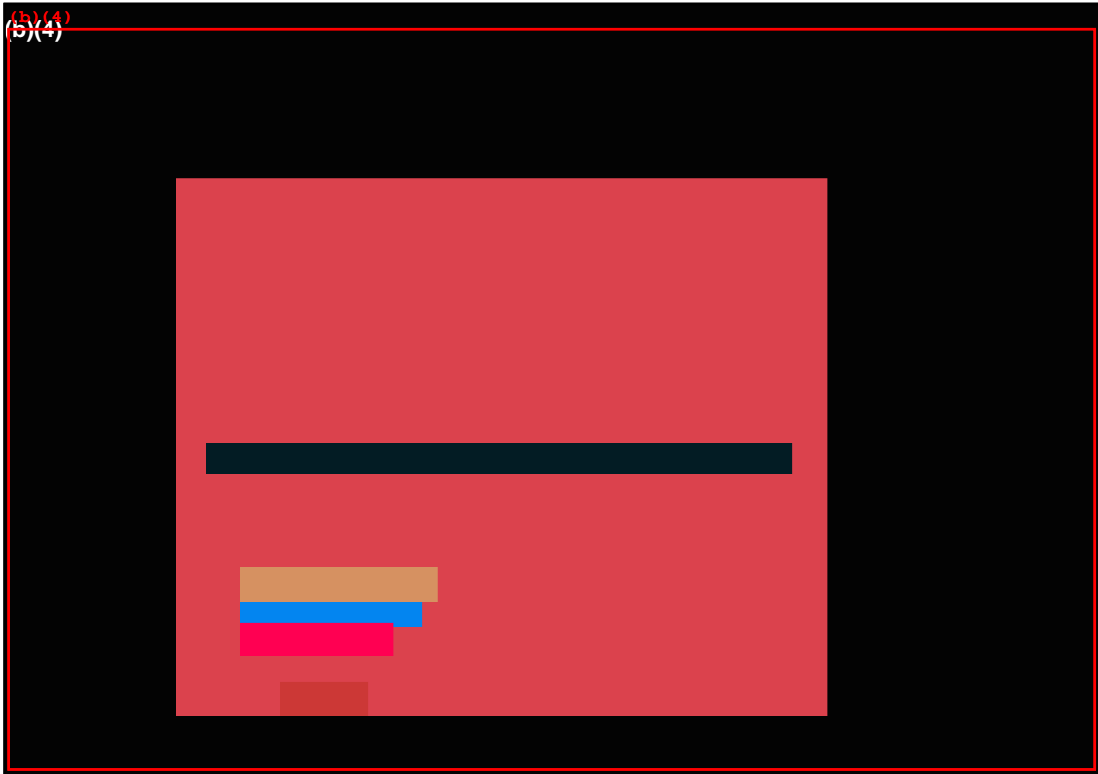
Distributed by: Elan Pharmaceuticals, Inc., San Diego, CA 92121

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TOUCH™ is a trademark of Elan Pharmaceuticals, Inc.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TY SABRI[®] RISK MINIMIZATION ACTION PLAN: SUMMARY OF TOUCH[™]

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

1. Prescribing Program

1.1 General Requirements

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

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

1.2 Pharmacy and Infusion Center Requirements

Biogen Idec, Inc. will limit the distribution of TYSABRI® through specialty and central pharmacies to authorized infusion centers. The agreements between Biogen Idec and the specialty and central pharmacies and infusion centers require the following:

- All pharmacies and infusion sites will be registered with the TOUCH™ program, and agree to comply with the TOUCH™ program.
- Infusion sites and central pharmacies will obtain TYSABRI® directly from a single contract distributor or specialty pharmacy.
- All appropriate pharmacy and infusion center staff will be trained by Biogen Idec and/or Elan Pharmaceuticals about the TOUCH™ program and about the known risks, potential benefits, and appropriate use of TYSABRI®.
- All appropriate pharmacy and infusion center 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, and deaths.
- Infusion center staff are to follow the infusion guidelines outlined below:
 - Accept only prescriptions from prescribers in the TOUCH™ program.
 - Only infuse patients who are enrolled in the TOUCH™ program.
 - Prior to infusing a patient, the infusion site will verify in the patient's medical record that the patient is authorized to receive TYSABRI®.
 - Prior to infusing a patient, the infusion site will, confirm that there is a current Notice of Patient Authorization on file, and confirm that there is not a Notice of Discontinuation on file.
 - Prior to infusing a patient, the infusion site will provide the patient the Medication Guide and give the patient time to read it.
 - Prior to infusing a patient, the infusion site will complete the Pre-Infusion Patient Checklist and confirm prescriber clearance if needed.
 - Within one day of completing the Pre-Infusion Patient Checklist, the infusion site will fax the form to Biogen Idec.
 - The infusion site will not dispense TYSABRI® if it is determined that the patient (or their prescriber) is not in conformance with the TOUCH™ program.
 - Keep a record of the TYSABRI® prescription, Notice of Patient Authorization, and the Pre-infusion Patient Checklist, with each TYSABRI® prescription for each corresponding patient.
- Central pharmacies are to follow the dispensing guidelines outlined below:
 - Fill valid prescriptions for TYSABRI® in accordance with all applicable laws and regulations
 - Dispense TYSABRI® only to affiliated authorized infusion sites.

