NEW DRUGS

Etravirine (Intelence) For HIV Infection

Etravirine tablets (Intelence, Tibotec/Ortho) have been approved by the Food and Drug Administration (FDA) after a priority review. This drug is indicated for the treatment of human immunodefieincy virus (HIV) infection in adults who have not responded to other antiretroviral agents.

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that helps to block an enzyme that the virus needs in order to multiply. When used with other active anti-HIV medications, it reduces the amount of virus in the blood and increases the number of white blood cells, which fight off other infections. Etravirine may also reduce the risk of death or infections that can occur with a weakened immune system.

The approval was based primarily on data from 599 adults in two randomized, double-blind, placebo-controlled trials.

(Source: FDA, January 18, 2008.)

Synthetic Starch (Voluven) Controls Blood Loss

The FDA has approved an intravenous (IV) starch solution (Voluven, Fresenius Kabi) that prevents and treats a loss of blood volume during and after surgery.

Significant blood losses can cause a rapid drop in the volume of red blood cells (RBCs) and plasma. This can lead to shock, which can be fatal. Blood volume expanders restore some of the lost volume so that the remaining RBCs can continue to deliver oxygen to the tissues.

Voluven is not recommended for patients receiving dialysis or for those with abnormal sensitivity to the synthetic starch in the product, fluid overload, kidney failure not related to low blood volume, intracranial bleeding, or increased blood levels of sodium or chloride.

A postmarketing clinical trial of patients with sepsis is planned.

For more information on Voluven, please see this month's Pharmaceutical Approval Update column on page 114.

(Source: FDA, December 28, 2007.)

Generic Kytril (Granisetron) To Prevent Nausea and Vomiting

Barr Laboratories, Inc., has received final approval from the FDA for its generic version of Roche's Kytril (granisetron HCl) 1 mg. This medication is prescribed to prevent nausea and vomiting in patients undergoing radiation and chemotherapy. The tablets are equivalent to 1 mg base. The company received final approval following the expiration of Roche's patent on December 28, 2007.

(Source: Barr Labs, January 2, 2008.)

Topical Patch for Pain (Flector)

Alphapharma's Flector patch has been approved as a topical therapy for acute pain caused by minor strains, sprains, and contusions.

The patch, available by prescription, measures about 4 inches x 5.5 inches and is applied directly to intact skin at the site of pain. Each patch contains 180 mg of diclofenac epolamine.

(Source: www.flectorpatch.com, January 23, 2008.)

NEW INDICATIONS

Thyrotropin Alfa (Thyrogen) For Thyroid Cancer

The FDA has approved a supplemental indication for thyrotropin alfa injection (Thyrogen, Genzyme). This agent is used with radioiodine to destroy remaining thyroid tissue after surgery to remove a cancerous thyroid gland in a procedure called remnant ablation.

As a recombinant form of thyroid-stimulating hormone (TSH), thyrotropin alfa enables patients to continue taking hormone supplements and to avoid the symptoms associated with hormone withdrawal. The new indication helps patients during their initial therapy for thyroid cancer. Thyrotropin alfa was originally approved in the U.S. in 1998 and Europe in 2001 for use in follow-up diagnostic procedures to detect recurrence.

(Sources: Genzyme, December 17, 2007, www.thyrogen.com.)

Micafungin (Mycamine) for Candidemia

Astellas Pharma, Inc., has announced the FDA's approval of its supplemental New Drug Application (sNDA) for the use of micafungin sodium (Mycamine for Injection) in the treatment of candidemia, acute disseminated candidiasis, candidal peritonitis, and abscesses.

Micafungin was approved in 2005 for the treatment of patients with esophageal candidiasis, and it is the only echinocandin approved for the prevention of candidal infections in patients undergoing hematopoietic stem cell transplantation.

Candidemia is a fungal infection that causes bloodstream infection with the potential to spread to another part of the body. According to the Centers for Disease Control (CDC), it is the fourth most common bloodstream infection among hospitalized patients in the U.S.

Micafungin inhibits an enzyme essential for fungal synthesis in the cell wall, and it is lethal to *Candida*. Isolated cases of anaphylaxis and anaphylactoid reactions, including shock, have been reported.

Micafungin is available in two vial sizes, 50 mg and 100 mg.

(Source: Wire services, Astellas, January 23, 2008.)

Adalimumab (Humira) For Plaque Psoriasis

Abbott Laboratories has received the FDA's approval to market adalimumab (Humira) to treat adults with moderate-

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to-severe chronic plaque psoriasis.

