Ezetimibe/Simvastatin (Vytorin™)

**Manufacturer:** Merck & Co./Schering-Plough Corp.

**Indication:** To treat elevated levels of low-density lipoprotein-cholesterol (LDL-C) (the “bad” cholesterol) in patients with primary hypercholesterolemia or mixed hyperlipidemia as adjunctive therapy to diet when diet alone is not enough to reduce LDL-C levels.

**Drug Classes:** Ezetimibe (Zetia®, Merck) selectively inhibits the absorption of cholesterol and related plant sterols through the small intestine. Simvastatin (Zocor®, Schering-Plough) is a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor that inhibits cholesterol production in the liver.

**Uniqueness of Drug:** Vytorin™ is the first product that treats the two sources of cholesterol: it inhibits the production of cholesterol in the liver and blocks the absorption of cholesterol, including cholesterol from food. In head-to-head trials, ezetimibe/simvastatin provided greater reductions in LDL-C than atorvastatin (Lipitor®, Pfizer) and simvastatin in all doses.

**Warnings for Simvastatin**

**Myopathy and Rhabdomyolysis.** Like other inhibitors of HMG–CoA reductase, simvastatin occasionally causes myopathy, which is manifested as muscle pain, tenderness, or weakness with creatine kinase (CK) above 10 times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis, with or without acute renal failure, secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high concentrations of HMG–CoA reductase inhibitory activity in plasma.

The risk of myopathy or rhabdomyolysis is increased by the concomitant use of simvastatin (particularly in higher doses) with potent inhibitors of cytochrome P450 (CYP3A4): cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, human immunodeficiency virus (HIV) protease inhibitors, nefazodone, and large quantities of grapefruit juice (more than one quart daily).

**Precautions for Ezetimibe:** The concurrent administration of ezetimibe with a specific HMG–CoA reductase inhibitor should be in accordance with its product labeling.

**Liver Enzymes.** In controlled clinical monotherapy studies, the incidence of consecutive elevations (more than three times the ULN) in serum transaminases was similar between ezetimibe (0.5%) and placebo (0.3%).

In controlled clinical combination studies of ezetimibe that were initiated concurrently with an HMG–CoA reductase inhibitor, the incidence of consecutive elevations (more than three times the ULN) in serum transaminases was 1.3% for patients receiving ezetimibe administered with HMG–CoA reductase inhibitors and 0.4% for patients given HMG–CoA reductase inhibitors alone.

These elevations in transaminases were generally asymptomatic with ezetimibe and were not associated with cholestasis. Values returned to baseline after the patients discontinued therapy or continued treatment.

When ezetimibe is coadministered with an HMG–CoA reductase inhibitor, liver function tests should be performed when therapy is begun and according to the protocols 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 (patients taking placebo or an HMG–CoA reductase inhibitor alone). However, myopathy and rhabdomyolysis are known adverse reactions to HMG–CoA reductase inhibitors and other lipid-lowering drugs.

In clinical trials, the incidence of creatine phosphokinase (CPK), when more than 10 times the ULN, was 0.2% for ezetimibe and 0.1% for placebo. When ezetimibe was administered with an HMG–CoA reductase inhibitor, the incidence of CPK was 0.1%. When HMG–CoA reductase inhibitors were given alone, the incidence of CPK was 0.4%.

**Hepatic Insufficiency.** Because of the unknown effects of the increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, the drug is not recommended in these cases.

**Precautions for Ezetimibe/Simvastatin**

**Skeletal Muscle.** Patients who experience muscle pain, tenderness, or weakness after taking Vytorin™ should inform their doctors promptly because these may be signs of a serious side effect. Therapy should be discontinued if myopathy is diagnosed or suspected. To help prevent serious side effects, doctors should advise patients about medications or foods to be avoided during therapy with this product.

**Serum Transaminases.** In three placebo-controlled, 12-week trials, the incidence of consecutive serum transaminase elevations (more than three times the ULN) was 1.7% overall for patients taking the drug and 2.6% for patients taking ezetimibe/simvastatin 10/80 mg.

In controlled long-term (48-week) extensions that included both newly treated and previously treated patients, the incidence of consecutive elevations (more than three times the ULN) in serum transaminases was 1.8% overall and 3.6% for patients taking 10/80 mg. These elevations were generally asymptomatic and were not associated with cholestasis. Values returned to baseline after patients discontinued therapy or continued treatment.

**Liver Enzymes.** Doctors should perform blood tests before and periodically during treatment, when clinically indicated, to check for liver problems. Patients taking the 10/80-mg dose should receive an additional liver function test before and three months after titration and periodically during the first year.

Because of the unknown effects of increased exposure to ezetimibe in patients with moderate or severe hepatic insufficiency, Vytorin™ is not recommended in these patients.

