NEW DRUGS

Rosuvastatin for Lowering Cholesterol

The Food and Drug Administration (FDA) has approved rosuvastatin (Crestor®, AstraZeneca) to lower serum cholesterol levels. Lowering cholesterol is a key to reducing the risk of heart disease.

Rosuvastatin is in the class of drugs called HMG-coenzyme A reductase inhibitors, also known as statins. These drugs partially block the synthesis of cholesterol in the liver. This process leads to increased removal of cholesterol from the blood.

Statins should be prescribed along with a low-cholesterol diet and an exercise program. The drugs lower levels of “bad” or low-density lipoprotein-cholesterol (LDL-C) and triglycerides and increase levels of “good” high-density lipoprotein-cholesterol (HDLC) in the blood.

Rosuvastatin was approved after multiple trials of at least six weeks in duration in which the drug was compared with placebo and other marketed statins. In these trials, rosuvastatin reduced total cholesterol, LDL-C, and triglycerides and it increased HDL-C; therapeutic responses occurred within one week and maximum responses occurred at four weeks. Approximately 12,000 patients received different doses of the medication.

Side effects included muscle aches, stomach pain, constipation, nausea, and weakness. In rare instances, severe muscle pain and muscle weakness resulting in kidney damage have been associated with statins. If general muscle aches persist, patients should call their physicians. Some users showed traces of protein in the urine.

Patients should be monitored for abnormalities of liver function before treatment, at 12 weeks following initial therapy, and with any elevation of the dose. Monitoring is recommended periodically thereafter.

Rosuvastatin is available in 5-, 10-, 20-, and 40-mg tablets. In the trials, most patients reached target LDL-C levels as recommended by the National Cholesterol Education Program after taking either the 5- or 10-mg starting dose. The 20-mg dose can be the initial dose for patients with very high cholesterol levels; the 40-mg dose is reserved for patients who have not achieved an adequate result with the 20-mg dose.

(Sources: FDA Talk Paper, August 12, 2003; Bloomberg News, as reported in the Philadelphia Inquirer, July 9, 2003.)

Miglustat Approved for Type-1 Gaucher Disease

Miglustat capsules (Zavesca®, Actelion Ltd.) have been approved as the first oral treatment option for type-1 Gaucher disease, a rare genetic lipid-storage disorder.

Type-1 Gaucher disease is a progressive condition that is caused by a deficiency of glucocerebrosidase, an important enzyme in the metabolism of key lipids in the body. A deficiency of this enzyme results in the accumulation of excess amounts of glycosphingolipids in specific cells, primarily in the liver, spleen, and bone marrow. Such accumulation leads to liver and spleen enlargement or dysfunction, anemia, bone disease, and pain.

Enzyme replacement is delivered by an intravenous infusion twice a month.

Miglustat is the first in a new class of drugs known as substrate-reduction therapy, which reduces the amount of glycosphingolipid production to a level that can be effectively cleared by the naturally occurring glucocerebrosidase in the cells. The drug is available in the U.K. and Germany and is scheduled to be available in the U.S. later this year.

Pregnant women and those of childbearing age should not take miglustat.

(Source: Actelion Ltd., August 1, 2003; Philadelphia Inquirer, July 9, 2003.)

NEW INDICATIONS

Gemifloxacin Mesylate for Resistant Community-Acquired Pneumonia

The FDA has approved gemifloxacin mesylate (Factive®, GeneSoft) to treat mild-to-moderate community-acquired pneumonia (CAP) caused by multidrug-resistant Streptococcus pneumoniae. Factive®, an orally administered, broad-spectrum fluoroquinolone, is the first antibiotic specifically indicated for CAP caused by this resistant organism.

In April 2003, Factive® was approved in the U.S. to treat mild-to-moderate CAP caused by other pathogens and for acute bacterial exacerbations of chronic bronchitis.

Pneumonia is the primary cause of death from infections. More than 25% of S. pneumoniae isolates in the U.S. are multidrug-resistant, defined as strains that are resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

(Sources: www.genesofinc.com; PR Newswire, July 29, 2003.)

