NEW DRUGS

Edarbyclor for Hypertension

Takeda has announced the FDA's approval of azilsartan medoxomil plus chlorthalidone (Edarbyclor) for adults with hypertension. This is the only fixed-dose therapy in the U.S. that combines an angiotensin II receptor blocker with a diuretic in a once-daily, single tablet.

The recommended starting dose of azilsartan/chlorthalidone is 40/12.5 mg; the maximum dose is 40/25 mg.

Azilsartan medoxomil (Edarbi) reduces blood pressure (BP) by blocking the action of angiotensin II, a natural vasopressor hormone. When Edarbi blocks the angiotensin II receptor, blood vessels can stay relaxed and open and BP can be decreased.

A boxed warning mentions that when pregnancy is detected, women should discontinue Edarbi or Edarbyclor as soon as possible because of the risk to the fetus.

Edarbyclor is discussed in detail in this month's Pharmaceutical Approval Update column on page 84.

Source: Takeda, December 20, 2011

Voraxaze Reduces Methotrexate Toxicity

Patients who receive high doses of methotrexate in chemotherapy are at high risk for kidney failure, but a newly approved intravenous (IV) drug can help keep methotrexate from building to toxic levels. Glucarpidase (Voraxaze, BTG International) is an enzyme that rapidly breaks methotrexate down into a form that can be eliminated from the body.

Prolonged exposure to high levels of methotrexate can also cause liver problems, mouth sores, damage to the intestinal lining, skin rashes, and death as a result of low blood counts.

In a clinical effectiveness study of 22 patients (between 5 and 84 years of age) glucarpidase was able to eliminate 95% of the methotrexate in all patients. In 10 patients, methotrexate fell below a critical level (≤1 µmol/L) within 15 minutes and stayed below that level for 8 days.

In two clinical trials involving 290 patients, side effects included hypotension, headache, nausea, vomiting, flushing, and paresthesias. No studies have been done to compare methotrexate plus supportive care versus supportive care alone in patients with toxic plasma methotrexate levels caused by impaired renal function. Thus, no data are available on the drug's effect on survival or toxic deaths caused by the drug. However, fatal methotrexate toxicity was not prevented in 3% of patients in the safety population.

The recommended dose is a single IV injection of 50 U/kg. In the 48 hours after administration, methotrexate levels can be reliably measured only by chromatography because of interference from metabolites; immunoassays can overestimate the methotrexate concentration. Leucovorin, a substrate for glucarpidase, should not be given within 2 hours before or after glucarpidase.

Source: FDA, January 17, 2012

Picato Topical Gel For Actinic Keratoses

Ingenol mebutate gel 0.015%, 0.05% (Picato, Leo Pharma) has been approved for the topical treatment of actinic keratosis, a precancerous condition caused by cumulative sun exposure.

The gel is used once daily on the face and scalp for 3 consecutive days and once daily on the trunk and extremities for 2 consecutive days. This is the first topical therapy for actinic keratoses that can be used for as little as 2 or 3 days.

In four phase 3 clinical studies, a significantly higher proportion of those using the gel saw complete clearance compared with those receiving placebo.

Source: Leo Pharma, January 25, 2012

NEW INDICATION

Prevnar 13 Vaccine For Adults Over 50

Prevnar 13 (Wyeth/Pfizer), a pneumococcal 13-valent conjugate vaccine, has received an accelerated approval for people 50 years of age and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*. Pneumococcal pneumonia is the most common disease in adults that is caused by *S. pneumoniae*. Each year, almost 300,000 individuals 50 years of age and older require hospitalization for the infection.

In randomized studies in the U.S. and Europe, Prevnar 13 induced antibody levels that were either comparable with or higher than the levels induced by Pneumovax 23 (Merck) for the 12 common serotypes.

Prevnar 13 is already approved for children 6 weeks through 5 years of age to prevent invasive disease caused by 13 different serotypes of *S. pneumoniae* and to prevent otitis media caused by seven serotypes of the bacterium.