**Drug–Drug Interactions.** The safety and effectiveness of
this drug, when taken with fibrates, have not been established; therefore, coadministration with fibrates is not recommended.

Caution should be exercised for patients being treated with cyclosporine when they begin ezetimibe/simvastatin therapy and for patients with severe renal insufficiency.

**Dosage and Administration:** Patients should follow a standard cholesterol-lowering diet before taking Vytorin™ and should continue this diet during treatment. The dosage should be individualized according to baseline LDL-C levels, the recommended goals of therapy, and patients’ responses.

Ezetimibe/simvastatin should be taken as a single daily dose in the evening, with or without food. The dosage ranges from 10/10 to 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day.

For patients who require less aggressive reductions of LDL-C, therapy may be initiated with 10/10 mg/day. Patients who require a larger reduction in LDL-C levels (greater than 55%) may begin therapy at 10/40 mg/day. After initiation or titration of Vytorin™, lipid levels may be analyzed after two or more weeks and the dosage may be adjusted if needed.

**P&T Committee Considerations:** Vytorin™ is the first of its kind to combine a popular statin (simvastatin) with a non-statin drug (ezetimibe) in a single formulation. Physicians are enthusiastic about the new medication because of studies showing that it can lower LDL-C more effectively than a statin alone. However, some physicians urge caution because it has not been proven that the drug actually prevents more cardiovascular events or deaths than do currently available drugs.

In one study of 788 adults, Vytorin™ reduced LDL-C concentrations by an average of 59%, whereas atorvastatin reduced it by an average of 53%. Lowering cholesterol as much as possible with statins is believed to prevent repeated heart attacks and death in patients with heart disease.

P&T committees should consider recommending the inclusion of ezetimibe/simvastatin in the formulary because of its potent ability to lower LDL cholesterol. If the drug cost is too high, perhaps administering individual doses of simvastatin and ezetimibe might be more practical.

**Botulinum Toxin Type A Purified Neurotoxin Complex (Botox®)**

**Manufacturer:** Allergan Pharmaceuticals

**Indication:** To treat severe underarm sweating (primary axillary hyperhidrosis) that cannot be managed by topical agents such as prescription antiperspirants.

**Drug Class:** Botulinum toxin type A is a protein that is produced by the bacterium *Clostridium botulinum*. Sterile, vacuum-dried, and purified, it is made from fermentation of Hall strain *C. botulinum* type A, which is grown in a medium containing casein hydrolysate, glucose, and yeast extract.

**Uniqueness of Drug:** When Botox® is used to treat primary axillary hyperhidrosis, small doses of an injectable form of the sterile purified botulinum toxin stop the release of the chemical messenger acetylcholine, temporarily blocking the nerves in the underarm that stimulate sweating.

**Warnings:** The recommended dosage and frequency of administration for botulinum toxin should not be exceeded. Risks resulting from higher dosages are not known.

**Hypersensitivity Reactions.** Serious and immediate hypersensitivity reactions have been reported rarely but include anaphylaxis, urticaria, soft-tissue edema, and dyspnea. In one fatal case of anaphylaxis, lidocaine was used as the diluent. As a result, the causal agent cannot be reliably determined. If such a reaction occurs, further injection of botulinum toxin should be discontinued and appropriate medical therapy should be instituted immediately.

**Pre-existing Neuromuscular Disorders.** Individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, motor neuropathy) or neuromuscular junction disorders (e.g., myasthenia gravis, Lambert–Eaton syndrome) should receive botulinum toxin only with caution. Patients with neuromuscular disorders may be at an increased risk of clinically significant systemic effects, including severe dysphagia (swallowing difficulty) and respiratory compromise from typical doses of the toxin. In rare cases, patients with known or unrecognized neuromuscular disorders who were given botulinum toxin showed extreme sensitivity to the systemic effects of typical clinical doses. In some of these patients, dysphagia lasted for several months and a gastric feeding tube was necessary.

**Dysphagia.** Dysphagia is a commonly reported adverse event following treatment of cervical dystonia in patients with all botulinum toxins. In these patients, there have been reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. In one case, a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

**Human Albumin.** The product contains albumin, a derivative of human blood. With effective donor screening and product manufacturing processes, it carries an extremely remote risk for the transmission of viral diseases. A theoretical risk for the transmission of Creutzfeldt–Jakob disease (CJD) is also considered remote. No cases of transmission of viral diseases or CJD have ever been identified as a result of albumin.

**Precautions:** The safe and effective use of botulinum toxin depends on proper storage of the product, the selection of the correct dose, and proper reconstitution and administration techniques. Caution is necessary with botulinum toxin treatment if inflammation is present at the proposed injection site.

Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without a confirmed diagnosis or treatment of the underlying disease. The safety and effectiveness of botulinum toxin for treating hyperhidrosis in other body areas have not been established.