Oxcarbazepine for Epilepsy in Children

The FDA has granted marketing clearance for oxcarbazepine (Trileptal®, Novartis) tablets and oral suspension for use as monotherapy in children four years of age and older with partial seizures. This is the first antiepileptic drug to be approved as a single-agent therapy in children since 1978.

Many children with epilepsy take multiple medications to control seizures, but treating seizure disorders with one medication is preferred; it usually means fewer side effects and better compliance. The approval of Trileptal® as a pediatric monotherapy is considered a step forward in the treatment of childhood epilepsy.
Trileptal® is currently approved in more than 60 countries for use as monotherapy and as adjunctive therapy in children and adults.

The availability of Trileptal® as a single-agent therapy should simplify dosing. A number of older medications for treating partial seizures have resulted in side effects (e.g., mental confusion and memory loss), which might impair concentration.

(Source: Novartis Pharmaceuticals Corporation, August 7, 2003.)

**Porfimer Sodium for Barrett’s Esophagus**

Porfimer sodium (Photofofin®, Axcan Scandipharm) injection has been approved for the ablation of precancerous lesions (high-grade dysplasia) in patients with Barrett’s esophagus who do not undergo esophagectomy (removal of the esophagus).

In Barrett’s esophagus, some of the esophageal lining is replaced by tissue similar to that normally found in the intestine. Barrett’s esophagus affects about 700,000 adults in the U.S. and is associated with gastroesophageal reflux disease (GERD).

Although Barrett’s esophagus itself does not always cause symptoms, the associated precancerous lesions can progress to an often deadly type of esophageal cancer in some people.

Porfimer is a photosensitizing agent used in photodynamic therapy (PDT), a treatment for some types of cancer. PDT is based on the discovery that photosensitizing agents can kill one-celled organisms when the organisms are exposed to a particular type of light. PDT destroys cancer cells by using a laser light combined with a photosensitizing agent.

The FDA first approved Photofofin® in 1998. In the clinical study supporting this new use of the drug, patients receiving porfimer PDT were more likely to achieve complete reversal of their precancerous lesions in Barrett’s esophagus than patients not receiving it. Two-year follow-up data showed that patients taking porfimer PDT had an 80% chance of being cancer-free and patients who did not receive this treatment had a 50% chance. The effectiveness of porfimer PDT in reducing the long-term risk of esophageal cancer has not been proven.

Side effects include photosensitivity reactions and esophageal strictures. Patients should avoid exposing their skin and eyes to bright light.

(Source: FDA Talk Paper, August 4, 2003; www.axcanscandipharm.com.)

**Etanercept for Ankylosing Spondylitis**

The FDA has approved the expanded use of etanercept (Enbrel®, Amgen/Wyeth) for patients with ankylosing spondylitis, a chronic inflammatory disease that primarily affects the lower back and joints. Approximately 350,000 patients in the U.S. have this condition.

In the 277-patient trial, the drug benefited 70% of patients younger than age 42 and 48% of patients older than age 42. The women had a lower response rate (45%) than the men did (65%). Of the patients receiving the drug, 58% showed significant improvement of measured pain, function, and inflammation after six months of twice-weekly treatments, compared with 23% of patients receiving placebo.

Etanercept patients who carried the HLAB27 genetic marker had a higher rate of response (65%) than patients who were HLAB27-negative (38%).

Etanercept was approved to treat rheumatoid arthritis in 1998, juvenile rheumatoid arthritis in 1999, and psoriatic arthritis in 2002.

(Source: FDA Advisory Committee.com, June 24, 2003; Dow Jones Newswires, July 24, 2003.)

**4-AP for Spine Injury**

Since 1993, 4-aminopyridine (4-AP) has been giving hope to patients with spinal injuries, according to a study at the Specialties Hospital in Mexico City. Twenty-seven patients were randomly assigned to receive either oral 4-AP 5 mg/day, increased to a maximum of 30 mg/day, or placebo for 12 weeks. Patients were then switched to the opposite treatment for 12 weeks.

The results from the first 12 weeks were used to test efficacy. Improved motor function, sensation, and independence were observed more often in the patients receiving 4-AP (69%) than in the placebo patients (46%). When each scale was considered separately, motor function was the only marker that improved significantly (92% in the drug group but only 46% in the placebo group).