The approval was based on two pivotal trials—REVEAL and CHAMPION—involving more than 1,400 adults. In these trials, nearly 75% of treated patients achieved 75% clearance or better at the 16th week, compared with those receiving placebo.

Adalimumab was approved to treat moderate-to-severe rheumatoid arthritis in 2002, psoriatic arthritis in 2005, ankylosing spondylitis in 2006, and moderate-to-severe Crohn's disease in 2007.

(Sources: *Am Acad Dermatol*, January 2008; *Br J Dermatol* online.)

Colesevelam (Welchol) For Glucose Control In Type-2 Diabetes

Colesevelam HCl (Welchol, Daiichi Sankyo) is now approved to help improve glycemic control (glycosylated hemoglobin, or HbA_{1c}) in adults with type-2 diabetes when it is used alone or with other antidiabetic agents such as metformin (Glucophage, Bristol-Myers Squibb) and insulin. This is the first medication approved to reduce both glucose levels and low-density lipoprotein-cholesterol levels (LDL-C) when compared with placebo.

Since 2000, this bile acid sequestrant has been used alone or with a statin to lower elevated LDL-C levels in patients with primary hypercholesterolemia. Unlike most other cholesterol-lowering drugs, such as statins, it is eliminated without traveling to the liver or kidneys; therefore, it is not expected to have drug interactions via the cytochrome P450 pathway. Colesevelam has also had beneficial effects on HDL-C and apolipoprotein-B levels.

Colesevelam should not be used in combination with fenofibrate, and it is not indicated for patients with type-1 diabetes, diabetic ketoacidosis, with bowel obstruction, triglyceride levels above 500 mg/dL, or hypertriglyceridemia-induced pancreatitis. It can increase serum triglyceride levels, particularly when it is used with sulfonylureas or insulin. Caution should be used for patients with triglyceride levels exceeding 300 mg/dL.

Patients should take vitamins A, D, E, and K at least four hours before taking this drug.

(Sources: FDA, Daiichi Sankyo, January 18, 2008.)

Natalizumab (Tysabri) For Crohn's Disease

Natalizumab (Tysabri, Biogen Idec/Elan) has been used since 2006 to treat some forms of multiple sclerosis. It is now approved for treating moderate-to-severe Crohn's disease in patients with inflammation who have not responded to or who cannot tolerate conventional therapies for Crohn's disease.

This drug must be infused by trained professionals. Patients, prescribers, pharmacies, and infusion centers must be enrolled in the Crohn's Disease–Tysabri Outreach Unified Commitment to Health (CD TOUCH) Prescribing Program and must agree to comply with strict monitoring guidelines. If there is no improvement after three months, treatment should be discontinued.

The label carries a boxed warning about progressive multifocal leukoencephalopathy, an opportunistic viral infection that affects the brain.

Patients who are taking steroids for Crohn's disease should begin tapering steroid doses while taking natalizumab. Treatment should be discontinued if steroids cannot be fully tapered within six months.

(Source: FDA, January 14, 2008.)

NEW FORMULATION

Aliskiren (Tekturna) HCT For Hypertension

Aliskiren combined with the diuretic hydrochlorothiazide (Tekturna HCT, Novartis/Speedel) is now available as a single tablet containing two drugs for high blood pressure. Aliskiren is the first approved direct renin inhibitor.

In clinical trials, the combination resulted in significant additional reductions in blood pressure compared with either drug alone. Aliskiren should be used after other medications have been tried.

The tablets are scheduled to be available in February in strengths of 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg.

The long-term potential of aliskiren and direct renin inhibition is being studied in ASPIRE HIGHER, a program that focuses on cardiovascular and kidney disease. Tekturna is known as Rasilez outside the U.S.

Aliskiren is the subject of this month's Drug Forecast column on page 92.

(Sources: Novartis/Speedel, January 21, 2008; www.tekturnahct.com.)

NEW DOSAGES

Lisdexamfetamine (Vyvanse): More Doses for ADHD

Three new dosage strengths have been approved for Shire's lisdexamfetamine dimesylate (Vyvanse), which is used to treat Attention-Deficit/Hyperactivity Disorder (ADHD). The added strengths of 20 mg, 40 mg, and 60 mg are expected to be available in the second quarter of 2008. Current strengths are 30 mg, 50 mg, and 70 mg.

Vyvanse is currently approved in the U.S. for use in children 6 to 12 years of age. The FDA is reviewing an sNDA for treating ADHD in adults.

Although Vyvanse was generally well tolerated in clinical studies, it should not be taken if a child has arteriosclerosis, symptomatic heart disease, hypertension, hyperthyroidism, an allergy to sympathomimetic amines, seizures, glaucoma, problems with alcohol or drugs, or

agitation. This agent is also contraindicated in children who have taken a monoamine oxidase inhibitor within the previous 14 days.