Weakness of hand muscles may occur in patients who are receiving botulinum toxin for palmar hyperhidrosis, and blepharoptosis (drooping of the upper eyelid) may result when the drug is used to treat facial hyperhidrosis.

**Dosage and Administration:** Injections are prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled, and the syringe is attached to an appropriate injection needle. The patency of the needle should be confirmed. A new sterile needle and syringe should be used to enter the vial on each occasion for removal of the toxin.

**P&T Committee Considerations:** Before being treated for...
primary axillary hyperhidrosis, patients should be evaluated for other potential causes of the problem, such as hyperthyroidism, to avoid symptomatic therapy for hyperhidrosis with botulinum toxin without addressing a potentially serious underlying disease that warrants other forms of treatment. After all other causes of axillary hyperhidrosis have been excluded, it is recommended that this botulinum product be considered for placement on the formulary to inhibit severe underarm sweating.

**Levofloxacin Tablets/Injection and Levofloxacin in 5% Dextrose Injection (Levaquin®)**

**Manufacturer:** Ortho-McNeil (Johnson & Johnson)

**Indication:** To treat multidrug-resistant strains of *Streptococcus pneumoniae* (MDRSP) in community acquired pneumonia (CAP).

**Drug Class:** Levofloxacin is a fluoroquinolone (a chiral fluorinated carboxyquinolone).

**Uniqueness of Drug:** Data from the Tracking Resistance in the U.S. Today (TRUST) trial have demonstrated that 98% of MDRSP isolates are susceptible to levofloxacin. TRUST, the largest and most comprehensive respiratory pathogen surveillance study in the U.S., has been conducted annually since 1997. However, *in vitro* activity does not necessarily correlate with clinical results. Levofloxacin is indicated to treat mild-to-severe CAP caused by *S. pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae.*

**Warnings:** The safety and efficacy of levofloxacin in children, adolescents younger than 18 years of age, pregnant women, and nursing women have not been established.

In immature rats and dogs, the oral and intravenous (IV) administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and are associated with signs of arthropathy in immature animals of various species.

Convulsions and toxic psychoses have been reported in patients receiving quinolines, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system (CNS) stimulation, which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions do occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures should be instituted.

As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that might predispose them to seizures or that lower the seizure threshold (e.g., severe cerebral arteriosclerosis or epilepsy) or patients with other risk factors for seizures (e.g., patients who are receiving certain drug therapies or who have renal dysfunction.)

**Precautions:** Prescribing levofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to benefit patients and increases the risk that drug-resistant bacteria will develop.

Because a rapid or bolus IV injection can result in hypotension, levofloxacin injection should only be administered by slow IV infusion over 60 or 90 minutes, depending on the dosage. **Dosage and Administration:** The usual doses of levofloxacin tablets or injection are as follows:

- 250 or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours
- 750 mg administered orally or by slow infusion over 90 minutes every 24 hours, as indicated by the infection

For patients with normal or impaired renal function, oral doses should be administered at least two hours before or two hours after magnesium or aluminum antacids, sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine (Videx®, Bristol-Myers Squibb).

For patients with CAP, the dose is either 500 mg every 24 hours for seven to 14 days or 750 mg once daily for five days.

- If creatinine clearance is from 50 to 80 ml/minute, no dosage adjustment is required.
- If creatinine clearance is from 20 to 49 ml/minute, 500 or 250 mg should be given every 24 hours.
- If creatinine clearance is from 10 to 19 ml/minute, 500 or 250 mg should be given every 48 hours.
- If the patient is receiving hemodialysis, 500 or 250 mg should be given every 48 hours.
- If the patient is receiving chronic ambulatory peritoneal dialysis, 500 or 250 mg should be given every 48 hours.

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of highly concentrated urine. Levofloxacin should be given with caution in patients with renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed before and during therapy because the elimination of levofloxacin may be reduced.

In patients with impaired renal function (i.e., a creatinine clearance below 50 ml/minute), the dosage regimen should be adjusted as necessary to avoid the accumulation of levofloxacin because of the decreased clearance.

**P&T Committee Considerations:** CAP affects almost four million people in the U.S. each year. *S. pneumoniae* is one of the primary bacteria that cause CAP. MDRSP are forms of bacteria that are resistant to two or more therapeutic classes of antibiotics (e.g., penicillin, second-generation cephalosporins, macrolides, tetracyclines, and sulfonamides. The presence of MDRSP has increased significantly over time and today represents almost 23% of all strains.

Levofloxacin may be used to treat CAP in a five-day, 750-mg once-daily regimen (Leva-pak), or 500 mg daily can be taken for seven to 14 days.

The Food and Drug Administration’s approval of this product is important because it increases the flexibility of physicians in terms of their ability to treat patients with drug-resistant bacterial infections using a safe medication. P&T committees should consider levofloxacin for patients with MDRP in CAP.