Source: FDA, December 30, 2011

DRUG NEWS

Label Changes

Boxed Warning for Adcetris, A Lymphoma Drug

A black-box warning has been added to the prescribing information (PI) for brentuximab vedotin (Adcetris, Takeda/Seattle Genetics). The product is approved in the U.S. to treat Hodgkin's lymphoma and anaplastic large-cell lymphoma. At the time of the approval, the FDA had noted one case of progressive multifocal leukoencephalopathy (PML), a rare brain infection. Since the drug's approval in August 2011, there have been two additional cases of PML.

PML is a progressive, demyelinating disease of the central nervous system that often leads to death or severe disability. PML is caused by reactivation of the John

Cunningham (JC) virus, which resides in latent form in 40% to 80% of healthy adults. The reactivation is associated with immunocompromised conditions and may occur months after immunosuppressive therapy has been stopped.

Although PML in lymphoma patients can be caused by underlying disease and previous therapies that affect the immune system, the company suggests that the contributory role of brentuximab cannot be ruled out. The FDA warns that brentuximab therapy should be stopped in patients thought to have PML and should be permanently discontinued if a diagnosis of PML is made.

An updated warning in the Contraindications section of the PI states that brentuximab should not be used with bleomycin sulfate (Blenoxane, Bristol-Myers Squibb), a cancer drug, because of a risk of lung toxicity.

Sources: FDA, *Bloomberg News,* and *The Wall Street Journal*, January 13, 2012; Seattle Genetics, www.seagen.com

Tysabri and PML Test

The FDA has approved a label change for Biogen Idec and Elan's multiple sclerosis (MS) therapy natalizumab (Tysabri) to identify anti-JCV (John Cunningham virus) antibody status as a risk factor for the development of progressive multifocal leukoencephalopathy (PML). The drug label states that anti-JCV antibody–negative status indicates that exposure to the JC virus has not been detected.

The link between JC virus infection and the development of PML is high in patients who have had immunosuppressive therapy and have taken natalizumab for more than 2 years. With or without prior therapy, about 55% of MS patients are positive for anti-JCV.

The parallel approval of the Stratify JCV test enables neurologists to determine the JC virus infection status of their MS patients to aid in treatment decisions. The assay will be offered by Quest's Focus Diagnostics laboratory in the U.S.

Since 2006, natalizumab has carried a boxed warning about the increased risk of PML, the new label retains the boxed warning and adds a notification that patients who have antibodies against the JC virus are more likely to develop PML while taking natalizumab than people who don't have the antibodies.

Sources: FDA, January 20, 2012; *GEN News Highlights,* January 23, 2012

Self-Administration With Berinert

The FDA has approved a label expansion for Berinert (CSL Behring), a therapy for acute attacks of hereditary angioedema (HAE). Berinert is also indicated for treating life-threatening laryngeal HAE attacks as well as facial and abdominal attacks.

Patients with training from a physician will now be able to administer the drug themselves by IV infusion at the first sign of a HAE attack. Patients are advised to seek medical assistance right after they use the IV treatment. Enrollment in a training program is open to all patients.

HAE, a rare and potentially fatal genetic disorder caused by a deficiency of C1-INH, can cause swelling in the face, abdomen, larynx, and extremities. Berinert was approved in October 2009.

Sources: *Philadelphia Business Journal*, January 3, 2012; www.berinert.com

Vytorin Lowers Cholesterol In Patients with Kidney Disease

An updated label for ezetimibe/simvastatin (Vytorin, Merck/Schering-Plough) includes results from the Study of Heart and Renal Protection (SHARP). In this study, a dose of 10/20 mg reduced low-density lipoprotein-cholesterol (LDL-C) in patients with moderate-to-severe chronic kidney disease (CKD), and major vascular events were reduced with the drug compared with placebo.

Because SHARP was not designed to assess the independent contributions of each drug, the FDA did not approve a new indication for Vytorin or for the company's Zetia (ezetimibe), and the study's efficacy results have not been incorporated into the label for ZETIA.

