RebifÒ (interferon beta-1a)

DESCRIPTION

Rebif® (interferon beta-1a) is a purified 166 amino acid glycoprotein with a molecular weight of approximately 22,500 daltons. It is produced by recombinant DNA technology using genetically engineered Chinese Hamster Ovary cells into which the human interferon beta gene has been introduced. The amino acid sequence of Rebif® is identical to that of natural fibroblast derived human interferon beta. Natural interferon beta and interferon beta-1a (Rebif®) are glycosylated with each containing a single N-linked complex carbohydrate moiety.

Using a reference standard calibrated against the World Health Organization natural interferon beta standard (Second International Standard for Interferon, Human Fibroblast GB 23 902 531), Rebif® has a specific activity of approximately 270 million international units (MIU) of antiviral activity per mg of interferon beta-1a determined specifically by an in vitro cytopathic effect bioassay using WISH cells and Vesicular Stomatitis virus. Rebif® 44 mcg contains approximately 12 MIU of antiviral activity using this method.

Rebif® (interferon beta-1a) is formulated as a sterile solution in a pre-filled syringe intended for subcutaneous (sc) injection. Each 0.5 ml (0.5 cc) of Rebif® contains either 44 mcg or 22 mcg of interferon beta-1a, 4 or 2 mg albumin (human) USP, 27.3 mg mannitol USP, 0.4 mg sodium acetate, Water for Injection USP.

CLINICAL PHARMACOLOGY

General

Interferons are a family of naturally occurring proteins that are produced by eukaryotic cells in response to viral infection and other biological inducers. Interferons possess immunomodulatory, antiviral and antiproliferative biological activities. They exert their biological effects by binding to specific receptors on the surface of cells. Three major groups of interferons have been distinguished: alpha, beta, and gamma. Interferons alpha and beta form the Type I interferons and interferon gamma is a Type II interferon. Type I interferons have considerably overlapping but also distinct biological activities. Interferon beta is produced naturally by various cell types including fibroblasts and macrophages. Binding of interferon beta to its receptors initiates a complex cascade of intracellular events that leads to the expression of numerous interferon-induced gene products and markers, including 2', 5'-oligoadenylate synthetase, beta 2-microglobulin and neopterin, which may mediate some of the biological activities. The specific interferon-induced proteins and mechanisms by which interferon beta-1a exerts its effects in multiple sclerosis have not been fully defined.

Pharmacokinetics

The pharmacokinetics of Rebif® (interferon beta-1a) in people with multiple sclerosis have not been evaluated. In healthy volunteer subjects, a single subcutaneous (sc) injection of 60 mcg of Rebif® (liquid formulation), resulted in a peak serum concentration (C_{max}) of 5.1 ± 1.7 IU/mL (mean ± SD), with a median time of peak serum concentration (T_{max}) of 16 hours. The serum elimination half-life ($t_{1/2}$) was 69 ± 37 hours, and the area under the serum concentration versus time curve (AUC) from zero to 96 hours was 294 ± 81 IU·h/mL. Following every other day sc injections in healthy volunteer subjects, an increase in AUC of approximately 240% was

observed, suggesting that accumulation of interferon beta-1a occurs after repeat administration. Total clearance is approximately 33-55 L/hours. There have been no observed gender-related effects on pharmacokinetic parameters. Pharmacokinetics of Rebif® in pediatric and geriatric patients or patients with renal or hepatic insufficiency have not been established.

Pharmacodynamics

Biological response markers (e.g., 2'-5'-OAS activity, neopterin and beta 2-microglobulin) are induced by interferon beta-1a following parenteral doses administered to healthy volunteer subjects and to patients with multiple sclerosis. Following a single sc administration of 60 mcg of Rebif® intracellular 2'-5' OAS activity peaked between 12 to 24 hours and beta-2-microglobulin and neopterin serum concentrations showed a maximum at approximately 24 to 48 hours. All three markers remained elevated for up to four days. Administration of Rebif 22 mcg three times per week (tiw) inhibited mitogen-induced release of pro-inflammatory cytokines (IFN-γ, IL-1, IL-6, TNF-α and TNF-β) by peripheral blood mononuclear cells that, on average, was near double that observed with Rebif® administered once per week (qw) at either 22 or 66 mcg.

The relationships between serum interferon beta-1a levels and measurable pharmacodynamic activities to the mechanism(s) by which Rebif® exerts its effects in multiple sclerosis are unknown. No gender-related effects on pharmacodynamic parameters have been observed.

CLINICAL STUDIES

Two multicenter studies evaluated the safety and efficacy of Rebif® in patients with relapsing-remitting multiple sclerosis.

Study 1 was a randomized, double-blind, placebo controlled study in patients with multiple sclerosis for at least one year, Kurtzke Expanded Disability Status Scale (EDSS) scores ranging from 0 to 5, and at least 2 acute exacerbations in the previous 2 years.[(1)] Patients with secondary progressive multiple sclerosis were excluded from the study. Patients received sc injections of either placebo (n = 187), Rebif® 22 mcg (n = 189), or Rebif® 44 mcg (n = 184) administered tiw for two years. Doses of study agents were progressively increased to their target doses during the first 4 to 8 weeks for each patient in the study (see DOSAGE AND ADMINISTRATION).

The primary efficacy endpoint was the number of clinical exacerbations. Numerous secondary efficacy endpoints were also evaluated and included exacerbation-related parameters, effects of treatment on progression of disability and magnetic resonance imaging (MRI)-related parameters. Progression of disability was defined as an increase in the EDSS score of at least 1 point sustained for at least 3 months. Neurological examinations were completed every 3 months, during suspected exacerbations, and coincident with MRI scans. All patients underwent proton density T2-weighted (PD/T2) MRI scans at baseline and every 6 months. A subset of 198 patients underwent PD/T2 and T1-weighted gadolinium-enhanced (Gd)-MRI scans monthly for the first 9 months. Of the 560 patients enrolled, 533 (95%) provided 2 years of data and 502 (90%) received 2 years of study agent.

Study results are shown in Table 1 and Figure 1. Rebif® at doses of 22 mcg and 44 mcg administered sc tiw significantly reduced the number of exacerbations per patient as compared to placebo. Differences between the 22 mcg and 44 mcg groups were not significant (p >0.05).

Table 1: Clinical and MRI Endpoints from Study 1

	Placebo	22 mcg tiw	44 mcg tiw
	n = 187	n = 189	n = 184
Exacerbation-related			
Mean number of exacerbations per patient over 2 years[1,2]	2.56	1.82**	1.73***
(Percent reduction)		(29%)	(32%)
Percent (%) of patients exacerbation-free at 2 years[3]	15%	25%*	32%***
Median time to first exacerbation (months)[1,4]	4.5	7.6**	9.6***
MRI	n = 172	n = 171	n = 171
Median percent (%) change of MRI PD-T2 lesion area at 2 years[5]	11.0	-1.2***	-3.8***

* p<0.05 compared to placebo ** p<0.001 compared to placebo *** p<0.0001 compared to placebo

(1) Intent-to-treat analysis

(2) Poisson regression model adjusted for center and time on study

(3) Logistic regression adjusted for center. Patients lost to follow-up prior to an exacerbation were excluded from this analysis (n = 185, 183, and 184 for the placebo, 22 mcg tiw, and 44 mcg tiw groups, respectively)

(4) Cox proportional hazard model adjusted for center

(5) ANOVA on ranks adjusted for center. Patients with missing scans were excluded from this analysis

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.