

Transatlantic Drug Information Sharing to Increase

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U.S. and European drug regulators have announced "intensified" information sharing and dialogue aimed at increasing cooperation in drug approval and surveillance activities in the world's two largest pharmaceutical markets.

At a March review meeting in Brussels, representatives from the Food and Drug Administration, the European Medicines Agency, and the European Commission judged as a success the implementation of a confidentiality agreement that has enabled greater transatlantic information sharing and dialogue on pharmaceutical regulations protecting 753 million people in 26 countries.

The three agencies hope to strengthen joint activities on vaccines in preparation

for potential pandemic flu outbreaks, as well as cancer, children's, and orphan drugs, and pharmacogenomics. Future activities will address counterfeit medicines.

The original agreement, signed in September 2003, paved the way for quarterly exchanges on information on new drug applications, regulatory guidance, and inspections of manufacturing plants, which began in 2004. The agreement also authorized ad hoc exchanges of information on drug safety and public health, includ-

ing advance notice of significant regulatory actions such as pulling drugs from the market. Such an exchange prevents other agencies from issuing contradictory advice when one agency takes significant regulatory action.

The ad hoc exchanges also have enabled "parallel" scientific guidance for drug applicants seeking the advice of the three agencies on how to proceed with research at such milestones as the conclusion of clinical trials. The first such paral-

lel scientific meeting occurred in September 2003, and as part of the initial confidentiality arrangement a 1-year pilot project was initiated in 2005.

The focus of those parallel meetings is breakthrough drugs, those for rare conditions, medication for children, or other new medicines considered important.

The three agencies agreed to extend the pilot project, although the document released by the agencies did not say how long it would be extended.

Use Unlisted Code 64999 for Pulsed Radiofrequency

SAN DIEGO — Reimbursement for pulsed radiofrequency, an experimental treatment for some types of chronic pain, now requires the use of unlisted procedure code 64999, as designated by the American Medical Association's Current Procedural Terminology (CPT).

The designation follows extended debate over a proposal by the North American Spine Society to assign pulsed radiofrequency to category 3 in the CPT section on emerging technology, said Dr. Eduardo M. Fraielfeld, chairman of the Coding and Reimbursement Committee of the American Academy of Pain Medicine (AAPM).

"When seeking reimbursement for pulsed radiofrequency, it is incorrect to use codes for radiofrequency ablation, including 64626 and 64627, which are neurolytic codes," Dr. Fraielfeld explained at the annual meeting of the AAPM.

In another pain-therapy CPT code overhaul, the AAPM's Coding and Reimbursement Committee eliminated the "Sedation With or Without Analgesia (Conscious Sedation)" category (99141-42) and replaced it with "Moderate (Conscious) Sedation." The new category has three codes for drug administration by the same physician performing the diagnostic or therapeutic service (99143-45) and three codes requiring an additional independent observer to monitor the patient (99148-50). These two categories are then broken down into three subcategories, which include under age 5 first 30 minutes intraservice time, age 5 and older first 30 minutes intraservice time, and an add-on code for each additional 15 minutes intraservice time, Dr. Fraielfeld said.

Other deletions this year include eight evaluation and management codes for "Follow-up Inpatient Consultations" (99261-3) and "Confirmatory Consultations" (99271-5).

—Bruce K. Dixon

*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-beta-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 beta-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 beta-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 LifeLines™ 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 & PERIPHERAL 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%
Bilirubinemia	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 RRMS 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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