TYSABRI® (natalizumab)

DESCRIPTION

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

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.

CLINICAL PHARMACOLOGY

General

TYSABRI® binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptor(s). The receptors for the α4 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-α4-integrin antibodies also block α4-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 α4-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 α4β1-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 multiple sclerosis patients, the mean maximum observed serum concentration was 98 ± 34 mcg/mL. Mean average steady-state natalizumab concentrations over the dosing period were approximately 30 mcg/mL. The mean half-life of 11 ± 4 days was observed with a clearance of 16 ± 5 mL/hour. The distribution volume of 5.7 ± 1.9 L was consistent with plasma volume.

Pharmacokinetics of TYSABRI® in pediatric multiple sclerosis patients 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 ongoing 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.

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. All patients continued to receive AVONEX® 30 mcg IM once weekly.

Results for each study were analyzed at a pre-specified time and are shown in Tables 1 and 2. Median patient time on study was 13 months in both studies. Safety and efficacy of treatment with TYSABRI® beyond one year are not known.

The exact relationship between MRI findings and the clinical status of patients is unknown. Changes in lesion area often do not correlate with changes in disability progression. The prognostic significance of the MRI findings in these studies has not been evaluated.

Table 1. 13-Month Clinical and 1-Year MRI Endpoints in Study 1 (Monotherapy Study)

	TYSABRI® n=627	**Placebo** n=315
Clinical Endpoints		
Annualized relapse rate	0.25	0.74
Relative reduction (percentage)	66%	
Percentage of patients remaining relapse-free	76%	53%
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	3.0
Percentage of patients with:		
0 lesions	60%	22%
1 lesion	18%	13%
2 lesions	6%	7%
3 or more lesions	16%	58%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	96%	68%
1 lesion	3%	13%
2 or more lesions	1%	19%

All analyses were intent-to-treat. For each endpoint, $p<0.001$. Determination of p-values: 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 MRI endpoints by ordinal logistic regression adjusting for baseline lesion number.

Table 2. 13-Month Clinical and 1-Year MRI Endpoints in Study 2 (Add-On Study)

	TYSABRI® plus AVONEX® n=589	**Placebo plus AVONEX®** n=582
Clinical Endpoints		
Annualized relapse rate	0.36	0.78
Relative reduction (percentage)	54%	
Percentage of patients remaining relapse-free	67%	46%

	TYSABRI® plus AVONEX® n=589	**Placebo plus AVONEX®** n=582
MRI Endpoints		
New or newly enlarging T2-hyperintense lesions		
Median	0.0	1.0
Percentage of patients with:		
0 lesions	67%	40%
1 lesion	26%	29%
2 lesions	4%	10%
3 or more lesions	3%	21%
Gd-enhancing lesions		
Median	0.0	0.0
Percentage of patients with:		
0 lesions	96%	76%
1 lesion	3%	12%
2 or more lesions	1%	12%

All analyses were intent-to-treat. For each endpoint, $p<0.001$. Determination of p-values: 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 MRI endpoints by ordinal logistic regression adjusting for baseline lesion number.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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 have experienced 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)**.

PRECAUTIONS

Immunosuppression

In Studies 1 and 2, concomitant treatment of relapses with a short course of corticosteroids was not associated with an increased rate of infection. The safety and efficacy of TYSABRI® in combination with other immunosuppressive agents have not been evaluated. Patients receiving these agents should not receive concurrent therapy with TYSABRI® because of the possibility of increased risk of infections.

Information to Patients

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 physician immediately **(see WARNINGS, Hypersensitivity)**.

Laboratory Tests

TYSABRI® induces increases in circulating lymphocytes, monocytes, eosinophils, basophils, and nucleated red blood cells. Observed increases 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.

Drug Interactions

After multiple dosing, interferon beta-1a (AVONEX® 30 mcg IM once weekly) reduced TYSABRI® clearance by approximately 30%. The similarity of the TYSABRI®-associated adverse event profile between Study 1 (without co-administered AVONEX®) and Study 2 (with co-administered AVONEX®) indicates that this alteration in clearance does not necessitate reduction of the TYSABRI® dose to maintain safety **(see ADVERSE REACTIONS, General)**.

