Ezetimibe (Zetia™)

Manufacturer: Schering Corporation, Kenilworth NJ, for Merck/Schering-Plough Pharmaceuticals, North Wales, PA (joint venture)

Indications: Primary hypercholesterolemia. Ezetimibe can be prescribed in several situations:

- **As monotherapy.** Ezetimibe, administered alone, is indicated as adjunctive therapy to an appropriate diet to reduce elevated total cholesterol (total-C), low-density lipoprotein-cholesterol (LDL-C, or the “bad” cholesterol), and apoB lipoprotein B (apoB) in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.
- **In combination with HMG–CoA reductase inhibitors.** Ezetimibe, administered in combination with a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG–CoA) reductase inhibitor, is indicated as adjunctive therapy to dietary measures to reduce elevated total-C, LDL-C, and apoB in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia.
- **As therapy for homozygous familial hypercholesterolemia** (HoFH). The combination of ezetimibe and atorvastatin or simvastatin is indicated to decrease elevated total-C and LDL-C levels in patients with hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or when such treatments are unavailable.
- **As therapy for homozygous sitosterolemia.** Ezetimibe is indicated as adjunctive therapy to dietary restriction to decrease elevated concentrations of the plant sterols sitosterol and campesterol in patients with homozygous familial sitosterolemia.

Therapy with lipid-altering agents should be a component of intervention in individuals with multiple risk factors who are at increased risk for atherosclerotic vascular disease caused by hypercholesterolemia. Lipid-altering agents should be used in addition to an appropriate diet (including restriction of saturated fat and cholesterol) and when the response to dietary and other nonpharmacological measures has been inadequate.

Drug Class: Ezetimibe is an antihyperlipidemic agent.

Uniqueness of Drug: Ezetimibe is classified as a lipid-lowering compound that selectively inhibits the intestinal absorption of cholesterol and related phytosterols (plant sterols). Ezetimibe causes reductions in total-C, LDL-C, apoB, and triglycerides and also causes increases in high-density lipoprotein-cholesterol (HDL-C, or the “good” cholesterol) in patients with hypercholesterolemia. Administration of ezetimibe with an HMG–CoA reductase inhibitor is effective in improving serum total-C, LDL-C, apoB, triglycerides, and HDL-C beyond either treatment alone.

Precautions: Concurrent administration of ezetimibe with a specific HMG–CoA reductase inhibitor should be used in accordance with the product labeling for the HMG–CoA reductase inhibitor.

Liver Enzymes: In controlled clinical monotherapy studies, the incidence of consecutive elevations (≥3 x the upper limit of normal) in serum transaminase levels was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ezetimibe that have been initiated concurrently with an HMG–CoA reductase inhibitor, the incidence of consecutive elevations (≥3 x the upper limit of normal) in serum transaminase concentrations was 1.3% for patients receiving ezetimibe along with HMG–CoA reductase inhibitors and 0.4% for patients receiving HMG–CoA reductase inhibitors alone. These elevated transaminase levels were generally asymptomatic, were not associated with cholestasis, and returned to baseline measurements with discontinuation of therapy or with continued treatment. When ezetimibe is co-administered with an HMG–CoA reductase inhibitor, liver function tests should be performed at initiation of therapy and according to the recommendations for the HMG–CoA reductase inhibitor.

Skeletal Muscle: In clinical trials, no excess of myopathy or rhabdomyolysis was associated with ezetimibe, compared with the relevant control arm (placebo or HMG–CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG–CoA reductase inhibitors and to other lipid-lowering drugs. In clinical trials, the incidence of creatine phosphokinase (CPK) above 10 times the upper limit of normal was 0.2% for ezetimibe versus 0.1% for placebo and 0.1% for ezetimibe co-administered with an HMG–CoA reductase inhibitor versus 0.4% for HMG–CoA reductase inhibitors alone.

Hepatic Insufficiency: Ezetimibe is not recommended in patients with moderate or severe hepatic insufficiency because of the unknown effects of the increased exposure to this drug.

Dosage: A standard cholesterol-lowering diet should be prescribed before the patient receives ezetimibe, and the patient should continue on this diet during medical therapy. The recommended dose is 10 mg once daily. Ezetimibe can be administered with or without food.

Ezetimibe may be administered with an HMG–CoA reductase inhibitor for an incremental effect. For convenience, the daily dose of ezetimibe may be taken at the same time as the HMG–CoA reductase inhibitor, according to the dosing recommendations for the latter.

