NEW DRUGS

Fosamprenavir Calcium for HIV Infection

GlaxoSmithKline has announced that the U.S. Food and Drug Administration (FDA) has granted marketing clearance for fosamprenavir calcium (Lexiva™), a new protease inhibitor (PI) for the treatment of human immunodeficiency virus (HIV) infection in adults in combination with other antiretroviral medications.

Lexiva™ can be taken as two 700-mg tablets twice daily, as two 700-mg tablets once daily combined with two 100-mg capsules of ritonavir (Norvir®, Abbott) once a day, or as one 700-mg tablet twice a day combined with one 100-mg capsule of ritonavir twice daily.

Lexiva™ is contraindicated in patients with previous hypersensitivity to any of the components of the product or to amneprevir. New-onset cases or exacerbations of diabetes mellitus and hyperglycemia and spontaneous bleeding in hemophiliac patients have been reported with PIs. Patients receiving antiretroviral therapy have experienced a redistribution or accumulation of body fat, including central obesity, dorsocervical fat enlargement (“buffalo hump”), peripheral wasting, facial wasting, breast enlargement, and a cushingoid appearance.

(Source: GlaxoSmithKline, October 21, 2003.)

Third Drug Approved for Erectile Dysfunction

The FDA has approved tadalafil (Cialis®, Eli Lilly), an oral medication to treat erectile dysfunction (ED) in men. Tadalafil stays in the body longer than the other currently approved products for ED do. It acts by relaxing muscles in the penis and blood vessels, thereby allowing increased blood flow into the penis, which produces an erection.

The drug was evaluated in randomized, placebo-controlled trials involving more than 4,000 men with ED. In two of these trials, ED was associated with diabetes mellitus or resulted after radical prostatectomy for prostate cancer.

The recommended starting dose for most patients is 10 mg taken before anticipated sexual activity. A higher dose of 20 mg is available for patients whose response to the 10-mg dose is not adequate. A lower dose (5 mg) may be necessary for patients taking other medications or having medical conditions that may decrease the body’s ability to metabolize tadalafil.

Patients should not take the drug more than once a day. It should not be used with nitrates (such as nitroglycerin tablets or patches) or with an alpha blocker other than tamsulosin (Flomax®, Boehringer Ingelheim), 0.4 mg daily, because the combination may lower blood pressure and lead to fainting or even death in some men.

Men for whom sexual activity is not advisable, because of an underlying heart condition, should not take this drug. In addition, men should inform their physicians about any previously experienced heart problems before they take the drug.

Before prescribing tadalafil, physicians should obtain a thorough medical history and should perform a complete physical examination to identify the underlying cause of the ED.

(Source: FDA Talk Paper, November 21, 2003.)

Low-Dose Hormonal Patch for Menopausal Symptoms

The FDA has granted marketing approval for a new estradiol/levonorgestrel transdermal (skin patch) system (Climara Pro®) for the treatment of menopausal symptoms. This thin, translucent patch is the first once-weekly combined hormone therapy approved in the U.S. Schering’s U.S. subsidiary, Berlex, Inc., plans to launch Climara Pro® in January 2004.

The transdermal (patch) technology allows for a continuous delivery of hormones at doses much lower than those in pills. Easily affixed to the skin, Climara Pro® delivers 0.015 mg/day of levonorgestrel and 0.045 mg/day of estradiol. Estradiol is the most active estrogen made by the ovary. This therapy is approved for the relief of moderate to severe vasomotor symptoms associated with menopause, such as hot flashes and night sweats.

Climara®, Schering’s once-weekly estrogen-only patch, is appropriate for women who have had a hysterectomy. With the addition of levonorgestrel, Climara Pro® is indicated for women with an intact uterus.

(Source: PRNewswire/First Call, November 24, 2003.)

Combination Option for Patients with Arthritis

The FDA has approved a combination of the acid suppressor lansoprazole (Prevacid®, TAP) and the nonsteroidal anti-inflammatory drug (NSAID) naproxen (Naprosyn®) for patients who must take NSAIDs to treat the signs and symptoms of rheumatoid arthritis (RA), osteoarthritis (OA), and ankylosing spondylitis. The product, called Prevacid® NapraPAC™, has been found to reduce the risk of recurrent NSAID-associated gastric ulcers in patients with a history of these ulcers.