Vytorin is indicated as adjunct to diet to reduce levels of total cholesterol, LDL-C, apolipoprotein B, triglycerides, and non–high-density lipoprotein-cholesterol and to increase HDL-C levels in patients with primary (heterozygous familial and nonfamilial) hyperlipidemia or mixed hyperlipidemia when diet alone is not enough.

Sources: www.pmpnews.com; the heart.org, January 25, 2012

Update: Polymyxin B, Vecuronium Bromide Recalls

Bedford Laboratories, a subsidiary of Boehringer Ingelheim, has issued updated guidelines on two products that were voluntarily recalled in August 2011:

- polymyxin B for injection USP, 500,000 units per vial. NDC #55390-139-10, lot 1942980, expiration date August 2013; lot 1895027, expiration date June 2013
- vecuronium bromide for injection, 10 mg per vial. NDC #55390-037-10, lot 1865067, expiration date May 2012
- vecuronium bromide for injection, 20 mg per vial. NDC #55390-039-10, lot 1865069, expiration date February 2012

The recalls were initiated after the discovery of visible glass particles in a few vials. Particulate matter, when injected into the bloodstream, can cause vein irritation, phlebitis, pulmonary dysfunction and granulomas, local tissue infarction, occlu- sion of capillaries and arteries, anaphylactic shock, and death. If particulate matter is introduced via the intrathecal route into cerebrospinal fluid, chemical meningitis may also result. Intro-

duction of a foreign body to the eye can cause corneal abrasions or lacerations, lacrimal gland tears, and irritation.

Polymyxin B is used to treat infections caused by susceptible strains of *Pseudomonas aeruginosa*. Vecuronium bromide is used as an adjunct to general anesthesia to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Source: FDA, January 10, 2012

Pradaxa and Heart Problems

Dabigatran (Pradaxa, Boehringer Ingelheim), which was approved in 2010 for atrial fibrillation (AF) and as a possible alternative to warfarin (Coumadin and Jantoven), may be linked to a small, increased risk of coronary problems.

In a meta-analysis of seven trials that included more than 30,000 patients, a Cleveland Clinic team found that dabigatran, an anticoagulant, was associated with an increased risk of heart attacks or acute coronary syndrome (ACS), when compared with warfarin and enoxaparin (Lovenox, Sanofi). Among patients taking dabigatran, 1.19% had a heart attack or ACS, compared with 0.79% of those taking one of the other drugs. Although there was a 33% increase in relative risk for a heart attack with dabigatran, the absolute increased risk was 0.27%.

Patients with AF are at a higher risk for stroke and often need an anticoagulant.

In the study that led to the approval of dabigatran, it was suggested that dabigatran might be linked to an increased risk of heart attacks, but the drug's benefit in AF was thought to outweigh the risk. It is possible that dabigatran might have indirect cardiac effects and might not be as effective as warfarin and aspirin in preventing heart attacks.

Some experts claimed that heart attacks were not related to dabigatran. Another expert said that the risk did not outweigh the benefit of the drug, especially when the risk of bleeding with warfarin is considered. Some specialists also prefer dabigatran because less monitoring is necessary, as with warfarin. About 10% of patients cannot tolerate dabigatran because of severe gastrointestinal side effects. Physicians should be cautious in prescribing dabigatran to those patients with known heart disease.

Sources: *Arch Intern Med* (online), *Health Day News*, Reuters, January 9, 2012

Low-Dose Aspirin Might Not Prevent a First Heart Attack

A new review suggests that low-dose aspirin therapy (81 mg daily) might not provide enough benefit to reduce the risk of dying from a first heart attack or cancer. The analysis, conducted in the United Kingdom, included nine studies and more than 102,000 participants who were observed for about 6 years. Daily low-dose aspirin resulted in a 10% reduction in heart attack or stroke, mainly driven by a reduction in nonfatal heart attacks. There was no reduction in death from heart disease, stroke, or cancer among people taking low-dose aspirin. The review also confirmed aspirin's risk of serious bleeding events.