(Sources: Shire, January 3, 2008; www.vyvanse.com.)

Once-Daily Tadalafil (Cialis)

Eli Lilly has received the FDA's approval to offer its erectile-dysfunction drug, tadalafil (Cialis), in once-daily dosages of 2.5 mg and 5 mg. This approval was based on results from three phase 3 randomized, double-blind, placebo-controlled studies.

Tadalafil in strengths of 5 mg, 10 mg, and 20 mg has been indicated for as-needed treatment since November 2003 in the U.S. It is the only drug for erectile dysfunction that is approved as a daily treatment regimen.

The wholesale price of the new dose will be comparable to the cost of taking two pills of the original formulation.

(Sources: Associated Press, January 9, 2008; Reuters, January 8, 2008; www.healthcentral.com.)

DRUG NEWS

Disparities in Treatment

Survival Decreases With Delayed Defibrillation

About one-third of patients experiencing cardiac arrest in hospitals are not getting a defibrillator within the recommended two minutes.

In a new study, 6,789 patients had heart attacks resulting from ventricular fibrillation in 369 hospitals. Overall, the hospital staff took an average of one minute to apply the paddles, but in nearly one-third of the cases, it took longer than the recommended two minutes.

Cardiac arrest occurs when the heart's electrical system misfires. Patient survival is increased if defibrillator paddles are used to shock the patient's heart back to life within two minutes, but for every minute lost, the chances of survival worsen. With a six-minute delay or more, the chances of remaining alive are only 25%, compared with immediate treatment. Patients who did not receive quick electric jolts died at nearly twice the rate of those who were treated promptly.

Late responses were seen most often for African-American patients, in hospitals with fewer than 250 beds, in hospital units not being monitored, at night, and on weekends. The data did not explain why African-Americans had longer waits.

Of the 370,000 to 750,000 patients who experience cardiac arrest and who need resuscitation each year, only 30% survive long enough to go home.

(Sources: *N Engl J Med* 2008;358:9–17; *USA Today*, January 2, 2008.)

Minorities Receive Less Pain Relief

African-American and Hispanic patients remain less likely than white patients to receive pain relievers in emergency departments (EDs), according to a study from the University of California, San Francisco.

Researchers analyzed nearly 375,000 ED visits over 13 years. About 42% of these visits were for pain. Between 1993 and 2005 at U.S. hospitals, 31% of whites received opioid drugs, compared with only 23% of African-Americans, 24% of Hispanics, and 28% of patients of Asian ancestry. In contrast, non-opioid pain relievers, such as acetaminophen and ibuprofen, were prescribed more often to non-whites (36%) than to whites (26%).

African-Americans received opioids less often than other groups for almost every type of pain-related ED visit, and differences in prescribing were greatest for people with the worst pain. About 52% of whites in severe pain received opioids, compared with only 42% of Hispanics and 39% of African-Americans.

Prescribing rates were particularly low for African-American and Hispanic children, African-Americans in county and state hospitals, Asians and Medicare patients, and non-white patients living in the northeastern states.

The study was not designed to determine the causes of these ethnic disparities. The authors called for ongoing education about pain for physicians and nurses and promotion of cultural awareness.

(Source: *JAMA,* January 2, 2008.)

Longer Waits For All Patients In Emergency Rooms

Waits for emergency care are getting longer each year for most patients. Researchers from the Cambridge Health Alliance and Harvard Medical School analyzed the time between arrival in the ED and when patients were first seen by a doctor. More than 90,000 ED visits nationwide were evaluated between 1997 and 2004.

Increasing delays affected all racial and ethnic groups; even patients with health insurance and critically ill patients waited longer for treatment.

Severely ill patients experienced the largest increase in waits. During the study, wait times increased by 36% for all patients (from 22 to 30 minutes), and for those needing immediate attention, wait times increased by 40% (from 10 to 14 minutes).

Most patients experiencing heart attacks also waited: 8 minutes in 1997 but 20 minutes in 2004 (a 150% increase). In 2004, 25% of heart attack victims waited 50 minutes or more before they could see a doctor.

Waits were slightly longer for African-American and Hispanic patients as well as women. Patients at rural hospitals had the shortest waits.

The number of ED visits increased

from 93.3 million to 110.2 million, but the number of hospitals operating 24-hour EDs decreased by 12%. In the remaining EDs, ambulances were sometimes diverted to another facility every minute.