NSAIDs, such as aspirin and naproxen, can cause ulcers by interfering with the stomach’s ability to protect itself from gastric irritants, such as acid.

Prevacid® NapraPAC™ is available as a daily dose of one Prevacid® 15-mg delayed-release capsule and two Naprosyn® tablets of either 375 mg or 500 mg.

The product is contraindicated in patients with known hypersensitivity to

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any component of either drug. Naproxen is contraindicated in patients in whom aspirin or other NSAIDs or analgesic drugs induce the syndrome of asthma, rhinitis, and nasal polyps. Both types of reactions have the potential to be fatal. Other naproxen-containing products should not be used concomitantly.

Serious gastrointestinal bleeding, ulceration, or perforation can occur with or without warning symptoms in patients receiving chronic NSAID therapy.

(Sources: IMS Health, National Prescription Audit Plus 7 Weekly™, November 2003; www.tap.com; www.prevacid.com.)

NEW MEDICAL DEVICES

NEW INDICATION

Voriconazole for Esophageal Candidiasis

Pfizer, Inc., has received FDA approval to market voriconazole (VFEND®), a broad-spectrum antifungal medicine, for the treatment of esophageal candidiasis. Initially, VFEND® was approved in the U.S. for the primary treatment of acute invasive aspergillosis and as salvage therapy for rare but serious fungal infections caused by the pathogen Sporothrix schenckii and Fusarium species.

Candida organisms are normally found on skin and mucous membranes in healthy individuals, but in people whose immune systems are weakened or compromised by cancer chemotherapy, organ transplantation, or human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), the organisms can multiply, causing potentially serious infections. In immunocompromised patients, esophageal candidiasis may coat much of the surface of the mouth, resulting in pain and difficulty swallowing, and may ultimately progress to more serious, invasive disease.

In a clinical trial of immunocompromised patients conducted in 15 countries, patients who received VFEND® showed a success rate of 98%; in patients who received fluconazole (Diflucan®, Pfizer), the rate was 95%. Both products had acceptable tolerability and safety.

The treatment-related adverse events that most often led to discontinuation in clinical trials were elevated liver-function test results, rash, and visual disturbances.

(Source: Pfizer; November 17, 2003.)
**Purpose:** The catheter is used to open coronary artery blockages caused by the accumulation of plaque material in the artery wall and in patients with one or more blockages. The catheter is particularly useful for treating coronary artery blockages that have returned after the application of a coronary stent and blockages that are expected to be resistant to balloon catheters that do not have the external wire. It is anticipated that the increased blood flow through the coronary arteries will improve heart function, decrease chest pain, and reduce the risk of a heart attack, stroke, and other events often experienced by patients with constricted coronary arteries.

**Precautions:** The catheter should not be used if the narrowing is situated in an unprotected left main coronary artery and if a spasm has occurred in the normal coronary artery.

**Name:** Computer-Aided Diagnosis (CADx)/Cervical Cancer ThinPrep™ Imaging System

**Manufacturer:** Cytyc Corporation, Boxborough, MA

**Approval date:** June 6, 2003

**Use Classification:** Imaging with an automated microscope to screen Papanicolaou (Pap test) slides for cervical cancer or its precursor lesions.

**Description:** The computer-aided imaging processor scans the entire microscope slide and identifies 22 fields of view containing the cells that are most likely to be diagnostically relevant. Using the automated microscope, a cytotechnologist can identify any abnormal cells in these 22 fields. If no abnormal cells are observed, the result is considered “negative” and no further review is necessary. If abnormal cells are found, the entire slide should be reviewed.

**Purpose:** The device is designed to screen for cervical cancer and can be used for all women who undergo a ThinPrep™ Pap Test. A clinical study has shown that using this device to review slides saves time and labor and produces diagnostic results as accurate as those obtained by manual microscopy.

**Precautions:** Health care workers should take care, while loading and unloading the glass slides, to prevent slide breakage or injury and to ensure that the slides are oriented correctly. Partially processed slide cassettes should not be removed from the image processor. The processor should be placed on a flat, sturdy surface, away from any vibrating machinery.

