

'Modest' Boost Given to Neurologic Device Pay

BY ALICIA AULT

Associate Editor, Practice Trends

The Centers for Medicare and Medicaid Services will increase payments for outpatient services by an average of 3.8% in 2008, with most of the neurologic, cardiac, and gynecologic procedures covered under the payment system being slated for small to moderate increases.

Overall, hospitals will be paid about

\$36 billion in 2008, a 10% increase from 2007, and \$1 billion more than was estimated in the proposed outpatient rule, according to CMS.

Some neurologic device implant procedures will see a reimbursement increase. Neurostimulators, used primarily for lessening of symptoms of movement disorders such as Parkinson's disease and essential tremor, as well as control of epilepsy and pain, are slated for a 3.1% increase. The electrodes required with the

devices will see a 3.4% rise in payment.

The changes aren't substantial enough to have any impact on the numbers of these procedures being done, said Dr. Rajesh Pahwa, director of the Parkinson's Disease and Movement Disorder Center at the University of Kansas, Kansas City, who called the increases "modest." "My guess would be less than 5% of the patients with those conditions undergo stimulator implants," he said.

Other neurological devices, which Dr.

Pahwa said "might include shunts for hydrocephalus," for example, will get a 37.4% rate increase, according to the document.

The 2008 Hospital Outpatient Prospective Payment System final rule also includes a revised method of paying for services in ambulatory surgical centers (ASCs). Starting in 2008, services performed in ASCs will be reimbursed at 65% of the rate paid for the same service in an outpatient hospital department. This rate is unchanged from the proposed rule.

"The revised system takes a major step toward eliminating financial incentives for choosing one care setting over another, thereby placing patients' needs first, increasing efficiencies, and leading to savings for both beneficiaries and the Medicare program," said CMS Acting Administrator Kerry Weems.

Hospitals will be required to report on seven quality measures, including five emergency department measures pertaining to transfer of acute myocardial infarction patients, and two surgical care improvement measures. Under the proposed rule, hospitals were going to be required to report on 10 measures. Three were dropped in the final rule: administration of an ACE inhibitor to heart failure patients, empiric antibiotics for community-acquired pneumonia, and hemoglobin A_{1c} control. Now, if hospitals do not report on the seven measures, they will get an automatic 2% reduction in inpatient pay in 2009, according to CMS.

CMS also said it was issuing three new composite ambulatory payment classification (APC) groups. The APC bundles frequently performed procedures together into a single payment, thus creating an episode-of-care-based payment. The new APCs in the final rule are for extended outpatient visits with observation, low dose-rate prostate brachytherapy, and cardiac electrophysiologic evaluation and ablation.

The agency is continuing its policy of bundling payments for certain ancillary services, to create efficiencies and to give hospitals more flexibility to manage costs. Among the services that will now be covered by a bundled payment: image processing services, intraoperative services, imaging supervision and interpretation services, diagnostic radiopharmaceuticals, contrast agents, and observation services.

Dr. Kim Allan Williams, nuclear cardiology director at the University of Chicago, said that bundled payments can often mean that a service is not properly reimbursed. But under the outpatient payment system, CMS has found a way to make sure that every service is appropriately covered, said Dr. Williams in an interview.

Most cardiac procedures are slated for an increase—from a modest 1.9% for pacemaker insertion or replacement, to 5.2% for bare metal stents, to 13.3% for drug-eluting stents. Implantation of left ventricular pacing leads (add-on) will be cut by 12.4%, but that comes on the heels of 3 years of 80%-180% increases.

And for gynecologic procedures, endometrial ablation will get a 17.9% increase in pay, and surgical hysteroscopy a 4.2% increase.



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% 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 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 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, 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)
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			
SGOT Increased	4%	20%	27%
SGPT 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%

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

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Revised: April 2007 07-19234