The lead study author suggested that EDs were closing because emergency patients are "money-losers" for hospitals. Planned admissions are usually more lucrative because patients can be scheduled more conveniently and can be prescreened for health insurance. However, he said, "these perverse incentives are causing dangerous delays in potentially lifesaving emergency care, even for those with insurance." EDs might also be overcrowded if patients have poor access to primary care. Adequate access to preventive care with appropriate drug therapy might help address medical problems before they become emergencies.

(Source: *Health Affairs* online, January 11, 2008.)

Safeguards Needed For Dispensing Cabinets

The use of automated dispensing or distribution cabinets (ADCs) can decrease the amount of time before a drug is available for administration, helps ensure greater security, and reduces the risk of medication errors—but only when certain safeguards are used consistently.

A survey conducted by the Institute for Safe Medication Practices (ISMP) in 2007 showed that although use of ADCs has become prevalent in the last decade, safety improvements have not been as widespread as needed to maximize the benefits of the technology.

For example, in both the 2007 and the ISMP's earlier 1999 survey, only 18% of respondents reported that another person verifies drug placement in the ADC. Requiring another practitioner to double-check a drug removed via an override, before pharmacy review, increased by only 10%. In 1999, only 28% of respondents had said that a pharmacist must verify orders before drugs could be removed from ADCs. In 2007, that percentage increased to 64%, but only 59% of the respondents reported that all cabinets could provide a direct interface between the pharmacy information system and ADCs so that pharmacists can approve the drugs before they are removed from the cabinet. New ADC guidelines to prevent errors were drafted in 2007.

(Sources: *ISMP Newsletter*, January 17, 2008, www.ismp.org/tools/guidelines/labelformats/comments/default.asp.)

Marketing for Heart Failure Drug (BiDil) Halted

Nitromed has stopped marketing its fixed-dose combination of isosorbide dinitrate and hydralazine (BiDil), a three-times-daily tablet indicated for African-Americans with heart failure. However, the currently approved version of the drug will still be available for patients while the company works on an extended-release formulation.

The FDA approved BiDil in 2005 after it was associated with a 43% drop in relative mortality and a 39% decrease in the relative risk of hospitalizations for heart failure over 10 months in the randomized African-American Heart Failure Trial (A-HeFT). Yet BiDil did not catch on, perhaps because some considered it a costly combination of two generically available drugs. Despite growth in prescriptions, the company believes that a larger marketing effort is needed. NitroMed is eliminating about 70 of its 90 positions. The company plans to file its NDA for the extended-release formulation in 2010.

(Sources: The Heart, January 16, 2008; Associated Press, January 17, 2008.)

Pregabalin (Lyrica) and Diabetic Peripheral Neuropathy

Twice-daily pregabalin (Lyrica, Pfizer) was safe, well tolerated, and significantly superior to placebo in reducing the pain of diabetic peripheral neuropathy (DPN), say researchers from Germany. In a 12-week, double-blind trial, 396 patients with painful DPN were randomly assigned to receive placebo or pregabalin 150, 300, or 600 mg/day. By the second week, pain scores among patients receiving 600 mg/day were significantly lower than scores of patients receiving placebo. The 600-mg dose also improved patients' overall health status. At all doses, the patients reported improved quality of life.

Treatment-related adverse effects included dizziness, peripheral edema, and somnolence, all of which increased with higher doses, but few patients stopped treatment because of adverse effects.

(Source: *Eur J Pain* 2008;203–213.)

Stress Echocardiography? Exercise ECG? Or Both?

Although electrocardiography (ECG) during exercise provides valuable information about the heart's rhythm and electrical activity, it might not always be accurate in its predictions, especially at an intermediate-to-high workload, say researchers from Italy. They compared the prognostic value of exercise ECG with pharmacological stress echocardiography using dipyridamole (Persantine, Boehringer Ingelheim) or dobutamine (Lilly). The study enrolled 131 patients with diabetes and 804 patients without diabetes who had positive exercise ECG findings.

Ischemia during stress echocardiography was independently associated with an increased risk of hard events (death and myocardial infarction [MI]), as well as major events (death, MI, and late revascularization); a non-ischemic test result predicted a favorable outcome.

The results of stress echocardiography added prognostic value to those of positive exercise ECG results. Both dia-

betic and nondiabetic patients with non-ischemic findings had lower rates of major events each year, compared with the overall population of diabetic and nondiabetic patients with positive exercise ECG results.

Over a median of 26 months of follow-up, 34 diabetic patients and 124 nondiabetic patients died or had MIs or late revascularizations. Independent predictors were age, diabetes, and ischemia at stress echocardiography. At five years, 24% of patients with ischemia and 4% of those without ischemia experienced MI or died; 46% of those with ischemia and 7% of those without experienced major events.