Results of studies in multiple sclerosis patients taking TYSABRI® and concomitant interferon beta-1a (AVONEX® 30 mcg IM once weekly) or glatiramer acetate were inconclusive with regard to the need for dose adjustment of the beta-interferon or glatiramer acetate.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No clastogenic or mutagenic effects of natalizumab were observed in the Ames or human chromosomal aberration assays. Natalizumab showed no effects on *in vitro* assays of α4-integrin positive tumor line proliferation/cytotoxicity. Xenograft transplantation models in SCID and nude

mice with two α4-integrin positive 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)

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.

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.

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, a decision should be made whether to discontinue nursing or TYSABRI® taking into account the importance of therapy to the mother.

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 multiple sclerosis patients 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 reactions with TYSABRI® were infections (2.1% versus 1.3% in placebo, including pneumonia [0.6%]), hypersensitivity reactions (1.3%, including anaphylaxis/anaphylactoid reaction [0.8%]), depression (0.8%, including suicidal ideation [0.5%]), and cholelithiasis (0.8%) **(see WARNINGS, Hypersensitivity and ADVERSE REACTIONS, Infections)**.

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 1,617 multiple sclerosis patients, in both controlled and uncontrolled studies, have been exposed to TYSABRI® with a median duration of exposure of 20 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 the placebo group. The adverse event profile in Study 2 was similar.

Table 3. Adverse Reactions in Study 1

Adverse Events (Preferred Term)	TYSABRI® n=627 Percentage	Control n=312 Percentage
General		
Headache	35%	30%

Adverse Events (Preferred Term)	TYSABRI® n=627 Percentage	Control n=312 Percentage
Fatigue	24%	18%
Arthralgia	15%	11%
Allergic reaction	7%	3%
Urinary urgency/frequency	7%	5%
Chest discomfort	4%	2%
Local bleeding	3%	1%
Rigors	3%	1%
Syncope	2%	1%
Infection		
Urinary tract infection	18%	15%
Lower respiratory tract infection	15%	14%
Gastroenteritis	9%	5%
Vaginitis*	8%	5%
Tonsillitis	5%	3%
Psychiatric		
Depression	17%	14%
Gastrointestinal		
Abdominal discomfort	10%	9%
Abnormal liver function test	5%	3%
Skin		
Rash	9%	7%
Dermatitis	5%	4%
Pruritus	4%	2%
Menstrual disorders*		
Irregular menstruation/dysmenorrhea	7%	2%
Amenorrhea	2%	0%
Neurologic		
Tremor	3%	2%

*percentage based on female n

Infections

In Studies 1 and 2, the rate of infection was approximately 1 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. Most patients did not interrupt treatment with TYSABRI® during the infection. In Study 1, the incidence of serious infection was 2.1% in TYSABRI®-treated patients versus 1.3% in placebo-treated patients. No

difference was seen between treatment groups in Study 2.

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 22% of TYSABRI®-treated multiple sclerosis patients experienced an infusion-related reaction, compared to 17% of placebo-treated patients. Events more common in the TYSABRI®-treated patients included headache, dizziness, fatigue, hypersensitivity reactions, 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.

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 and Study 2 were tested for antibodies to natalizumab every 12 weeks. The assays used in these studies were unable to detect low to moderate levels of antibodies to natalizumab. Antibodies were detected in approximately 10% of multiple sclerosis patients receiving TYSABRI® at least once during treatment with persistent antibody-positivity in 6% of patients. Approximately 90% of patients who became persistently antibody-positive by this assay had 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. Across studies, the week 12 pre-infusion mean natalizumab serum concentrations in antibody-negative patients were approximately 17 mcg/mL compared to <1 mcg/mL in antibody-positive patients. Persistent antibody-positivity to natalizumab was associated with a substantial decrease in the effectiveness of TYSABRI®. In Study 1, the annualized relapse rate of persistently antibody-positive TYSABRI®-treated patients (0.75) was similar to the annualized relapse rate in subjects who received placebo (0.74). A similar phenomenon was also observed in Study 2.

Infusion-related reactions most often associated with persistent antibody-positivity included hypersensitivity reactions, urticaria, rigors, nausea, vomiting, and flushing. Additional adverse events more common in persistently antibody-positive patients included myalgia, hypertension, dyspnea, anxiety, and tachycardia.

The long-term immunogenicity of TYSABRI® and the effects of low to moderate levels of antibody to natalizumab are unknown **(see 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.

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

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.

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

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.

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TYSABRI® (natalizumab)

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