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- 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.
- To determine that a patient has a relapsing form of MS based on clinical and radiological evidence before prescribing TYSABRI®.
- That he/she is capable of diagnosing and managing opportunistic infections and PML, or prepared to refer to specialists with those abilities.
- 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 not prescribe TYSABRI® to any patient who is inappropriate for receiving the drug under the TOUCH™ program.
- To sign and complete the Prescriber/Patient Enrollment form for each patient, 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, 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 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 registered in the TOUCH™ 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 Prescriber/Patient Enrollment Form 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™ program if they switch infusion sites and/or prescribers
- Must provide information about other medicines and treatments 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™ 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™ Educational Materials and forms include:

- The Patient Medication Guide and Package Insert (for patients and prescribers)
- TOUCH™ Prescribing Education Slide Set
- TYSABRI® and TOUCH™ Prescribing Program Slide Set (for prescribers and patients)
- TOUCH™ Prescribing Program Overview (general description)
- Prescriber/Patient Enrollment Form (signed by patients and prescribers)
- Infusion Site Enrollment Form (for infusion site enrollment)
- Central Pharmacy Enrollment Form (for central pharmacy enrollment into TOUCH™)
- TYSABRI® Inventory Tracking Log (central pharmacies use to document dispensing of TYSABRI® to affiliated authorized infusion sites)
- Patient Status Report and Reauthorization Questionnaire (filled out ever 6 months by prescribers)
- TYSABRI® Patient Discontinuation Notification Form (for prescribers to de-enroll a patient from the program)
- TYSABRI® Patient Discontinuation Questionnaire (for prescribers to complete at discontinuation and 6 months after the patient discontinues TYSABRI®)
- TOUCH™ Enrollment Kit (for prospective prescribers -- contains above information and describes program)
- Dear Doctor and Dear Patient Letters
- Patient Getting Started Brochure (information for patients about TOUCH™ and TYSABRI®)
- Healthcare Professional Infusion Guide (for infusion sites)
- Guidance for Evaluation of New Neurologic Symptoms in Patients Receiving TYSABRI® (for healthcare professionals)

2.2 Additional Information Sources

- www.TYSABRI.com
- Biogen Idec's Call Center: a call center designed to respond to healthcare provider, pharmacist, infusion center, and patient questions and requests for information.

3. Reporting: Biogen Idec, Inc. will implement a reporting and collection system for safety information as follows:

- All spontaneous and solicited adverse event reports from any post-marketing source will be reported as per 21 CFR 600.80.
- Within 15 calendar days a report for all confirmed cases of PML will be sent to FDA. Summary numbers for possible cases as flagged by the pre-infusion checklist will be reported in the periodic report.
- Within 15 calendar days a report of any other serious opportunistic infections or deaths of any cause will be reported to FDA.

Biogen Idec, Inc. will also establish a Pregnancy Registry in the US to determine the safety of TYSABRI® in pregnant patients. The primary objective will be to evaluate any pattern or increase in birth defects in children of women with MS who were exposed to TYSABRI® at any time within 3 months prior to conception, or at any time during pregnancy, where the outcome of the pregnancy is unknown at the time of enrollment.

4. TOUCH™ Safety Surveillance

Biogen Idec, through the TOUCH™ prescribing program will systematically follow and actively solicit information regarding the occurrence of PML and other serious opportunistic infections through a variety of mechanisms on every TYSABRI®-treated patient in the U.S. The various mechanisms include: through collection and assessment of Pre-Infusion Patient Checklists and the Prescriber/Patient Enrollment form; through serious adverse event reporting; and through contact with prescribers every 6 months in the form of a Patient Status Report and Reauthorization Questionnaire. In addition, attempts will be made to find and follow for 6 months patients who discontinue TYSABRI® treatment. Biogen Idec and Elan Pharmaceuticals are also creating a joint TYSABRI® Safety Review Committee to review safety data and determine any appropriate corrective actions, if needed.

5. TOUCH™ Program Evaluation

Biogen Idec, Inc. will evaluate the effectiveness of the TYSABRI® RiskMAP and will report the results quarterly for the first year, then every 6 months for 2 years, and annually thereafter to FDA. Each submission to FDA will include analyses of two major datasets:

- Health Outcomes Data (e.g. PML rate, overall safety)
- Systems/Process Data, Quality and Compliance Metrics

Biogen Idec, Inc. is also establishing a multi-disciplinary TYSABRI® Risk Management Review Committee to evaluate the effectiveness of the risk management plan. The decisions and outcomes of the Committee will be included in the TYSABRI® RiskMAP reports to FDA. In addition, Biogen Idec, Inc. and Elan Pharmaceuticals will create a joint TYSABRI® Compliance Review Committee to facilitate RiskMAP compliance.