Antianginal therapy at the time of testing was associated with an increased risk of major events in all patients. In particular, the annual rate of major events was more than three times higher in diabetic patients and more than twice as high in nondiabetic patients with a non-ischemic test result during therapy, compared with patients not receiving therapy.

For both groups of patients, a non-ischemic test result predicted an uneventful six-month period and a 2% rate for a major event at one year. As expected, diabetes was a strong multivariable predictor; thus, non-ischemic stress test results had less prognostic value in those patients.

Angiography seemed to be appropriate for diabetic and nondiabetic patients with ischemia at stress echocardiography. Conversely, a conservative strategy based on adequate treatment of risk factors and periodic assessment with stress testing was considered appropriate in patients without ischemia who were not taking antianginal therapy. More frequent noninvasive evaluation is advised for diabetic patients after the first year of follow-up.

(Source: *Am J Cardiol* 2007;100:1744–1749.)

Does C-peptide Prevent Diabetes Complications?

A compound formed during insulin production—and once dismissed as irrelevant in diabetes—might be a key factor in preventing the complications that make type-1 diabetes such a serious disease.

Scientists previously believed that the compound, called C-peptide, had little biological activity and was a useless by-product of insulin production. More recently, however, they have observed beneficial effects of C-peptide in patients with type-1 diabetes, including improved kidney function, nerve function, and blood flow. New laboratory research suggests that C-peptide might enhance the ability of red blood cells to use glucose.

According to the American Chemical Society, type-1 diabetes afflicts about 800,000 people in the U.S. alone and sharply raises the risk of heart attacks, vision loss, and kidney failure.

(Source: *Chem Eng News,* January 14, 2008, http://pubs.acs.org/cen/science/86/8602sci1.html.)

Diuretics Still Best For Hypertension In Metabolic Syndrome

In a new study of patients with high blood pressure as part of the metabolic syndrome, diuretics offer greater protection against cardiovascular disease, including heart failure, and are at least as effective for lowering blood pressure as newer, more expensive medications. People with metabolic syndrome have three or more risk factors for heart disease, including elevated blood pressure, low HDL levels, and diabetes or pre-diabetes.

These findings, from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), run counter to current practices that favor angiotensin-converting enzyme (ACE)–inhibitors, alpha-blockers, and calcium-channel blockers for those with metabolic syndrome. The results also support the use of diuretics for initial blood pressure-lowering therapy in African-Americans with the syndrome.

ALLHAT compared a diuretic (chlorthalidone) with three newer classes of medications to treat high blood pressure: a calcium-channel blocker (amlodipine besylate [Norvasc, Pfizer]), an alpha-blocker (doxazosin mesylate [Cardura, Roerig/Pfizer]), and an ACE-inhibitor (lisinopril [Zestril, AstraZeneca]). Even among patients with metabolic syndrome, and for both black and non-black participants, the less costly diuretics control blood pressure consistently and were equally beneficial in preventing heart attack and coronary heart disease death. They are also more beneficial than newer drugs in preventing cardiovascular disease, including heart failure and stroke.

In 2002, the study had reported that diuretics were the most beneficial of the drug classes for hypertension and for protecting against adverse cardiovascular outcomes.

(Sources: *Arch Intern Med*, January 28, 2008; *Diabetes Care,* February 2008; www.nhlbi.nih.gov.)

Breast Cancer Risk: Lower Than Thought?

The risk of breast cancer varies widely in women with BRCA1 and BRCA2 genetic mutations, according to a study sponsored by the National Cancer Institute. Women with certain gene mutations might be at a lower risk than previously believed.

Researchers from Memorial Sloan-Kettering Cancer Center suggested that there is no single risk associated with BRCA1 or BRCA2 carrier status. Previous studies had reported on the overall increased risk of breast cancer among women with BRCA1 and BRCA2 gene mutations, but they had not focused on

variation in risk.

The team analyzed data from more than 2,000 women enrolled in WECARE, a study involving 1,394 women with breast cancer and an additional 704 women with contralateral breast cancer (separate cancer in both breasts). The women were younger than age 55 at diagnosis, and cancer had not spread beyond the regional lymph nodes.

The study focused on the incidence of breast cancer in the first-degree relatives of the 181 women with a mutation in BRCA1 or BRCA2. Relatives of the women with a breast cancer diagnosis at age 35 or younger had a higher incidence of breast cancer than relatives of women with a diagnosis between 45 and 54 years of age. The risk also varied among families and according to lifestyle and environment.

