

POLICY & PRACTICE

Imaging Accreditation

The Intersocietal Commission for the Accreditation of Magnetic Resonance Laboratories (ICAMRL) has expanded its program to include accreditation for body, cardiovascular, musculoskeletal, and neurologic imaging. The revised accreditation process, which went into effect Nov. 1, was instituted because of widespread interest from neurologists, cardiologists, orthopedic surgeons, radiologists, and others. "It is crucial to the future of this imaging modality that all specialties have access to a fair and equitable accreditation program that enables them to receive peer review of their work and to document to insurers that they are providing quality magnetic resonance studies consistent with established clinical guidelines," ICAMRL President Edward T. Martin, M.D., said in a statement. Labs can apply in any or all of the specialty areas. In addition, the ICAMRL process enables labs using extremity-only magnets to apply for accreditation.

New Neuroscience Site Coming

The National Institutes of Health is developing a Neuroscience Information Framework to provide information for neuroscientists. The framework, which will be accessible through the Internet, will provide links to neuroscience databases, results of neuroscience-related trials, and tools for exploring information about the brain. It will be designed by a consortium led by Cornell University's Weill Medical College. "Our goal is to make scientific data and findings available in order to help further research and promote a greater understanding of brain function and disease," said Daniel Gardner, Ph.D., principal investigator for the initiative and head of the neuroinformatics laboratory at the medical college. The framework will be supported through a \$550,000 grant for the first 15 months, followed by a \$1.1-million grant for the second phase.

Autism and Genetics

Five institutes at the National Institutes of Health and three private organizations have formed a consortium to identify genes that may contribute to the development of autism and autism spectrum disorders. The consortium has funded five grants totaling \$10.8 million, to be given out over a 5-year period. "This initiative seeks to expand our knowledge of the genetic factors involved in this disorder that affects so many families," said Thomas R. Insel, director of the National Institute of Mental Health, one of the consortium members. The other members from NIH are the National Institute on Deafness and Other Communication Disorders, the National Institute of Environmental Health Sciences, the National Institute of Neurological Disorders and Stroke, and the National Institute of Child Health and Human Development. The private organizations are the National Alliance for Autism Research, Cure Autism Now, and the Southwest Autism Research and Resource Center.

Improving End-of-Life Care

The nation's approach to end-of-life care needs to change, according to a new re-

port from the Hastings Center. "In the modern acute care hospital, virtually everything is oriented toward using life-sustaining equipment and techniques, not toward forgoing them," Thomas H. Murray and Bruce Jennings wrote. "The informal culture of specialty medicine, the reward system, the institutional pressures faced by family members, the range of choices people in extremis are being asked to make—each of these factors and more make up a system that is remarkably resistant to change." Mr. Murray and Mr. Jennings recommend inte-

grating advance directives more fully into patient care and paying more attention to the appropriate role of patients' family members in surrogate decision making. The report is available online at www.thehastingscenter.org/default.asp.

DTC Ad Guidelines Draw Criticism

Voluntary guidelines for direct-to-consumer (DTC) prescription drug advertising released by the Pharmaceutical Research and Manufacturers of America have drawn criticism from politicians and consumer groups who say they don't go far enough. "While I wish the PhRMA guidelines would have gone farther and

proposed a moratorium on DTC advertising of newly approved drugs, I hope individual pharmaceutical manufacturers will seriously consider such a measure," Senate Majority Leader Bill Frist, M.D. (R-Tenn.), said in a statement. Sidney Wolfe, M.D., director of the Public Citizen Health Research Group, called the PhRMA announcement "a meaningless attempt to fool people into believing the guidelines are stronger than they really are." The guidelines, which more than 20 companies have signed onto, are available online at www.phrma.org/publications/policy//2005-08-02.1194.pdf.

—Joyce Frieden

*Evidence of Interferon Dose-response: European North American Comparative Efficacy study.
†Prevention of Relapses and Disability by Interferon β -1a Subcutaneously in Multiple Sclerosis study.
References: 1. Data on file. Serono, Inc. 2. The PRISMS Study Group, and the University of British Columbia MS/MRI Analysis Group. PRISMS-4: long-term efficacy of interferon- β -1a in relapsing MS. *Neurology*. 2001;56:1628-1636.



BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Rebif[®] (interferon- β -1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif[®] in chronic progressive multiple sclerosis has not been established.

Clinical Studies

Two multicenter studies evaluated the safety and efficacy of Rebif[®] in patients with relapsing-remitting multiple sclerosis. Study 1 demonstrated that Rebif[®] significantly reduced the number of relapses per patient compared to placebo at 2 years. Study 2 was a comparative trial comparing Rebif[®] 44 mcg sc tiw and Avonex[®] 30 mcg im qw. The results of this trial demonstrated that patients treated with Rebif[®] 44 mcg sc tiw were more likely to remain relapse-free at 24 and 48 weeks than were patients treated with Avonex[®] 30 mcg im qw. Adverse reactions over 48 weeks were generally similar between the two treatment groups. Exceptions included injection site disorders (83% of patients on Rebif[®] vs. 28% of patients on Avonex[®]), hepatic function disorders (18% on Rebif[®] vs. 10% on Avonex[®]), and leukopenia (6% on Rebif[®] vs. <1% on Avonex[®]), which were observed with greater frequency in the Rebif[®] group compared to the Avonex[®] group.

CONTRAINDICATIONS

Rebif[®] (interferon β -1a) is contraindicated in patients with a history of hypersensitivity to natural or recombinant interferon, human albumin, mannitol USP, sodium acetate, or Water for Injection USP.

WARNINGS

Rebif[®] (interferon β -1a) should be used with caution in patients with depression, a condition that is common in people with multiple sclerosis. Depression, suicidal ideation, and suicide attempts have been reported to occur with increased frequency in patients receiving interferon compounds, including Rebif[®]. Patients should be advised to report immediately any symptoms of depression and/or suicidal ideation to the prescribing physician. If a patient develops depression, cessation of treatment with Rebif[®] should be considered.

Severe liver injury, including some cases of hepatic failure requiring liver transplantation has been reported rarely in patients taking Rebif[®]. Symptoms of liver dysfunction began from one to six months following the initiation of Rebif[®]. If jaundice or other symptoms of liver dysfunction appear, treatment with Rebif[®] should be discontinued immediately due to the potential for rapid progression to liver failure. Asymptomatic elevation of hepatic transaminases (particularly SGPT) is common with interferon therapy (see ADVERSE REACTIONS). Rebif[®] should be initiated with caution in patients with active liver disease, alcohol abuse, increased serum SGPT (>2.5 times ULN), or a history of significant liver disease. Also, the potential risk of Rebif[®] used in combination with known hepatotoxic products should be considered prior to Rebif[®] administration, or when adding new agents to the regimen of patients already on Rebif[®]. Reduction of Rebif[®] dose should be considered if SGPT rises above 5 times the upper limit of normal. The dose may be gradually re-escalated when enzyme levels have normalized.

Anaphylaxis has been reported as a rare complication of Rebif[®] use. Other allergic reactions have included skin rash and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use.

PRECAUTIONS

General: Caution should be exercised when administering Rebif[®] to patients with pre-existing seizure disorders. Seizures have been associated with the use of beta interferons. A relationship between occurrence of seizures and the use of Rebif[®] has not been established. Leukopenia and new or worsening thyroid abnormalities have developed in some patients treated with Rebif[®]. Regular monitoring for these conditions is recommended.

Information for Patients

All patients should be instructed to read the Rebif[®] Medication Guide supplied to them. Patients should be cautioned not to change the dosage or the schedule of administration without medical consultation.

Patients should be informed of the most common and the most severe adverse reactions associated with the use of Rebif[®]. Patients should be advised of the symptoms associated with these conditions, and to report them to their physician.

Female patients should be cautioned about the abortifacient potential of Rebif[®].

Patients should be instructed in the use of aseptic technique when administering Rebif[®]. Appropriate instruction for self-injection or injection by another person should be provided, including careful review of the Rebif[®] Medication Guide. If a patient is to self-administer Rebif[®], the physical and cognitive ability of that patient to self-administer and properly dispose of syringes should be assessed. The initial injection should be performed under the supervision of an appropriately qualified health care professional. Patients should be advised of the importance of rotating sites of injection with each dose, to minimize the likelihood of severe injection site reactions or necrosis.

