New combo makes it more convenient to lower cholesterol

Although an estimated 37 million Americans could benefit from lipid-lowering drugs, only about 14 million people in this country take them. This statistic could soon change, however. National Cholesterol Education Program guidelines now recommend that those who have had a myocardial infarction (MI) or are at high risk for cardiovascular disease lower their low-density lipoprotein (LDL) cholesterol to 70 mg/dL.

NEW DRUG

The Food & Drug Administration recently approved ezetimibe/simvastatin (Vytorin, Merck/Schering-Plough Pharmaceuticals) as adjunctive therapy to diet for the reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B, triglycerides, and non-high-density lipoprotein (HDL) cholesterol and to increase HDL cholesterol in those with primary hypercholesterolemia or mixed hyperlipidemia. The drug is also indicated for the reduction of elevated total cholesterol and LDL cholesterol in those with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering therapies or if such treatments are unavailable.

According to Merck/Schering-Plough, ezetimibe/simvastatin is the first and only product approved to reduce LDL cholesterol through dual inhibition of the two sources of cholesterol with one tablet. The drug will be widely available in U.S. pharmacies in the near future.

The availability of simvastatin (Zocor) and ezetimibe (Zetia) in one drug should improve patient compliance, remarked Judy Cheng, Pharm.D., an associate professor of pharmacy practice at the Arnold & Marie Schwartz College of Pharmacy and Health Sciences at Long Island University in Brooklyn, N.Y. In addition, paying one price for a combination product makes more financial sense than paying for two separate drugs, she said.

Cheng said that the key issue relevant to this product concerns the best way to help patients reach the new, more stringent cholesterol goals. If the statin dose is increased, she said, so, too, is the risk of myopathy/rhabdomyolysis and hepatic toxicity.

Very strong data suggest, however, that aggressive, high-dose statin therapy reduces MI risk in addition to lowering LDL cholesterol levels, Cheng noted. On the other hand, although ezetimibe is not associated with increased adverse effects when added to statin therapy, no clinical data to date indicate that the drug reduces the risk of MI.

No new or additive adverse effects are associated with this combination product, Cheng said. The manufacturer cautioned that the concomitant use of ezetimibe/simvastatin with inhibitors of the cytochrome P450 3A4 enzyme system is contraindicated. The concomitant use of the drug with fibrates is also contraindicated.

Across the dosing range, the ezetimibe component of Vytorin is held constant at 10 mg; the simvastatin component ranges from 10 mg to 80 mg. The recommended starting dose is 10/20 mg, taken once daily. The recommended dosage for those with homozygous familial hypercholesterolemia is 10/40 mg or 10/80 mg, taken once daily in the evening.

Dosage adjustment is unnecessary in older persons. It is also unnecessary in those with mild hepatic insufficiency. Ezetimibe/simvastatin is not recommended for use in those with moderate to severe hepatic insufficiency. It is contraindicated in those with active liver disease or unexplained persistent elevations in serum transaminases.

Dosage adjustment is unnecessary as well in those with mild to moderate renal insufficiency, according to the company. Therapy with this product should not be started in those with severe renal insufficiency unless the patient has tolerated simvastatin therapy at a dose of 5 mg or higher.

Ezetimibe/simvastatin treatment should not be initiated in those taking cyclosporine unless they have already tolerated therapy with simvastatin at a dose of 5 mg or higher. The dose of ezetimibe/simvastatin should not exceed 10/10 mg daily in these patients. The dose should not exceed 10/20 mg daily in those taking amiodarone or verapamil.

For those who still need to lower their LDL cholesterol level after therapy with a maximally tolerated statin dose, ezetimibe/simvastatin is an excellent therapeutic option, Cheng concluded.

Charlotte LoBuono

TIPS TO REMEMBER *Vytorin*

- Vytorin is contraindicated in those with hypersensitivity to any component of the product.
- Vytorin is contraindicated in pregnant or lactating women.
- Dosing of Vytorin should take place two or more hours before, or four or more hours after, administration of a bile acid sequestrant. DT

VYTORIN (oral)

Vytorin lowers cholesterol and triglycerides (fatty acids) in your blood. This medicine contains a "statin" drug.

GENERIC NAME

Ezetimibe/simvastatin

WHEN YOU SHOULD NOT USE THIS MEDICINE

You should not use this medicine if you have had an allergic reaction to ezetimibe or simvastatin. **Do not use this medicine if you are pregnant or breast-feeding, or if you have liver disease.**

HOW TO USE THIS MEDICINE

Tablets:

•Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed several times before you are able to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you to.

•Carefully follow your doctor's instructions about any special diet.

•If you also use another medicine called cholestyramine (Questran), take it at least two hours after or four hours before you take ezetimibe/simvastatin.

If you miss a dose:

•If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, wait until then to use the medicine and skip the missed dose.

•Do not use extra medicine to make up for a missed dose.

HOW TO STORE AND DISPOSE OF THIS MEDICINE

•Store the medicine at room temperature in a closed container, away from heat, moisture, and direct light.

•Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after you have finished your treatment. You will also need to throw away old medicine after the expiration date has passed.