The risks were generally higher in families with multiple cases of breast cancer, but the likelihood of breast cancer developing in a healthy woman without a family history after testing positive for a BRCA1 or BRCA2 mutation tended to be lower than current estimates of lifetime risk in carriers.

Women carrying mutations in one of two genes face a 40% to 51% risk of developing breast cancer by age 70; this rate is lower than the commonly cited risk of 50% to 80%.

About 0.5% of women in the U.S. carry these genes, which are also linked to ovarian cancer risk. Women were at a higher risk if a relative's breast cancer was diagnosed at a young age or if it had occurred in both breasts. Genetic testing is recommended only for women with families already affected by cancer.

(Sources: *JAMA* and *The Wall Street Journal*, January 9, 2008.)

Methadone And Sudden Cardiac Death

Methadone has proved useful in many situations, for example, in opioid withdrawal, as a long-acting analgesic for neuropathic pain syndromes, and as a low-cost alternative to more expensive opiates. However, therapeutic-use methadone has been linked with sudden cardiac death. Researchers from Oregon Health and Science University in Portland performed a four-year community-based study to evaluate the association.

They identified 72 patients with sudden cardiac death and evidence of methadone at a toxicologic screening. Of those patients, 43 who had died of a methadone overdose, recreational drug-use, or an overdose were excluded from the case group. Of the remaining 29 patients, only 22 underwent a detailed autopsy. All of the patients had therapeutic levels of methadone: 12 had been using it for pain control, three for opioid withdrawal; three as a recreational drug, and four for unknown reasons.

The researchers compared those patients with 106 patients with sudden cardiac death who had no evidence of methadone use, recreational drug use, or a drug overdose. Among the patients using methadone, five (23%) had a cardiac abnormality that might have caused sudden cardiac death; all of these had significant coronary artery disease. With the other 17 patients, no significant cardiac abnormality was found. By contrast, 60% of patients who were not using methadone had cardiac abnormalities, most of them significant.

There have been concerns about two potentially lethal adverse effects of methadone: acquired prolonged QT syndrome, which can increase the risk of torsades de pointes, and respiratory de-

pression, especially during sleep. Either effect is likely to be potentiated by specific drugs used concomitantly with methadone. It is possible that some patients might have died from synergistic or potentiated effects of other drugs.

Because many people benefit from methadone, a large prospective evaluation of methadone therapy is warranted. The researchers also recommend additional safeguards for methadone treatment, such as an electrocardiogram and assessment of the potential for respiratory depression.

(Source: *Am J Med* 2008;121:66–71.)

More Studies Suggest Risks of Anemia Drugs

The FDA is reviewing new data from two studies that suggest further evidence of the risks of erythropoiesis-stimulating agents (ESAs). Patients with breast or advanced cervical cancers who received these drugs to treat anemia caused by chemotherapy died sooner or had more rapid tumor growth than similar patients who did not receive an ESA.

These two recent studies are in addition to the six studies described in the earlier revised labeling approved by the FDA in November 2007. The boxed warnings and labeling changes concerned Amgen's Aranesp and Epogen and Ortho-Biotech/J&J's Procrit in cancer patients (see Drug News, page 644, in the December 2007 issue of *P&T*).

All eight studies showed more rapid tumor growth or shorter survival when patients with breast, non–small-cell lung, head and neck, lymphoid, or cervical cancer received ESAs, compared with patients not receiving this treatment.

In all of these recent studies, ESAs were given in an attempt to achieve a hemoglobin level of 12 g/dL or greater, although many patients did not reach that level. The FDA plans to revisit the risks and benefits of using ESAs for patients with chemotherapy-induced anemia in the next few months.

ESAs are indicated for treating anemia in patients with chronic kidney failure; for cancer patients with anemia caused by chemotherapy; and for patients with human immunodeficiency virus (HIV) infection when anemia results from zidovudine (AZT). ESAs are also used to reduce the number of transfusions during and after major surgery.

(Source: FDA, January 3, 2008.)

FDA Challenges Bio-identical Hormones

The FDA has warned seven pharmacy operations that their claims about the safety and effectiveness of their bio-identical hormone replacement therapy (BHRT) products are not supported by medical evidence. The FDA letters state that the pharmacy operations have violated federal law by making false claims.

These operations claim that their drugs, which contain hormones such as estrogen, progesterone, and estriol, are superior to FDA-approved menopausal hormone therapy drugs and that they prevent or treat Alzheimer's disease, stroke, and cancer. However, estriol is not a component of any FDA-approved drug and has not proved safe or effective.