Laboratory Tests: In addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, blood cell counts and liver function tests are recommended at regular intervals (1, 3, and 6 months) following introduction of Rebif[®] therapy and then periodically thereafter in the absence of clinical symptoms. Thyroid function tests are recommended every 6 months in patients with a history of thyroid dysfunction or as clinically indicated. Patients with myelosuppression may require more intensive monitoring of complete blood cell counts, with differential and platelet counts.

Drug Interactions: Drug interaction studies have not been conducted with Rebif[®]. Due to its potential to cause neutropenia and lymphopenia, proper monitoring of patients is required if Rebif[®] is given in combination with myelosuppressive agents.

Also, the potential for hepatic injury should be considered when Rebif[®] is used in combination with other products associated with hepatic injury, or when new agents are added to the regimen of patients already on Rebif[®] (see WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility: No carcinogenicity data for Rebif[®] are available in animals or humans. Rebif[®] was not mutagenic when tested in the Ames bacterial test and in an *in vitro* cytogenetic assay in human lymphocytes in the presence and absence of metabolic activation. No studies have been conducted to evaluate the effects of Rebif[®] on fertility in humans. In studies in normally cycling female cynomolgus monkeys given daily sc injections of Rebif[®] for six months at doses of up to 9 times the recommended weekly human dose (based on body surface area), no effects were observed on either menstrual cycling or serum estradiol levels. The validity of extrapolating doses used in animal studies to human doses is not established. In male monkeys, the same doses of Rebif[®] had no demonstrable adverse effects on sperm count, motility, morphology, or function.

Pregnancy Category C: Rebif[®] treatment has been associated with significant increases in embryolethal or abortifacient effects in cynomolgus monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area) either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies. These effects are consistent with the abortifacient effects of other type I interferons. There are no adequate and well-controlled studies of

Rebif[®] in pregnant women. However, in Studies 1 and 2, there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif[®] groups. If a woman becomes pregnant or plans to become pregnant while taking Rebif[®], she should be informed about the potential hazards to the fetus and discontinuation of Rebif[®] should be considered. A pregnancy registry has been established to monitor pregnancy outcomes of women exposed to Rebif[®] while pregnant. Register patients online at www.RebifPregnancyRegistry.com or call MS LifeLinesSM at 1-877-447-3243.

Nursing Mothers: It is not known whether Rebif[®] is excreted in human milk.

Pediatric Use: The safety and effectiveness of Rebif[®] in pediatric patients have not been studied.

Geriatric Use: Clinical studies of Rebif[®] did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects.

ADVERSE REACTIONS

The most frequently reported serious adverse reactions with Rebif[®] were psychiatric disorders including depression and suicidal ideation or attempt (see WARNINGS). The incidence of depression of any severity in the Rebif[®]-treated groups and placebo-treated group was approximately 25%. In post-marketing experience, Rebif[®] administration has been rarely associated with severe liver dysfunction, including hepatic failure requiring liver transplantation (see WARNINGS). The most commonly reported adverse reactions were injection site disorders, influenza-like symptoms (headache, fatigue, fever, rigors, chest pain, back pain, myalgia), abdominal pain, depression, elevation of liver enzymes and hematologic abnormalities. The most frequently reported adverse reactions resulting in clinical intervention (e.g., discontinuation of Rebif[®], adjustment in dosage, or the need for concomitant medication to treat an adverse reaction symptom) were injection site disorders, influenza-like symptoms, depression and elevation of liver enzymes (see WARNINGS). Injection site necrosis was rare.