•Keep all medicine away from children, and never share your medicine with anyone.

DRUGS AND FOODS TO AVOID

•Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

•Make sure your doctor knows if you are also using hormones or steroids. Your doctor should know if you also use amiodarone (Cordarone), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), digoxin (Lanoxin), erythromycin (E.E.S., E-Mycin, Ery-Tab), or fenofibrate (Tricor). Tell your doctor if you also use gemfibrozil (Lopid), itraconazole (Sporanox), ketoconazole (Nizoral), nefazodone (Serzone), niacin, or verapamil (Calan, Covera).

•Tell your doctor if you are using a blood thinner, such as warfarin (Coumadin). Tell your doctor if you use medicine to treat HIV or AIDS, such as lamivudine, stavudine, zidovudine, Combivir, Epivir, Kaletra, Videx, or Zerit.

•Avoid drinking large amounts of alcohol or grapefruit juice while you are using this medicine.

WARNINGS

•Use an effective form of birth control to keep from getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away.

•Make sure your doctor knows if you have diabetes, thyroid problems, liver disease, or kidney disease, or if you regularly drink alcohol.

•Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep all appointments.

POSSIBLE SIDE EFFECTS

Call your doctor right away if you notice any of these side effects:

•Allergic reaction: itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing

•Dark-colored urine or pale stools

•Fever; chills; cough; sore throat; body aches; muscle pain, tenderness, or weakness

•Nausea, vomiting, loss of appetite, pain in your upper stomach

•Yellowing of your skin or the whites of your eyes

IF YOU HAVE OTHER SIDE EFFECTS THAT YOU THINK ARE CAUSED BY THIS MEDICINE, TELL YOUR DOCTOR.

COURTESY OF YOUR LOCAL PHARMACY

New antiretroviral for AIDS combines efficacy, simplicity

Combination products make treatment regimens for HIV/AIDS easier to follow, because such regimens often require the simultaneous use of three or more drugs from different classes. The Food & Drug Administration recently approved abacavir/lamivudine (Epzicom, GlaxoSmithKline) 600 mg/300 mg tablets for the treatment of HIV infection. The drug will be available in U.S. pharmacies by the end of August or in early September. The agency also approved another fixed-dose combination antiretroviral, tenofovir/emtricitabine (Truvada, Gilead Sciences) 300 mg/200 mg tablets, at the same time.

Epzicom may help those who have compliance issues, said Jeff Julian, Pharm.D., pharmacy manager for StatScript pharmacy in Kansas City, Mo. When the dosing schedule and adverse-effect profile are compatible with the patient's lifestyle, adherence is improved, he said.

No new or additive adverse effects are associated with this combination product, said Julian. He mentioned the findings of the CNA30021 study, which indicated comparable efficacy between 300 mg of abacavir (Ziagen, GlaxoSmithKline) dosed twice daily and 600 mg of abacavir dosed once daily, when given in combination with lamivudine (Epivir, GlaxoSmithKline) and efavirenz (Sustiva, Bristol-Myers Squibb).

The product labeling for abacavir/lamivudine contains a boldfaced warning about the risk of hypersensitivity reactions, lactic acidosis and severe hepatomegaly, and exacerbations of hepatitis B. The manufacturer said that treatment with abacavir should be discontinued immediately if a hypersensitivity reaction is suspected. The company also advised clinicians not to reinitiate therapy with abacavir or any abacavir-containing product following a hypersensitivity reaction, because fatal rechallenge reactions have been associated with readministration of the drug.

Julian said that pharmacists will distribute a medication guide and laminated warning card summarizing the symptoms of an abacavir hypersensitivity reaction with each prescription and refill. The manufacturer has established an Abacavir Hypersensitivity Registry to facilitate the reporting of hypersensitivity reactions and collection of information about each case. Physicians can register patients by calling (800) 270-0425.

The recommended dose of abacavir/lamivudine is one tablet, taken daily in combination with other antiretroviral agents. Abacavir/lamivudine is not recommended for use with other nucleoside/nucleotide reverse transcriptase inhibitors. It is recommended for use with nonnucleoside reverse transcriptase inhibitors and protease inhibitors.

According to the company, abacavir/lamivudine is contraindicated for use in those with a creatinine clearance rate of less than 50 mL/min. The product is also contraindicated in those with hepatic impairment. The manufacturer reported that the pharmacokinetics of abacavir/lamivudine in pediatric patients is under investigation. Insufficient data exist to recommend a dose at this time, however, so abacavir/lamivudine is contraindicated for use in children.

Julian recommended that pharmacists explain to patients that this new product actually contains two drugs, making their old medications unnecessary. He said pharmacists should also make patients aware that adherence to a medication taken once daily is particularly important, because missing a dose means missing a whole day of therapy, leaving patients vulnerable to resistance. If patients miss a dose of medication that is dosed twice daily, he explained, at least they are not missing a whole day of treatment.