The researchers also measured whether the drug’s effects persisted after therapy was stopped. At week 24, they found lasting effects in sensation (in 67%) and independence (in 83%) of the 25 patients who finished the study. Five patients experienced a small loss of 4-AP improvements beginning three to four days after they started taking placebo and mainly one week after discontinuing treatment, but no other patients experienced this change.

One patient who had received 4-AP was partially impaired during the first two weeks of placebo treatment but then improved progressively to reach higher scores on both motor and sensory tests at the end of his placebo treatment—significant differences were seen in his scores at the end of the 4-AP treatment.

Fourteen patients had adverse reactions, which were mostly mild to moderate and transitory.

Although 4-AP is safe, the researchers suggest that patients be monitored for possible peripheral vasospasm and, at
the highest dose, for changes in enzyme levels and platelet counts.

(Source: Pharmacotherapy 2003;23: 823–834.)

Renoprotective Effects of ACE-Inhibitors in Diabetes
Angiotensin-converting enzyme (ACE) inhibitors have been the treatment of choice for patients with diabetic nephropathy, but no ACE-inhibitors were used as active controls in recent studies of angiotensin-receptor blockers, say researchers from Albany College of Pharmacy and Albany Medical Center.

After conducting a meta-analysis of 11 prospective randomized trials, they concluded that ACE-inhibitors significantly reduced proteinuria in patients with type-2 diabetes and had significant renoprotective effects. Reduction of proteinuria is considered to be the hallmark of effective therapy in preserving renal function in nondiabetic renal disease. Furthermore, in one study, microalbuminuria was the best predictor of risk for the development of nephropathy in patients with either type-1 or type-2 diabetes.

Finally, treating all patients with type-2 diabetes with ACE-inhibitors was the most cost-effective approach, compared with screening for microalbuminuria or gross proteinuria.

(Source: Pharmacotherapy 2003;23: 909–915.)

Anticoagulants Safe for Older Patients with Atrial Fibrillation
Should elderly patients with atrial fibrillation (AF) and previous episodes of upper gastrointestinal (GI) tract bleeding be given an anticoagulant to prevent stroke? What about older patients with hypertension who have fallen in the past?

Patients like these are less likely to be given warfarin sodium (Coumadin®, DuPont)—and that’s regrettable, say investigators from Ottawa Health Research Institute, University of Ottawa, Sisters of Charity Ottawa Health Service, and the University of Toronto in Canada. They charge that the possibility of major bleeding has scared clinicians away from prescribing anticoagulants for some older patients who might benefit from them.

The researchers, who reviewed studies performed between the 1960s and 2002, say that some “risk factors” do not truly pose a danger after all. For instance, in the era of routine clinical *Helicobacter pylori* testing and treatment of patients with peptic ulcer bleeding not induced by nonsteroidal anti-inflammatory drugs (NSAIDs), previous episodes of upper GI bleeding do not seem to increase the risk of anticoagulant-related bleeding.

Similarly, old age and a predisposition to falling, in and of themselves, are not influential factors in bleeding. Even when patients take anticoagulants, the risk of subdural hematoma from falling is so small that patients with an average risk of stroke from AF (5% per year) would have to fall approximately 300 times in a year for the risks of anticoagulant therapy to outweigh its benefits, the researchers say. In addition, for many clinically accepted contraindications, such as alcohol abuse, thrombocytopenia, and noncompliance with monitoring, the evidence is minimal or conflicting.

Old age might confer a slightly higher risk of anticoagulant-related bleeding complications, but the researchers emphasize that, of all age groups, people older than age 65 are also at highest risk of stroke from AF. With multiple studies revealing that older persons with AF are the least likely to receive anticoagulant therapy, it seems that many clinicians are overly concerned about the possible negative effects and tend to underemphasize the potential benefits of anticoagulants. Thus, the investigators conclude, in selecting patients with AF for anticoagulant therapy, stroke risk is a more important consideration than bleeding risk.

(Source: Arch Intern Med 2003;163: 1580–1586.)

