**NEW DRUGS**

**Pandemic H5N1 Vaccine**

The FDA has approved GlaxoSmithKline’s pandemic Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted (Q-Pan H5N1 influenza vaccine) for the immunization of adults 18 years of age and older. The vaccine is composed of monovalent, inactivated, split A/H5N1 influenza virus antigen and an AS03 adjuvant. In clinical studies, the adjuvanted formulation stimulated the required immune response with a smaller amount of antigen compared with a formulation that lacked the adjuvant.

GlaxoSmithKline will make this vaccine available in the U.S. only if it is directed by the U.S. Department of Health and Human Services’ Office of the Assistant Secretary for Preparedness and Response.

The vaccine is also approved in Europe as Pumarix and in Canada as Arepanrix H5N1.

Source: FDA, November 25, 2013

**Velphoro for High Phosphorus Levels in Chronic Kidney Disease**

Sucroferric oxyhydroxide (Velphoro, PA21) has received the FDA’s approval for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) who are being treated with dialysis. In trials, the drug controlled hyperphosphatemia with fewer pills (3.3 pills per day) after 52 weeks compared with sevelamer carbonate, the current standard of care in patients with CKD on dialysis.

The recommended starting dose of Velphoro is three tablets per day.

Velphoro, an iron-based, calcium-free, chewable phosphate binder, was developed by Vifor Pharma. In 2011, all rights were transferred to Vifor Fresenius Medical Care Renal Pharma, a company of Galenica and Fresenius Medical Care.

In the U.S., Velphoro will be marketed by Fresenius Medical Care North America. The active ingredient is produced by Vifor Pharma in Switzerland. Velphoro will be launched in the U.S. by Fresenius Medical Care North America in 2014.

Source: Galenica, November 28, 2013

**Two Approvals for HCV Infection Olysio**

Simeprevir (Olysio, Janssen) was approved in a priority review for the treatment of chronic hepatitis C virus (HCV) infection in adults with compensated liver disease, including cirrhosis, who had not received treatment or for those who did not respond to previous treatment.

HCV causes inflammation of the liver that can lead to diminished liver function or liver failure. According to the Centers for Disease Control and Prevention, about 3.2 million Americans have the infection.

Simeprevir, a protease inhibitor, blocks a protein needed by HCV to replicate. It is intended to be used as part of a combined antiviral treatment regimen. In clinical studies, it was evaluated in combination with peginterferon-alfa and ribavirin.

Boceprevir (Victrelis, Merck) and telaprevir (Incivek, Vertex) are also approved for the treatment of HCV infection.

Source: FDA, November 22, 2013

**Varithena for Varicose Veins**

Polidocanol injectable foam (Varithena, BTG) is approved for patients with incompetent veins and visible varicosities of the great saphenous vein system. Formerly known as Varisolve PEM, this pharmaceutical-grade, low-nitrogen polidocanol foam is dispensed from a canister. The product is designed to dissolve the veins as an alternative to surgery.

It took more than a decade for Varithena to win the FDA’s approval, because BTG was required to address concerns that the active agent in polidocanol could enter the bloodstream.

Varithena was tested in two pivotal, phase 3 trials (VANISH-I and VANISH-2). This is the only approved therapy that improved the patient’s symptoms and appearance for varicose veins both above and below the knee. The treatment is minimally invasive, and neither tumescent anesthesia nor sedation is required.

Sources: BTG and Reuters, November 26, 2013

**Esomeprazole Strontium Delayed-Release Capsules**

Amneal Pharmaceuticals LLC has launched Esomeprazole Strontium 49.3-mg delayed-release capsules. This brand-name drug contains the same active moiety (esomeprazole) in a different salt form as is found in AstraZeneca’s proton-pump inhibitor Nexium (esomeprazole magnesium). The medication is indicated for the short-term treatment of gastroesophageal reflux disease (GERD) in adults.

Amneal is selling the 505(b)(2) product in the U.S. under an exclusive license and distribution agreement with Hanmi Pharmaceutical Co. Ltd. of South Korea.

Each 49.3-mg capsule provides the equivalent of 40 mg of esomeprazole base, an equivalent amount of esomeprazole that is present in the corresponding Nexium dose. Amneal’s capsules are sold
Anoro Ellipta for COPD

The FDA has approved Anoro Ellipta (umeclidinium and vilanterol inhalation powder) for the once-daily, long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Developed by GlaxoSmithKline, the medication helps the muscles around the airways of the lungs stay relaxed to increase airflow. COPD is the third leading cause of death in the U.S.

A boxed warning states that long-acting beta-2-adrenergic agonists (LABAs) increase the risk of asthma-related deaths. Anoro Ellipta is not approved for the treatment of asthma, and it should not be used as a rescue therapy to treat acute bronchospasm.