No dosage adjustment is necessary in patients with mild hepatic insufficiency, in patients with renal insufficiency, or in geriatric patients. Dosing of ezetimibe should take place either at or more than two hours before, or at or more than four hours after, the administration of a bile acid sequestrant.

Dr. Goldenberg is Executive Director of Pharmaceutical and Scientific Services for MMG Associates in Westfield, New Jersey, and coordinates the Pharmaceutical-Approval Update column.
P&T Committee Considerations: Ezetimibe is the first in a new class of cholesterol-lowering agents that inhibit the intestinal absorption of cholesterol. The Food and Drug Administration (FDA) has approved the once-daily tablet of 10 mg for use either alone or together with statins in patients with high cholesterol levels to reduce LDL-C and total-C. Of the estimated 13 million patients taking statins, 60% continue to have higher-than-recommended LDL-C concentrations; thus, it is thought that ezetimibe, in combination with statins, might provide a new option to help patients achieve therapeutic goals. This is particularly important in view of last year’s changes in the National Institutes of Health’s cholesterol guidelines, which substantially increased the number of Americans eligible for drug therapy and proposed lower cholesterol goals for many patients. Co-administered with atorvastatin or simvastatin, ezetimibe further lowered LDL-C, decreased triglyceride levels, and increased HDL cholesterol levels.

Ezetimibe should be included in the formulary as an option in the treatment of hypercholesterolemia as therapy alone or in combination with an HMG–CoA reductase inhibitor when diet and exercise have been inadequate for cholesterol control. The average wholesale price (AWP) of ezetimibe is $57.90 for a bottle of 30 tablets (a month’s supply).

Atomoxetine Hydrochloride (Strattera™)

Manufacturer: Eli Lilly and Company, Indianapolis, IN

Indication: Attention-deficit hyperactivity disorder (ADHD)

Drug Class: Atomoxetine is classified as a selective norepinephrine reuptake inhibitor.

Uniqueness of Drug: The precise mechanism by which atomoxetine produces its therapeutic effects in ADHD is unknown, but it is thought to be related to selective inhibition of the presynaptic norepinephrine transporter. Atomoxetine is the first nonstimulant medication approved for the treatment of ADHD in children, adolescents, and adults. It is the only FDA-approved ADHD medication that has proved clinically effective for adults. It is not considered a controlled substance.

Warnings: Although uncommon, allergic reactions—such as angioneurotic edema, urticaria, and rash—have been reported in patients receiving atomoxetine.

The weight and growth of the patient should be monitored during treatment. During acute-treatment studies, patients taking atomoxetine lost an average of 0.4 kg of body weight, whereas placebo-treated patients gained an average of 1.5 kg; in addition, patients receiving atomoxetine grew only an average of 0.9 cm, whereas patients receiving placebo grew an average of 1.1 cm. Patients who require long-term therapy should periodically re-evaluate the long-term usefulness of the drug for each patient.

Maintenance and Extended Treatment: No evidence is available from controlled trials to indicate how long the patient with ADHD should be treated with atomoxetine. Most investigators generally agree, however, that pharmacological treatment of ADHD might be needed for prolonged periods. Nevertheless, the physician who elects to prescribe atomoxetine for extended periods should periodically re-evaluate the long-term usefulness of the drug for each patient.

Adjustments for Patients with Hepatic Impairment: For patients with ADHD who have hepatic insufficiency, dosage adjustments are recommended. For patients with moderate hepatic insufficiency (Child-Pugh Class B), the initial and target doses should be reduced to 50% of the normal dose (e.g., as for patients without hepatic insufficiency). For patients with severe hepatic insufficiency (Child-Pugh Class C), the initial and target doses should be reduced to 25% of the normal dose.

Adjustments for Use with a Strong CYP2D6 Inhibitor:

- **Children and adolescents weighing up to 70 kg.** Atomoxetine should be initiated at a total daily dose of approximately 0.5 mg/kg of body weight and increased after a minimum of three days to a target total daily dose of approximately 1.2 mg/kg. The drug should be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening.

No additional benefit has been demonstrated when doses higher than 1.2 mg/kg per day were given. The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

- **Children and Adolescents Weighing More Than 70 kg and Adults.** Atomoxetine should be initiated at a total daily dose of 40 mg; after a minimum of three days, the dose should be increased to a target total daily dose of approximately 80 mg. The drug should be administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon or early evening. After two to four additional weeks, the dose may be increased to a maximum of 100 mg in patients who have not achieved an optimal response.

No data have supported increased effectiveness at higher doses. The maximum recommended total daily dose for adults and for children and adolescents weighing more than 70 kg is 100 mg.