The modest benefit for those without cardiovascular disease should be balanced against the risk of bleeding caused by the drug. Although the risk is small, the advantage in a lower-risk population might be as great as had been thought. The study results do not apply to those who already have heart disease.

Sources: *Arch Intern Med* and *Health Day News*, January 9, 2012

Do Statins Raise Diabetes Risk?

Statins, which help lower cholesterol levels, have the potential to increase the risk of type-2 diabetes. In a large observational study that tracked the health of postmenopausal women for many years, there was a modest risk among those who used various statins.

Statins can be lifesaving for patients with heart disease, but it is unclear how much they help people who don't yet have cardiovascular disease but who might have other risk factors (smoking, hypertension, or diabetes). Statins are recommended for people with at least a 10% chance of having a heart attack in the next 10 years.

The researchers evaluated the records of more than 153,000 women who did not have diabetes when they enrolled in the Women's Health Initiative in the 1990s. Only 7% were taking statins at that time. By 2005, nearly 10% of the statin users had developed diabetes, compared with 6.4% of older women who had not used the drugs at the study's start.

The benefits of statins may outweigh their potential side effects, but the drugs can cause severe muscle problems. Whether statins cause glucose levels to rise enough to lead to diabetes is unclear.

Sources: *Arch Intern Med*, January 9, 2012 (online); Associated Press, January 10, 2012

New REMS Rules For Fentanyl Pain Products

A shared Risk Evaluation and Mitigation Strategy (REMS) is now approved for transmucosal immediate-release fentanyl (TIRF) products. The new system replaces the individual REMS for each of these narcotic pain products, and prescribers and pharmacies will be able to enroll into one system.

Affected medications include fentanyl; sublingual tablets (Abstral, ProStrakan), oral transmucosal fentanyl (Actiq, Cephalon), fentanyl citrate (Fentora, Cephalon), fentanyl nasal spray (Lazanda, Archimedes Pharma US), and fentanyl buccal soluble film (Onsolis, Meda).

The TIRF REMS Access Program, scheduled to begin in March, is expected to ease the burden on the health care

system. Until then, prescribers, patients, and pharmacies should continue to enroll in the individual REMS programs.

Some of the products already have an individual REMS in place. Prescribers and pharmacies currently enrolled in an individual REMS program for at least one TIRF product will automatically be transitioned to the shared TIRF REMS Access Program.

Health care professionals who prescribe TIRF drugs that are used only in hospitals, hospices, or long-term care facilities, as well as patients who receive TIRF drugs in an inpatient setting, will not have to enroll in the TIRF REMS program. Long-term-care and hospice patients who obtain their medications from outpatient pharmacies must still enroll in the new program.

Source: FDA, December 29, 2011

DEVICE NEWS

Risks of Reused Devices

Some medical devices (clamps, forceps, endoscopes, bronchoscopes, and colonoscopes) are reused repeatedly in surgical and diagnostic procedures. The FDA is taking steps to ensure that the instruments and devices are safely reused and is working to reduce the risk of infection resulting from inadequate reprocessing (disinfecting and sterilizing). The agency also wants to ensure that all clinicians understand reprocessing instructions.

Source: FDA, December 28, 2011

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: AtriCure Synergy Ablation System

Manufacturer: AtriCure, Inc., Cincinnati, Ohio

Approval Date: December 16, 2011

Purpose: The ablation system is used to treat persistent and longstanding atrial fibrillation (AF) in patients undergoing concomitant coronary artery bypass graft (CABG) surgery and/or valve replacement or valve repair. The device is used to ablate heart tissue that is beating abnormally.

Description: A hand-held clamp destroys the heart tissue, which is grasped between the clamp's jaws during open-heart surgery. A generator delivers radiofrequency (RF) to the clamp during ablation. Scars are created in a specific pattern on the upper chambers of the heart.