A patient medication guide includes instructions for use and information about the potential risks of taking the drug. Anoro Ellipta may cause paradoxical bronchospasm, cardiovascular effects, acute narrow-angle glaucoma, and worsening of urinary retention.

Source: FDA, December 18, 2013

Generic Approvals

Cabergoline to Prevent Lactation

Mylan Pharmaceuticals, Inc., has launched cabergoline tablets USP, 0.5 mg, for the treatment of hyperprolactinemic disorders, which can be idiopathic or caused by pituitary adenomas. The drug is the equivalent of Dostinex (Pfizer).

Cabergoline is a dopamine receptor agonist that prevents the onset of lactation during the puerperium (the 6-week period after childbirth) for certain medical reasons, such as the birth of a stillborn baby, neonatal death, conditions that interfere with breastfeeding, or acute or chronic mental illness or medical conditions, and maternal disease in which the mother’s medications might be excreted through breast milk. The tablets are not indicated for suppressing already established postpartum lactation.

Source: Mylan, December 5, 2013

Fenofibric Acid for Lipid Disorders

Lupin has launched its generic fenofibric acid delayed-release capsules 45 mg and 135 mg. The capsules are the generic equivalent of Trilipix Delayed-Release Capsules 45 mg and 135 mg, made by AbbVie.

The medication is taken with statins for the treatment of mixed dys-lipidemia, severe hypertriglyceridemia, and primary hypercholesterolemia or mixed dyslipidemia.

Source: Lupin, December 6, 2013

Abacavir/Lamivudine/Zidovudine For HIV Infection

Lupin has received approval to sell abacavir sulfate/lamivudine/zidovudine tablets, 300 mg (base)/150 mg/300 mg. This is the generic version of ViIV Healthcare’s Trizivir. The tablets are used with other antiretrovirals or alone for the treatment of HIV-1 infection. Lupin was the first applicant to file an Abbreviated New Drug Application (ANDA) for Trizivir tablets and will be entitled to 180 days of marketing exclusivity.

Source: Lupin, December 11, 2013

Delayed-Release Duloxetine For Depression

The FDA has approved the first generic versions of Cymbalta (duloxetine delayed-release capsules) for patients with depression and other conditions. Aurobindo, Dr. Reddy’s Laboratories, Lupin, Sun Pharma, Teva, and Torrent may now sell duloxetine in various strengths.

Duloxetine and other antidepressant drugs have a boxed warning describing the increased risk of suicidal thinking and behavior during initial treatment in children, adolescents, and young adults 18 to 24 years of age.

Patients starting therapy with these agents should be closely monitored. Duloxetine must be dispensed with a patient medication guide.

Source: FDA, December 11, 2013

NEW INDICATIONS

Nexavar Approved to Treat Late-Stage Thyroid Cancer

Sorafenib (Nexavar, Bayer/Onyx) is now approved to treat metastatic differentiated thyroid cancer. Sorafenib works by inhibiting multiple proteins in cancer cells, limiting cancer cell growth and division. The drug’s new use is intended for patients with locally recurrent or metastatic, progressive differentiated thyroid cancer that no longer responds to radioactive iodine treatment. In a clinical study, sorafenib increased progression-free survival by 41%.

The FDA completed its review of the new indication under its priority review program.

Sorafenib was approved in 2005 to treat advanced kidney cancer in 2005. In 2007, the drug’s label was expanded to treat inoperable liver cancer.

Source: FDA, November 22, 2013
**Xiaflex for Peyronie’s Disease**

Auxilium’s Xiaflex (collagenase *Clostridium histolyticum*) is the first FDA-approved drug for men with a curvature of the penis known as Peyronie’s disease. The condition is caused by scar tissue that develops under the skin of the penis. This scar tissue causes an abnormal bend during erection. Xiaflex, a biologic, is made from the protein product of a living organism.

The FDA first approved Xiaflex in 2010 for the treatment of Dupuytren’s contracture, a progressive hand disease that prevents patients from straightening and properly using the fingers.

It is thought that Xiaflex breaks down the buildup of collagen that causes the curvature deformity. The treatment consists of a maximum of four cycles. Each treatment cycle consists of two Xiaflex injections and one penile modeling procedure performed by a health care professional.

When prescribed for Peyronie’s disease, Xiaflex is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

Source: FDA, December 6, 2013

**NEW FORMULATION**

**Noxafil Delayed-Release Tablets For Fungal Infections**

A delayed-release formulation for posaconazole (Noxafil, Merck) 100 mg has been approved. Patients take a loading dose of 300 mg (three 100-mg delayed-release tablets) twice daily on the first day, followed by a once-daily maintenance dose of 300 mg (three 100-mg delayed-release tablets) starting on the second day of therapy. A 40-mg/mL oral suspension is also available and is taken three times daily.