The companies imply that their drugs are natural or "identical" to the hormones made by the body and state that their products are better than FDA-approved menopausal hormones. The agency does not review compounded drugs for safety and effectiveness, and it encourages patients to use FDA-approved drugs whenever possible.

Firms that do not address the violations in the warning letters risk seizure of their drugs. The FDA is not targeting pharmacists who practice traditional pharmacy compounding, in which a pharmacist prepares a drug for a patient after receiving a valid prescription. In these cases, the practitioner has decided that the patient has special medical needs that cannot be met by FDA-approved drugs.

Patients should consult their health care providers to determine whether compounded drugs are their best option. If patients or practitioners encounter problems with these compounded products, they can file a report with MedWatch at www.fda.gov/medwatch.

(Sources: FDA, January 9, 2008; www.fda.gov/cder/pharmcomp/default.htm; www.fda.gov/consumer/updates/bioidenticals 010908.html.)

Label Update For Ortho Evra Birth Control Patch

The FDA has approved more changes to the labeling of Ortho-McNeil's Ortho Evra Contraceptive Transdermal Patch. In a new epidemiologic study, patients were at higher risk of developing venous thromboembolism (VTE) than women using oral birth control tablets.

The label changes are based on a study conducted by the Boston Collaborative Drug Surveillance Program on behalf of Johnson & Johnson. The patch was studied in women 15 to 44 years of age. These recent findings supported an earlier study that also said women in this group were at higher risk for VTE.

The patch, applied once weekly, releases ethinyl estradiol (estrogen) and norelgestromin (a progestin hormone) through the skin into the bloodstream.

Women using the product are exposed to about 60% more estrogen than if they use typical birth control pills containing 35 mcg of estrogen. Increased levels of estrogen may raise the risk of side effects, including VTE. The FDA considers Ortho Evra safe and effective when it is used according to the labeling.

(Sources: FDA, Ortho, January 18, 2008.)

Ezetimibe (Zetia) Shows Little Benefit In Heart Disease

A clinical trial of ezetimibe (Zetia), a cholesterol-lowering drug taken by about one million people each week, has not shown medical benefits, according to its manufacturers, Merck and Schering-Plough. About 60% of patients who take Zetia do so by taking Vytorin, which contains Zetia plus simvastatin (Zocor, Merck) in a single tablet.

Zetia lowers cholesterol by 15% to 20% in most patients, but no trial has shown that it can reduce heart attacks, strokes, or even fatty plaques in arteries that can cause heart problems. The ENHANCE trial was designed to show that Zetia could reduce the growth of plaques; however, over two years, the plaques grew almost twice as fast in patients taking Vytorin than in those taking Zocor alone.

Patients who took Zocor alone reduced their LDL-cholesterol by 41% on average, but patients using Vytorin reduced their cholesterol by 58%. However, the Vytorin patients had more growth in fatty plaques in their carotid arteries than patients taking Zocor.

The trial was completed in 2006, and in December 2007, the companies finally agreed that they would release the results. Even before Zetia was introduced in 2002, some cardiologists argued that Zetia lacked the benefits of statins, which had positive cardiovascular effects beyond their ability to reduce cholesterol.

The companies are conducting three large trials with Vytorin. No incremental benefit of Vytorin on cardiovascular morbidity and mortality, over and above that shown for Zocor, has been established.

In the U.S., Zetia and Vytorin together account for 20% of the overall cholesterol-lowering drug market. Both drugs cost about $3 a day.

(Sources: *The New York Times*, January 14, 2008; Merck/Schering-Plough.)

Alert for EDTA

The FDA is issuing a public health advisory alert about edetate disodium. Patients have died when they mistakenly received this agent instead of edetate calcium disodium (Calcium Disodium Versenate) or when edetate disodium was used for chelation therapy or other nonapproved uses.

Both drugs are often called EDTA and are easily mistaken for each other. They bind with heavy metals or minerals in the body and allow them to be eliminated through the urine.

The FDA approved edetate disodium as an emergency treatment for hypercalcemia and for arrhythmias resulting from high levels of digitalis. Newer drugs have been approved since then, but edetate disodium is still used to treat severe lead poisoning.

The FDA suggests that hospitals:

- evaluate whether they need to keep it in stock; if not, it should be removed to prevent confusion.
- treat lead poisoning only with edetate calcium disodium.
- use the full product name, not EDTA.
- include the indication for the product's use on the prescribing order.
- check the prescription and drug label to confirm that the correct drug has been selected.

(Sources: FDA, January 17, 2008; *Morb Mortal Wkly Rep*, www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a3.htm.)