Table 1. Adverse Reactions and Laboratory Abnormalities in Study 1

| BODY SYSTEM Preferred Term | Placebo tiw (n=187) | Rebif [®] 22 mcg tiw (n=189) | Rebif [®] 44 mcg tiw (n=184) |
|--|---------------------|---------------------------------------|---------------------------------------|
| BODY AS A WHOLE | | | |
| Influenza-like symptoms | 51% | 56% | 59% |
| Headache | 63% | 65% | 70% |
| Fatigue | 36% | 33% | 41% |
| Fever | 16% | 25% | 28% |
| Rigors | 5% | 6% | 13% |
| Chest Pain | 5% | 6% | 8% |
| Malaise | 1% | 4% | 5% |
| INJECTION SITE DISORDERS | | | |
| Injection Site Reaction | 39% | 89% | 92% |
| Injection Site Necrosis | 0% | 1% | 3% |
| CENTRAL & PERIPH NERVOUS SYSTEM DISORDERS | | | |
| Hypertonia | 5% | 7% | 6% |
| Coordination Abnormal | 2% | 5% | 4% |
| Convulsions | 2% | 5% | 4% |
| ENDOCRINE DISORDERS | | | |
| Thyroid Disorder | 3% | 4% | 6% |
| GASTROINTESTINAL SYSTEM DISORDERS | | | |
| Abdominal Pain | 17% | 22% | 20% |
| Dry Mouth | 1% | 1% | 5% |
| LIVER AND BILIARY SYSTEM DISORDERS | | | |
| SGPT Increased | 4% | 20% | 27% |
| SGOT Increased | 4% | 10% | 17% |
| Hepatic Function Abnormal | 2% | 4% | 9% |
| Bilirubinaemia | 1% | 3% | 2% |
| MUSCULO-SKELETAL SYSTEM DISORDERS | | | |
| Myalgia | 20% | 25% | 25% |
| Back Pain | 20% | 23% | 25% |
| Skeletal Pain | 10% | 15% | 10% |
| HEMATOLOGIC DISORDERS | | | |
| Leukopenia | 14% | 28% | 36% |
| Lymphadenopathy | 8% | 11% | 12% |
| Thrombocytopenia | 2% | 2% | 8% |
| Anemia | 3% | 3% | 5% |
| PSYCHIATRIC DISORDERS | | | |
| Somnolence | 1% | 4% | 5% |
| SKIN DISORDERS | | | |
| Rash Erythematous | 3% | 7% | 5% |
| Rash Maculo-Papular | 2% | 5% | 4% |
| URINARY SYSTEM DISORDERS | | | |
| Micturition Frequency | 4% | 2% | 7% |
| Urinary Incontinence | 2% | 4% | 2% |
| VISION DISORDERS | | | |
| Vision Abnormal | 7% | 7% | 13% |
| Xerophthalmia | 0% | 3% | 1% |

The safety of Rebif[®] (22 mcg and 44 mcg) vs placebo was studied in 560 patients with RRMIS who were treated for 24 months (Study 1). Table 1 enumerates adverse events and laboratory abnormalities that occurred at an incidence that was at least 2% more in either Rebif[®]-treated group than was observed in the placebo group.

Immunogenicity: As with all therapeutic proteins, there is a potential for immunogenicity. Serum NAB were detected in 31% and 24% of Rebif[®]-treated patients at the 22 mcg and 44 mcg tiw dose respectively at one or more times during Study 1. The clinical significance of the presence of NAB to Rebif[®] is unknown. Comparison of the incidence of antibodies to other products may be misleading.

DOSAGE AND ADMINISTRATION

Dosages of Rebif[®] shown to be safe and effective are 22 mcg and 44 mcg sc tiw. Rebif[®] should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days (e.g. Monday, Wednesday, and Friday) at least 48 hours apart each week. Generally, patients should be started at 20% of the prescribed dose and increased over a 4-week period to the targeted dose, either 22 mcg or 44 mcg sc tiw. Leukopenia or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif[®] administration until toxicity is resolved.

Rebif[®] is intended for use under the guidance and supervision of a physician. It is recommended that physicians or qualified medical personnel train patients in the proper technique for self-administering subcutaneous injections using the pre-filled syringe. Patients should be advised to rotate sites for sc injections. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms on treatment days. Rebif[®] should be inspected visually for particulate matter and discoloration prior to administration.

Rx only.

Manufacturer: Serono, Inc., Rockland, MA 02370 U.S. License # 1574

Co-marketed by: Serono, Inc., Rockland, MA 02370 Pfizer, Inc., New York, NY 10017

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