

## POLICY & PRACTICE

### U.S. Investigating Botox Promotions

The U.S. Attorney's office for the northern district of Georgia has subpoenaed Allergan, seeking documents that might show off-label promotion of Botox (botulinum toxin type A) for treatment of headache. The company confirmed the inquiry in a statement, and said that while it currently has Botox in phase III studies for headache, "it is Allergan's policy to promote its products only in a manner consistent with the FDA-approved product labeling." Allergan also intends to comply "with all applicable laws, rule and regulations," according to the statement. Botox is Allergan's second-biggest-selling product, with \$1.2 billion in sales in 2007.

### New Neurotechnology Legislation

In an effort to expand neurotechnology research at the federal level, Rep. Patrick Kennedy (D-R.I.) plans to introduce legislation that would create a National Neurotechnology Initiative within the federal government. The legislation would coordinate neurotechnology research and development at the federal level and in partnership with small businesses, authorize \$80 million in fiscal year 2009 for the ongoing Blueprint for Neuroscience Research at the National Institutes of Health, and authorize an additional \$30 million in FY 2009 to increase neuroscience staff at the FDA. "With so many Americans suffering from brain-related illnesses, it is crucial for us as a society to maximize our efforts and continue learning about the many facets of the brain, leading to a healthier life for all Americans," Rep. Kennedy said in a statement.

### Parkinson's Disease Data Available

Researchers can now access data from genomewide association studies on Parkinson's disease through the National Institutes of Health. The data will be added to dbGaP (the database of Genotype and Phenotype). Having access to these raw data will allow researchers to combine them with their own data to improve analytical power. The database contains individual-level data on genotype, genetic makeup, phenotype, and observable traits and characteristics, according to NIH. The data comes from a study conducted by researchers at the Mayo Clinic in Rochester, Minn., and Perlegen Sciences Inc. in Mountain View, Calif. This is the second genomewide Parkinson's study available through the NIH database. Re-

searchers can access the information online at [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov).

### Fallout From Pay Uncertainty

Current uncertainties about Medicare payments is causing physician groups to postpone hiring and technology investment, and even to stop accepting new Medicare patients, according to a survey from the Medical Group Management Association. For example, 46% of respondents said that in light of a potential 10.6% cut in Medicare payments expected in July, they will refuse to accept new Medicare pa-

tients or will limit the number of new Medicare patients. Nearly 28% said they would limit the number of appointments for Medicare patients. The pending cut could also affect the implementation of health IT systems, including e-prescribing.

### Woodcock Named CDER Head

Dr. Janet Woodcock has been named director of the FDA's Center for Drug Evaluation and Research. Dr. Woodcock, a rheumatologist, served as director of CDER once before, in the 1990s, and has served as acting director since October 2007. The drug industry's chief lobbying group, PhRMA, welcomed the appoint-

ment. Dr. Woodcock "has demonstrated willingness to work with diverse partners, including researchers, Congress, the White House, patients, and pharmaceutical research companies," said a statement from the group. But Public Citizen's health research group director Dr. Sidney Wolfe said in an interview that he's "not terribly hopeful" that Dr. Woodcock will lead the center well, because she doesn't like conflict or controversy. "She's aware of a number of drugs on the market that should be taken off the market, but I don't think she has the fortitude to do something about it," Dr. Wolfe said.

—Mary Ellen Schneider



#### 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. The 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% on Rebif® vs. 28% 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 and other allergic reactions (some severe) have been reported as a rare complication of Rebif®. 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.

**Immunization:** Patients taking Rebif® may receive concomitant influenza vaccination and achieve similar positive antibody response to the vaccination as patients not receiving Rebif®. The exact relationship of antibody titers to vaccine efficacy is unknown in patients taking Rebif®.

**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](http://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, backpain, 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	Rebif® Placebo tiw (n=187)	Rebif® 22 mcg tiw (n=189)	44mcg tiw (n=184)
<b>BODY AS A WHOLE</b>			
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%
<b>INJECTION SITE DISORDERS</b>			
Injection Site Reaction	39%	89%	92%
Injection Site Necrosis	0%	1%	3%
<b>CENTRAL &amp; PERIPH NERVOUS SYSTEM DISORDERS</b>			
Hypertonia	5%	7%	6%
Coordination Abnormal	2%	5%	4%
Convulsions	2%	5%	4%
<b>ENDOCRINE DISORDERS</b>			
Thyroid Disorder	3%	4%	6%
<b>GASTROINTESTINAL SYSTEM DISORDERS</b>			
Abdominal Pain	17%	22%	20%
Dry Mouth	1%	1%	5%
<b>LIVER AND BILIARY SYSTEM DISORDERS</b>			
SGPT Increased	4%	20%	27%
SGOT Increased	4%	10%	17%
Hepatic Function Abnormal	2%	4%	9%
Bilirubinaemia	1%	3%	2%
<b>MUSCULO-SKELETAL SYSTEM DISORDERS</b>			
Myalgia	20%	25%	25%
Back Pain	20%	23%	25%
Skeletal Pain	10%	15%	10%
<b>HEMATOLOGIC DISORDERS</b>			
Leukopenia	14%	28%	36%
Lymphadenopathy	8%	11%	12%
Thrombocytopenia	2%	2%	8%
Anemia	3%	3%	5%
<b>PSYCHIATRIC DISORDERS</b>			
Somnolence	1%	4%	5%
<b>SKIN DISORDERS</b>			
Rash Erythematous	3%	7%	5%
Rash Maculo-Papular	2%	5%	4%
<b>URINARY SYSTEM DISORDERS</b>			
Micturition Frequency	4%	2%	7%
Urinary Incontinence	2%	4%	2%
<b>VISION DISORDERS</b>			
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 maybe misleading.

**DOSAGE AND ADMINISTRATION**  
Doses 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: EMD Serono, Inc., Rockland, MA 02370

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

Rebif is a registered trademark of EMD Serono, Inc. MS LifeLines is a service mark of EMD Serono, Inc. Avonex is a registered trademark of Biogen Idec. Revised: April 2007 07-19234



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