NEW MEDICAL DEVICES

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Name: QuantiFERON-TB Gold In-Tube Method

Manufacturer: Cellestis, Inc., Melbourne, Australia, and Valencia, Calif.

Approval Date: October 12, 2007

Use Classification: The device is a blood test that detects cellular immune responses to proteins associated with tuberculosis (TB) infection.

Description: A single test is required, and objective and reproducible results are given. The In-tube format enables blood collection at remote sites. The device measures immune responses to peptides that simulate *Mycobacterium tuberculosis* proteins, which are not present in the bacille Calmette-Guérin (BCG) vaccine or in most non-TB mycobacteria. The test is 99% specific, and a positive result strongly predicts true infection with *M. tuberculosis*. Because people who are thought to have TB infection are normally recommended for TB therapy, which carries risks of liver toxicity and nerve damage, this test can reduce unnecessary therapy and overtreatment.

Purpose: The test provides a reliable screening method of TB control in the U.S. Cost savings are also realized because common false-positive results of the tuberculin skin test are eliminated.

Benefit: The new format, used in Europe and Asia, simplifies testing and fits with existing laboratory equipment. Virtually no labor or setup time is required for blood incubation.

Sources: www.pharmacyonesource.com; www.cellestis.com; www.rapidmicrobiology.com

Name: Realize Adjustable Gastric Band

Manufacturer: Ethicon Endo Surgery, Inc., Cincinnati, Ohio

Approval Date: October 20, 2007

Use Classification: This surgical implant is indicated for weight reduction and improvement in obesity-related health conditions, such as type-2 diabetes, in morbidly obese patients.

Description: A soft, adjustable silicone band is wrapped around the stomach to create two chambers. After the procedure, the upper stomach can hold

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only about four ounces of food. When the band is in place, the surgeon attaches the injection port to the abdominal wall beneath the skin. Using the injection port applier, the surgeon can complete this step in less than one minute, thereby decreasing the duration of anesthesia. The port enables doctors to inject or remove saline to tighten or loosen the band. The tighter the band, the more quickly the upper stomach fills up and the less food can be eaten. Adjustments can be made periodically according to patient needs.

Purpose: The band is used for people with a body mass index (BMI) of at least 40 kg/m^2 or a BMI of at least 35 kg/m^2 with one or more comorbid conditions.

Benefit: The gastric band is beneficial for morbidly obese patients who cannot lose weight with more conservative alternatives, such as supervised dietary, exercise, and behavior-modification programs.

Sources: www.pharmacyonesource.com; www.ethiconendo.com; www.jnj.com

Name: Follicle-Stimulating Hormone Immunoassay Test

Manufacturer: QuantRx Biomedical Corporation, Doylestown, Pa.

Approval Date: October 26, 2007

Use Classification: This over-the-counter fertility test is used to detect levels of follicle-stimulating hormone (FSH) at 10 ng/mL in women who wish to conceive.

Description: This is the only one-step lateral flow test on the market. Its technology makes it ideal for testing urine.

Purpose: The test determines ovarian reserve indirectly by measuring FSH in the first morning urine. The product is intended to aid women who are experiencing difficulty in conceiving.

Benefit: Results are produced within 15 minutes, approximately half the time of the only other competing product.

Sources: www.pharmacyonesource.com; www.quantrx.com/NR_07_11.htm

Devices in the News

Product Liability. The Bush administration has told the Supreme Court that FDA-approved medical devices are shielded from product-liability lawsuits in state courts. This position supports Medtronic in a case that has broad implications for devices makers.

The concern is whether patients can sue the makers of medical devices through state law if the FDA has already approved a product. Medtronic argues that the Food, Drug, and Cosmetic Act expressly pre-empts state law claims brought by patients who were hurt by devices that received pre-market FDA approval. Unlike the case with medical devices, there is no statute providing pre-emption for drugs.

Source: www.pharmalot.com

Infusion Pump Recall. On October 29, 2007, Cardinal Health recalled its Alaris Infusion Pump module (formerly, the Medley Pump module), Model 8100. All Alaris infusion pumps shipped before September 27, 2007, are subject to this recall. A list of serial numbers of the pumps affected by the recall is available at the firm's Web site (www.cardinal.com).

The electronic infusion pumps deliver controlled amounts of medications or other fluids to patients through an IV, intra-arterial, epidural, or other route.

During the manufacturing or servicing of the mechanism assembly, the occluder springs were misassembled, overlapping, missing, bent, or broken, possibly resulting in the potential for an inaccurate flow rate. This error can harm patients because of the resulting over-infusion.

Sources: www.fda.gov/cdrh/recalls/recall-102907.html ■