When the clamp is placed in a desired location on the heart, the surgeon begins delivering RF energy by pressing a foot switch. The RF energy flows through the electrodes in the clamp, heating the heart tissue held by the clamp, and creating a scar on the heart tissue that is the shape of the clamp.

Benefit: The creation of scars blocks the abnormal electrical conduction in the heart that causes AF. In a clinical study, the procedure was effective in treating AF in 37 of 50 patients for 6 months. The FDA's approval, which was based on results from the ABLATE study, includes a physician training program and the implementation of a 350-patient post-approval study, in which 46 patients had enrolled as of December.

Precaution: The AtriCure System should not be used for sealing blood vessels during contraceptive surgery of the fallopian tubes.

Sources: http://ir.atricure.com; www.theheart.org; www.fda.gov

Name: Ingenuity TF Whole Body PET/MR Imaging System

Manufacturer: Philips Healthcare, Guildford, Surrey, United Kingdom

Approval Date: November 28, 2011

Purpose: The device, which combines positron emission tomography (PET) and magnetic resonance imaging (MRI), has the potential to enhance the field of diagnostic body imaging.

Description: The system provides MRI alone as well as hybrid PET/MR scanning. The patient table rotates between each mode, allowing flexibility and eliminating the need for multiple scanners. This imaging system also saves space needed to house the equipment. Time-of-flight technology enhances image quality by reducing noise and providing increased sensitivity. Superior soft-tissue contrast is used to visualize disease proliferation.

Benefit: PET and MRI are combined to produce high-fidelity diagnostic images. The system can superimpose PET scans over MR images to detect abnormalities. This capability had not been possible because the two previously incompatible imaging studies took place at different times, with different conditions, and with different patient positions. The new system should prove useful in supporting patient care cycle from detection and diagnosis through long-term disease management.

The program to develop a combined PET/MR system was formally launched in 2007. Philips was the first company to bring the combined system to market, earning the CE Mark in Europe in January 2011. Mount Sinai and University Hospitals/Case Western Reserve University are scheduled to be the first institutions to receive the device in the U.S.

The Wall Street Journal selected the Ingenuity system as a 2011 runner-up in the medical device category for its annual Technology Innovation Awards.

Source: www.medicalnewstoday.com/articles/238318.php

Device Recalls

AVEA Ventilator. The FDA has notified health care professionals of a class I recall of CareFusion's AVEA ventilators. There is a potential for failure if the ventilator activates a false extended high-

continued on page 98

continued from page 79

peak alarm, opens the safety valve, and stops ventilating. Without the intervention of a health care professional, life-threatening injury or death could occur. The device is used for continuous breathing support in patients of all ages (neonates through adults) who require mechanical ventilation. The recalled ventilators were manufactured between March 1, 2009, and June 30, 2011.

If any ventilators exhibit a sustained extended high peak alarm, followed by the opening of the safety valve, customers have been instructed to remove the device from service, provide alternative ventilation, and contact CareFusion Technical Support at 1-800-231-2466.

Source: FDA, December 23, 2011

INOmax DS Drug Delivery System.

This device is used with ventilators to deliver a preset concentration of nitric oxide for inhalation by critically ill individuals. In an investigation conducted by Ikaria in April 2010, it was learned that fretting corrosion (or micromovement at the electrical contact interface of non-noble metals such as tin) was the cause of erratic nitric oxide monitoring readings during delivery of nitric oxide to patients. Adverse consequences may include hypoxia, hypotension, bradycardia, cardiac arrest, organ damage, acute respiratory distress syndrome, neurological deficits, or death.

Serial numbers include DS20070005 through DS20100865. The product was made from March 12, 2007, through February 2, 2011, and distributed from September 4, 2007, through February 2, 2011.

On December 22, 2011, Ikaria advised health care professionals about the completion of this recall and stated that no further action was necessary. Ikaria implemented a service process change involving the application of Deox-IT, an anti-corrosion lubricant.

Sources: FDA, January 4, 2012; www.inomax.com, www.ikaria.com ■