Adjustments for Use with a Strong CYP2D6 Inhibitor:

- **Children and adolescents weighing up to 70 kg.** Administration of strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, quinidine, atomoxetine) should be initiated at 0.5 mg/kg per day. The dose should be increased to the usual target dose of 1.2 mg/kg per day only if symptoms do not improve after four weeks and if the initial dose is well tolerated.

- **Adults and children and adolescents weighing more than 70 kg.** Strong CYP2D6 inhibitors should be initiated at 40 mg/day. The dose should be increased to the usual target dose of 80 mg/day only if symptoms do not improve after four weeks and if the initial dose is well tolerated.

P&T Committee Considerations: Atomoxetine is the first new drug in three decades that is intended for the treatment of ADHD symptoms, which include inattention, hyperactivity, and impulsiveness. Atomoxetine’s mechanism of action differs...
from that of the stimulant-like drugs that have been used to treat ADHD in the past. Because atomoxetine does not appear to have a potential for abuse, it is not classified as a controlled substance; however, a prescription is required.

According to the American Psychiatric Association, ADHD affects approximately 3% to 7% of children and approximately 4% of adults. People with ADHD may make careless mistakes, fidget, interrupt others, talk excessively, and have problems paying attention. Although the disorder is not as well defined in adults, symptoms can include a lack of organization, daydreaming, irritability, and lack of motivation.

The drug’s safety and effectiveness have been established in six double-blind, placebo-controlled studies in patients with ADHD. Atomoxetine should be included in the formulary, and perhaps it can be carefully used to replace the controlled-substance drugs.

The AWP of atomoxetine is the same for all capsule strengths: $90.00 for 30 capsules per bottle.

Teriparatide (rDNA Origin) Injection (Forteo®)

Manufacturer: Lilly, France, for Eli Lilly and Company, Indianapolis, IN

Indication: Stimulation of new bone formation in patients with osteoporosis

Drug Class: Teriparatide is a recombinant human parathyroid hormone (PTH), which is the primary regulator of calcium and phosphate metabolism in bones. It has an identical sequence to the 34-N-terminal amino acids (the biologically active region) of the 84-amino acid human PTH.

Uniqueness of Drug: Patients taking teriparatide 20 mcg/day, along with calcium and vitamin D supplementation, experience statistically significant increases in bone mineral density at the spine and hip compared with patients who are receiving only calcium and vitamin D supplementation. Teriparatide works by increasing the action of osteoblasts, the body’s bone-building cells. As a result, the bones become denser and more resistant to fractures. Teriparatide reduces the risk of vertebral and nonvertebral fractures in postmenopausal women.

“Black-Box” Warnings: In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and duration of treatment. The effect was observed at systemic exposures to teriparatide ranging from three to 60 times the exposure in humans who were given a 20-mcg dose. Because of the uncertain relevance of the osteosarcoma finding to humans, teriparatide should be prescribed only when the potential benefits are considered to outweigh the risks in each patient. Teriparatide is contraindicated for the following groups:

- patients who are at increased risk, at baseline evaluation, for osteosarcoma, including patients with Paget’s disease of bone or with unexplained elevations of alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton
- children or growing adults
- patients with bone metastases or with a history of skeletal malignancies
- patients with metabolic bone diseases other than osteoporosis
- patients with high levels of calcium in the blood, because of the possibility of increasing the degree of hypercalcemia.

Dosage and Administration: Teriparatide 20 mcg is administered once a day as a subcutaneous self-injection into the thigh or abdominal wall. For the initial dose, the patient should be able to sit or lie down if symptoms of orthostatic hypotension occur. The drug is available in a 3-ml disposable pen device that can be used for up to 28 days after the first dose has been taken.

P&T Committee Considerations: Teriparatide injection is based on the patient’s level of PTH, which is ordinarily secreted by tiny glands in the neck. It is the first in a new class of drugs called bone-formation agents, which stimulate new bone by increasing the number and action of osteoblasts.

Teriparatide injection is intended for the treatment of osteoporosis in postmenopausal women who are at high risk for bone fractures, and the drug is approved as a means of increasing bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. The drug is also indicated for men (or women) with a history of osteoporosis-related fracture, individuals with multiple risk factors for fracture, or patients who have not responded to, or who were intolerant to, previous osteoporosis therapy.

Teriparatide injection should not be considered the primary medication in the formulary for the treatment of osteoporosis, but prescribing physicians should carefully consider it for possible use.

The AWP for a single 3-ml pen device is $560.00.