NEWS FROM THE FDA

New Rosuvastatin Indication Backed

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 12-4, with 1 abstention, that data support the use of rosuvastatin for the primary prevention of major cardiovascular adverse events in men aged 50 years and older and in women aged 60 years and older with a fasting LDL cholesterol level below 130 mg/dL, high-sensitivity C-reactive protein (hsCRP) level of 2.0 mg/L or more, triglyceride level below 500 mg/dL, and no prior history of cardiovascular events or disease.

Those criteria are based on a multinational, randomized placebo-controlled study of 17,802 people who did not have hyperlipidemia but did have an elevated level of hsCRP. The study was stopped early because of the positive results (N. Engl. J. Med. 2008;359:2195-207).

The panel was not asked specifically to vote on whether to approve rosuvastatin for the indication.

AstraZeneca markets rosuvastatin as Crestor. First approved in 2003, rosuvastatin has been approved for several indications, most related to lipid lowering.

Three safety issues were raised by the FDA reviewers: a greater number of deaths due to gastrointestinal disorders, confusion-related events, and a significant increase in investigator-diagnosed cases of diabetes among the patients in the rosuvastatin arm.

Diclofenac Hepatotoxicity Cited

Warnings about potential hepatotoxicity associated with the use of diclofenac have been added to the labels of all products containing the NSAID, the FDA announced.

A notice posted on the FDA's MedWatch site said that the manufacturers—Endo Pharmaceuticals and Novartis Consumer Health—had revised the "hepatic effects" section of the diclofenac topical gel label to include new warnings and precautions.

There have been postmarketing reports of severe hepatic reactions, including liver necrosis, jaundice, fulminant hepatitis with and without jaundice, and liver failure, according to the FDA. Some of the cases have been fatal or resulted in liver transplantation.

Because a patient may develop severe hepatoxicity without symptoms, clinicians should periodically measure transaminase levels in patients taking diclofenac long-term. Levels should be monitored within 4-8 weeks after initiating treatment, according to the FDA notice.

Desipramine Gets Safety Warnings

Warnings related to the risk of sudden death and cardiac dysrhythmias associated with desipramine have been added to the label of the tricyclic antidepressant, according to the FDA.

A notice on the FDA's MedWatch site states that "extreme caution" should be used when desipramine is prescribed to patients who have a family history of sudden death, cardiac dysrhythmias, and cardiac conduction disturbances. Also added is the statement that "seizures precede cardiac dysrhythmias and death in some patients."

Desipramine, approved in 1964, is marketed as Norpramin by Sanofi-Aventis, which issued a Dear Healthcare Professional letter about the label changes.

Panel Backs New Tiotropium Claim

An FDA advisory panel voted 11-1 that data from two studies provided enough evidence to support approval of a claim that treatment with the inhaled, dry-powder formulation of tiotropium reduces exacerbations in patients with chronic obstructive pulmonary disease.

The FDA's Pulmonary-Allergy Drugs Advisory Committee also voted 11-1 that data from the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, "adequately addressed" the potential safety signals of an increased risk of stroke and adverse cardiovascular outcomes identified in pooled data and meta-analyses.

The dry-powder formulation of tiotropium, marketed as the Spiriva HandiHaler by Boehringer Ingelheim and Pfizer, was approved in the United States in 2004 for long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disorder, including chronic bronchitis and emphysema. Administered once daily, each inhalation contains 18 mcg of tiotropium, an anticholinergic.

Sibutramine Tied to Cardiac Events

As part of an ongoing safety review of the weight-loss drug sibutramine, the FDA is looking at recent data suggesting a higher cardiovascular event rate with the medication, compared with placebo.

A statement on the agency's MedWatch site notes these preliminary findings "highlight the importance of avoiding the use of sibutramine" in patients with coronary artery disease, heart failure, arrhythmias, or stroke, as recommended in the current sibutramine label.

Sibutramine is marketed as Meridia by Abbott Laboratories. It was approved in 1997 for the management of obesity, including weight loss in conjunction with a reduced-calorie diet, and is recommended only for obese patients.

The FDA reported preliminary results from about 10,000 patients aged 55 years or older. Events in the study's primary end point—MI, stroke, resuscitated cardiac arrest, or death—were reported in 11.4% of those on sibutramine and in 10% of those on placebo. The FDA described the difference as "higher than expected, suggesting that sibutramine is associated with an increased cardiovascular risk in the study population."

Valproate Teratogenicity Highlighted

The high risk of neural tube defects and other major malformations in babies exposed during the first trimester to valproate sodium and the related products, valproic acid and divalproex sodium, is the focus of an FDA notice.

The risk of a neural tube defect in a baby born to a mother who took valproate or one of the two related products during the first 12 weeks of pregnancy is 1 in 20, compared with the U.S. background rate of 1 in 1,500, and the major malformation rate in babies is nearly fourfold greater with valproate than with a different antiepileptic: 10.7% vs. 2.9%.

Marketed as Depakene and as Stavzor, valproic acid was approved in 1978 for treating epilepsy. Valproate, marketed as Depacon, was approved more recently for treating bipolar disorder and migraine headaches. Divalproex sodium, marketed as Depakote, Depakote CP, and Depakote ER, is approved for migraine prophylaxis, manic episodes associated with bipolar disorder, and epilepsy.

Inhaled Antibiotic Eyed for Use in CF

Studies of an inhaled formulation of the monobactam antibiotic aztreonam in patients with cystic fibrosis show that it is a safe and effective treatment for *Pseudomonas aeruginosa* lung infections in this population, a federal advisory panel concluded in a 15-2 vote.

The FDA's Anti-Infective Drugs Advisory Committee found that the manufacturer, Gilead Sciences, had provided substantial evidence that inhaled aztreonam, administered at a dose of 75 mg three times a day for 28 days, was safe and effective for the proposed indication: improvement of respiratory symptoms and pulmonary function in patients who have cystic fibrosis with *P. aeruginosa*. If approved, the company plans to market it as Cayston, along with a novel, portable handheld nebulizer. The panel was not asked to vote specifically on whether to recommend approval.

Inhaled aztreonam has been approved for this indication in the European Union, Canada, and other countries. The intravenous formulation was approved in 1986 in the United States for indications that include *P. aeruginosa* infections, but not specifically for CF patients.

—From staff reports