(Source: www.fda.gov/cdrh/newpg.html)

**DRUG NEWS**

**Abacavir and Hypersensitivity**

Abacavir sulfate (Ziagen®, Glaxo-SmithKline), a nucleoside reverse transcriptase inhibitor (NRTI) used to treat human immunodeficiency virus 1 (HIV-1) infection in combination with other antiretroviral agents, is well tolerated except for the development of hypersensitivity reactions. These effects are the main reason for stopping the drug within the first months of therapy.

Abacavir can be associated with drugs that are known to induce allergic reactions in the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome, such as nevirapine (Viramune®, Roche), efavirenz (Sustiva®, Bristol-Myers Squibb), and cotrimoxazole (sulfamethoxazole/trimethoprim: Septra®, Monarch/Bactrim®, Women First).

Gastrointestinal or respiratory symptoms that accompany a rash or fever suggest abacavir hypersensitivity, whereas rash with maculopapulous or morbilliform eruption or bullous eruption is more common with nevirapine hypersensitivity, as are hepatic disorders.

If reactions worsen, drug therapy should be stopped. If symptoms resolve or do not worsen, the drug can be cautiously continued while other possible causes are investigated.

(Source: Ann Pharmacother 2003;37: 1392–1397.)

**Women and Depression in the Workplace**

An estimated five million American working women suffer from depression, and 83% of them perceive it as the number one barrier to success in the workplace, according to a survey sponsored by the American Medical Women’s Association and the National Mental Health Association.

The women reported behaviors such as leaving work early or not returning from lunch, avoiding contact with coworkers, and being unable to face work as a result of their depression.

According to the survey, the benefits of treatment are significant. Ninety-four percent of the women noticed improvements at work after seeking treatment (e.g., psychotherapy and/or medication). Only 47% of the women who received treatment sought help immediately, however.

When asked why they did not seek treatment right away, many women reported not knowing where to go for help, pressure from work-related time constraints, fears that insurance would not cover the costs, or worries that they could lose their jobs. Others attributed their delay to the stigma of depression or to feeling that depression was a sign of weakness or a character flaw.

The study was funded by Wyeth Pharmaceuticals.


**Adverse Reactions with Drug-Coated Stents**

The Cypher Coronary Stent (Cordis Corporation), approved in April 2003 for...
patients undergoing angioplasty procedures to open clogged coronary arteries, was hailed as a great advance in keeping arteries from reclogging after implantation of the device. A thin polymer coating contains the drug sirolimus, which is slowly released into the patient’s arteries and is intended to reduce the rate of recurrent blockage that occurs with other stents. More recently, the FDA has informed physicians about adverse events associated with the stent.

The FDA has received more than 290 reports of thrombosis (clotting) occurring one to 30 days after the procedure. In more than 60 of these reports, the use of the stent was associated with deaths; in the remainder, it was associated with injuries requiring medical or surgical intervention.

More than 50 reports have also noted possible hypersensitivity reactions. Symptoms include pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes.

So far, hundreds of thousands of patients have been successfully treated with Cypher stents. The FDA has not determined whether the thrombosis and hypersensitivity reactions occurring with these stents differ from the effects experienced with bare metal stents.

The FDA and Cordis are working to determine the cause of these events. The agency is encouraging physicians to look for any patient symptoms that might be attributed to hypersensitivity. Patients who have the Cypher stents should continue to follow their regularly scheduled plan for follow-up appointments with their doctors.

As a condition of approval, the FDA is requiring Cordis to conduct a 2,000-patient post-approval study and to continue evaluating patients from ongoing clinical trials to assess the long-term safety and effectiveness of the stents and to look for rare side effects. Doctors and patients who have observed any adverse stent-related events are encouraged to notify the FDA. Physicians can consult www.fda.gov/cdrh/safety/cypher.html.

(Source: FDA Talk Paper, October 29, 2003.)

**Synthetic Cholesterol Removes Plaque from Coronary Arteries**

A new study suggests that five weekly infusions of a synthetic form of high-density lipoprotein-cholesterol (HDL, or “good,” cholesterol) can remove significant amounts of plaque from the arteries.

Approximately 25 to 30 years ago, researchers discovered 40 residents of Northern Italy who appeared perfectly healthy even though they had very low levels of HDL-cholesterol. Ordinarily, such people would have a high risk of heart disease, but these people did not. Intrigued, the researchers discovered that they had a variant in a protein known as apolipoprotein A-I, a component of HDL. This variant was named ApoA-I Milano (Esperion Therapeutics) after the city of Milan, where the initial laboratory work was performed. The company’s investigational treatment consists of a recombinant version of ApoA-I Milano plus a phospholipid.