The availability of a nucleoside backbone as a combination product will likely improve patient compliance, which represents the major "Achilles' heel" in the treatment of HIV infection, said Marshall Kubota, M.D., a clinical professor at the University of California at San Francisco. Findings of studies done over the past several years that enrolled thousands of patients attest to the efficacy of the abacavir/lamivudine combination, he continued. The two-in-one tablet represents a highly simplified therapy with a history of proven efficacy as part of an antiretroviral regimen, he concluded.

Charlotte LoBuono

TIPS TO REMEMBER *Epzicom*

- Epzicom can be taken with or without food.
- Epzicom is classified as Pregnancy Category C. It should be used during pregnancy only if the benefits to the mother outweigh the potential risks to the fetus. The Centers for Disease Control & Prevention recommends that HIV-infected mothers not breast-feed their infants while taking Epzicom, as it is not yet known whether the drug passes into breast milk.
- The use of Epzicom in combination with zalcitabine (HIVID, Roche) is not recommended. DT

Pulmonary hypertension guidelines include latest drugs

The medical treatment of pulmonary arterial hypertension (PAH) has historically been difficult. Through the mid-1980s, idiopathic PAH (IPAH), formerly known as primary pulmonary hypertension (PPH), was associated with a median survival of approximately 2.8 years from the date of diagnosis.

The estimated prevalence of PAH in the United States is greater than 100,000, with several thousand new cases diagnosed each year. Although PAH could potentially affect anyone, the incidence is highest among women aged 20 to 40 years.

The American College of Chest Physicians (ACCP) first formed a consensus panel to study the pathophysiology, diagnosis, and treatment of PPH 10 years ago. Fortunately, the past decade has seen remarkable improvements in therapy. Selection of the most appropriate therapy is still a complex matter, however.

An interdisciplinary expert committee convened by the ACCP recently developed guidelines regarding medical therapy for PAH. The document was published in a supplement to the July issue of the journal *Chest*. The guidelines were developed with the support of Actelion Pharmaceuticals U.S., Encysive Pharmaceuticals, and GlaxoSmithKline.

The panel adopted the nomenclature developed at the 1998 World Health Organization International Conference and updated at the 2003 Third World International Conference, replacing the term *primary pulmonary hypertension* with the term *idiopathic pulmonary arterial hypertension*. Pulmonary arterial hypertension refers to IPAH and PAH associated with other conditions, such as scleroderma.

Those with PAH should undergo acute vasoreactivity testing using a short-acting vasodilator such as intravenous epoprostenol sodium (Flolan, GlaxoSmithKline), adenosine, or inhaled nitric oxide, said Richard Channick, M.D., an associate professor of medicine at the University of California at San Diego Medical Center, and codirector of the PAH program at UCSD. In the absence of right-heart failure, persons with PAH who demonstrate a favorable acute response to a vasodilator with a fall in pulmonary artery pressure to near-normal levels should be considered candidates for a trial of calcium-channel blockers (CCBs), he said. The ACCP committee said that nifedipine, diltiazem, and amlodipine (Norvasc, Pfizer) are the most commonly used CCBs, and verapamil should be avoided because of negative inotropic effects.

Patients with PAH in New York Heart Association (NYHA) functional class III who are not candidates for, or who have failed, therapy with CCBs are candidates for long-term therapy with bosentan (Tracleer, Actelion Pharmaceuticals), Channick continued. The authors of the guidelines said that these patients are also candidates for therapy with epoprostenol, subcutaneous treprostinil (Remodulin, United Therapeutics), inhaled iloprost (Berlex Laboratories), or beraprost (Toray Industries). The latter two agents are not currently FDA-approved, said Channick.

The treatment of choice for those in NYHA functional class IV who are not candidates for, or who have failed, CCB therapy is epoprostenol, said Channick. Treatment with sildenafil (Viagra, Pfizer) for persons with PAH who have failed or are not candidates for other available therapies should be considered, the ACCP panel said.

Community pharmacists can counsel PAH patients about their medications—particularly CCBs, which may be prescribed at higher doses than usual for the treatment of PAH, said Ronald DeBellis, Pharm.D., an associate professor of pharmacy practice at the Massachusetts College of Pharmacy and Health Science.

Pharmacists can also advise patients about PAH drugs' potential side effects, DeBellis added. For example, he said, bosentan therapy is associated with an elevation in liver enzymes. Patients who have not had their liver enzyme levels checked should be encouraged to do so.

DeBellis pointed out that patients with PAH for whom sildenafil is prescribed may feel uncomfortable. Community pharmacists can educate patients regarding sildenafil's role in dilating the pulmonary arteries versus its use as a therapy for erectile dysfunction, he said.

Hospital pharmacists, too, have a significant role in the management of PAH, said Channick. Depending on the size of the institution and the level of expertise of the nursing staff, hospital pharmacists may need to guide those with less experience in working with epoprostenol, he said.

PAH is an underdiagnosed condition, said DeBellis, and, until now, no in-depth review of the literature with a focus on disease class has been done. He explained that case reports and reviews by experts in the field previously served as the guiding force for the management of PAH. With the establishment of the new guidelines, health professionals now have at their disposal a peer-reviewed and evidence-based treatment algorithm that makes use of available pharmacotherapies, he concluded.

Charlotte LoBuono