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

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