The traditional therapies for atherosclerosis have focused on lowering levels of low-density lipoprotein-cholesterol (LDL-cholesterol).

The ApoA-I Milano trial, which was conducted from November 2001 to March 2003, enrolled patients with acute coronary syndrome. All of the patients had experienced unstable angina or a heart attack. Patients were assigned to take a placebo, a low dose, or a high dose of intravenous recombinant ApoA-I Milano/phospholipid complex. The study drug was administered as a weekly IV infusion for a total of five weeks.

Patients who received the synthetic protein showed a dramatic decrease in arterial plaques, whereas a comparison group of patients who received saline showed no change.

More testing is needed, because the recent clinical trial was a small study. (Sources: *JAMA* 2003;290(17):2292–2300; The Cleveland Clinic Foundation, November 4, 2003.)

**Valsartan Saves Lives After Heart Attacks**

On the basis of positive results from the Valsartan in Acute Myocardial Infarction Trial (VALIANT), Novartis Pharmaceuticals plans to file for a new indication for valsartan (Diovan®). This is the only cardiovascular agent ever shown in a rigorous head-to-head trial to have all of the proven benefits of captopril (Capoten®, Apothecon), an angiotensin-converting enzyme (ACE) inhibitor, after a heart attack, or myocardial infarction (MI).

Valsartan, known for its efficacy in treating hypertension, was beneficial as a first-line, post-MI treatment in high-risk patients in terms of cardiovascular protection, tolerability, antihypertensive efficacy, and ease of adherence to therapy. It is estimated that valsartan might be able to save 30,000 lives in the U.S. each year.

VALIANT is the largest long-term study ever conducted in survivors of MIs. It was conducted at 931 centers in 24 countries. Patients were aged 18 and over (excluding those of child-bearing age) and were enrolled between 12 hours and 10 days after an MI that was complicated by temporary heart failure or left ventricular systolic dysfunction. Patients also received recommended “background” therapy, including aspirin, cholesterol-lowering agents (statins), and beta blockers.

Valsartan preserved 99.6% of the benefit of captopril by reducing mortality rates to the same degree as the proven treat-

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ment. This finding translates into a 25% reduction in premature death by valsartan in patients at high risk after an MI.

Pregnant women should not take valsartan, and patients with heart failure should not take it concomitantly with ACE inhibitors or beta blockers.

Because of the risk of hypotension, caution should be observed for post-MI patients and patients with heart failure. Patient evaluations should always include a renal assessment.

The most common side effects in patients with heart failure were dizziness, hypotension, and diarrhea.


**High-Dose Lipitor® Halts Plaque Buildup**

According to findings presented at the annual meeting of the American Heart Association, patients taking the cholesterol-lowering medication atorvastatin calcium (Lipitor®, Pfizer) experienced a greater reduction in the progression of atherosclerosis than did patients taking pravastatin (Pravachol®, Bristol-Myers Squibb).

The Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study included 502 patients who had coronary heart disease and required cardiac catheterization. Patients had at least one arterial vessel with 20% or more constriction causing a buildup of plaque. The investigators compared the effectiveness of atorvastatin (80 mg/day) and pravastatin (40 mg/day).

The average low-density lipoprotein-cholesterol (LDL-C, or “bad” cholesterol) levels of the patients at the beginning of the study were 150 mg/dl (accepted guidelines recommend levels below 100 mg/dl). Before enrollment, patients were not taking any medications to treat cholesterol and they had other heart disease risk factors, such as a history of diabetes, hypertension, or a previous heart attack.

It was theorized that atorvastatin might have had a greater impact on C-reactive protein (CRP), an indicator of inflammation and an independent risk factor for cardiovascular disease. Patients taking atorvastatin experienced a 36.4% reduction in CRP; patients taking pravastatin experienced a 5.2% reduction.

Of the patients taking atorvastatin, 97% reached their recommended LDL-C goals; in contrast, 67% of the patients taking pravastatin reached their target goals.

(Sources: Dow Jones Business News online at http://biz.yahoo.com; Pfizer news release, November 12, 2003.)