Cervical Cancer Vaccine: Ineffective During Ovulation?
A vaccine that protects against human papillomavirus 16 (HPV16), the virus that causes cervical cancer, produces antibodies against HPV16 at the site where cervical cancer develops—a promising indication of the vaccine’s effectiveness. Because antibody levels appear to decrease around the time of ovulation, however, the vaccine might be less effective during that time.

A vaccine is considered promising if it produces an immune response (as determined by antibody levels) at disease-specific sites (e.g., the cervix). Although previous studies showed that an HPV16 vaccine can trigger an immune response and can protect against HPV16 infection, most of these studies involved women who were taking oral contraceptives (which regulate menstruation), and it is unclear what influence changes in hormone levels during the natural menstrual cycle would have on the vaccine’s effectiveness.

To examine the influence of menstrual cycle stage and oral contraceptive use on antibody levels, researchers administered the HPV16 vaccine to seven women who were taking oral contraceptives and to 11 women who were ovulating. They collected blood and cervical secretions twice a week for five weeks and determined concentrations of anti-HPV16 antibodies during different phases of the menstrual cycle.

After immunization, all of the women had relatively high levels of antibodies in their cervical secretions. Antibody levels
in the women taking oral contraceptives remained relatively constant throughout the menstrual cycle. In contrast, levels of vaccine-specific and total antibodies in ovulating women were highest during the proliferative phase of the menstrual cycle and lowest around ovulation, suggesting that sex hormones might play a role in regulating antibody concentration at the cervix.

Given these findings, it is important to determine whether the vaccine will be as effective at protecting ovulating women from HPV16 infections as it appears to be for women taking oral contraceptives. The authors suggest that the decrease in antibody levels during ovulation might be a mechanism to protect sperm from antibodies. Whether such a decrease in antibodies translates into a decrease in vaccine effectiveness remains unclear.

(Sources: J Natl Cancer Inst 2003;95:1128–1137; www.docguide.com, August 6, 2003; © PSL Consulting Group, Inc.)

HRT Not Helpful for Pre-existing Heart Disease

Estrogen, whether given alone or with progestin to reduce the discomforts of menopause, does not keep arteries with pre-existing lesions from narrowing further, according to findings of separate trials of hormone replacement therapy (HRT) in postmenopausal women.

The Women’s Estrogen–Progestin Lipid-Lowering Hormone Atherosclerosis Regression Trial (WELL-HART) found that HRT was ineffective against established coronary artery disease in older postmenopausal women. The lead investigator emphasized that WELL-HART and similar trials clearly indicate that estrogen and progestin should not be used to treat atherosclerosis in women with cardiovascular disease, but he cautioned that these findings might not automatically apply to healthy younger women without pre-existing cardiovascular disease who are currently in menopause.

In the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), estrogen without progestin slowed the progression of atherosclerosis in postmenopausal women, but the EPAT women had no pre-existing cardiovascular disease and were younger than the WELL-HART women.

In a trial at Brigham and Women’s Hospital in Boston, heart-attack risk rose by 81% in the first year in older women taking estrogen and progestin.


FDA Clears Generic Paxil®

Apotex Corp. has announced that the FDA has given final approval to its Abbreviated New Drug Application (ANDA) for paroxetine HCl tablets. The drug is rated “AB,” which means that the FDA considers it therapeutically equivalent to its brand name counterpart, Paxil®, manufactured by GlaxoSmithKline (GSK). The drug will be available in strengths of 10, 20, 30, and 40 mg.

Apotex was the first generic drug manufacturer to challenge GSK’s patents covering Paxil® and the first to gain FDA approval for an AB-rated generic version of the popular drug.

Apotex submitted its ANDA for paroxetine HCl in March 1998 and continues to be in litigation with GSK regarding generic versions of several products. GSK’s patent for Paxil® expires in 2006. In March 2003, it was ruled that its patent in the U.S. covering the hemihydrate form of Paxil® is valid but not infringed by Apotex’s rival product. Apotex plans to launch its generic version by 2005 at the latest.

(Sources: Apotex Corp., Dow Jones Newswires, and Reuters, July 31, 2003.)