The tablets and the oral suspension are indicated for preventing invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older with a severely compromised immune system. The tablets are not interchangeable with the oral suspension because of dosage differences in the formulations.

Source: Merck, November 26, 2013

**DRUG NEWS**

**Fewer Restrictions for Avandia**

The FDA is requiring the removal of certain restrictions that were imposed on the diabetes drug rosiglitazone (Avandia, GlaxoSmithKline) to reflect new information regarding cardiovascular risk.

Results from the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) clinical trial showed no elevated risk of heart attacks or deaths with rosiglitazone compared with standard-of-care diabetes drugs. A meta-analysis of clinical trials first reported in 2007 had indicated an increased risk of heart attacks.

Certain prescribing restrictions regarding cardiovascular safety, the REMS program, and a postmarketing study requirement are being eliminated. After the changes are made, rosiglitazone can be prescribed for more patients than previously. The FDA anticipates that the new indication will be similar to that of other currently available diabetes drugs.

Physicians, pharmacists, and patients will not have to enroll in the REMS program to prescribe, dispense, or receive rosiglitazone, and patients will be able to buy it at retail stores and through mail-order pharmacies. Health care providers who are likely to prescribe drugs containing rosiglitazone must receive up-to-date training.

GlaxoSmithKline will not have to conduct a postmarketing trial, known as Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE), to compare rosiglitazone with pioglitazone (Actos, Takeda/Eli Lilly).

Rosiglitazone is available alone and in combination with metformin (Avandamet) and with glimepiride (Avandaryl).

Source: FDA, November 25, 2013

**Warning: Skin Reactions From Clobazam**

The antiseizure drug clobazam (Onfi, Lundbeck) carries a small risk of severe skin reactions, and the label is being revised to reflect this risk.

Twenty patients worldwide, including six in the U.S., developed Stevens–Johnson syndrome or toxic epidermal necrolysis after taking clobazam. One patient lost all vision as a result, and all 20 patients had to be hospitalized. Five of the patients were children. In all but one case, patients were taking multiple drugs, mostly other antiseizure medications but also antibiotics and sulfasalazine.

Clobazam is indicated as an adjunctive therapy for seizures associated with Lennox–Gastaut syndrome in adults and children as young as 2 years of age. The drug is a benzodiazepine, but other benzodiazepines have not been associated with this problem.

Patients should be monitored for skin reactions, especially during the first 8 weeks of therapy. The new label emphasizes that clobazam therapy be stopped at the first sign of a skin rash unless the rash is proven to be unrelated to therapy.

The patient medication guide will include instructions to seek immediate evaluation if skin peeling, rashes, hives, or blisters develop.

Source: FDA and MedPage Today, December 3, 2013

**Fast-Track Designations**

**CERC-301 for Major Depression**

CERC-301 (Cerecor, Inc.) is a once daily, oral, adjunctive, selective NMDA receptor subunit 2B (NR2B) antagonist. It is designed to treat major depressive disorder (MDD) in patients who have not adequately responded to their therapy and who report recent suicidal ideation.

continued on page 25
CERC-301 has the potential to be a first-in-class oral medication that is complementary to existing treatments that have not elicited an adequate response. Cerecor has initiated a 135-patient phase 2 clinical study of CERC-301 as an adjunctive treatment for subjects with MDD. Results are expected by year-end 2014.

Source: Pharma e-Track, November 26, 2013

VB-111 for Brain Cancer

VB-111 (VBL Therapeutics) is being studied for its ability to prolong survival in patients with recurrent glioblastoma multiforme (rGBM). GBM is an aggressive form of brain cancer that carries a poor prognosis with current therapy. VB-111 was already granted orphan drug status for GBM in the U.S. and in Europe.

Given as an intravenous (IV) infusion, this gene-therapy drug targets endothelial cells in the tumor vasculature and acts as a “biological knife.” This is the first agent based on transcriptional targeting of tumor endothelium to be assessed in a clinical trial.

VB-111 is also being evaluated in multidose phase 2 clinical trials for differentiated thyroid cancer and ovarian cancer.

Source: Pharma e-Track, November 27, 2013

Orphan Drug Designations

Cer reproduction.

CMC-001, a Contrast Agent in MRI

CMC Contrast AB is developing a targeted contrast agent, CMC-001, for use in magnetic resonance imaging (MRI). CMC-001 is designed to detect and localize focal liver lesions in patients who cannot receive gadolinium-based contrast agents. For these patients, including those with severe chronic renal insufficiency, important diagnostic information may be missed because of a lack of contrast-enhanced MRI.

The company is planning a phase 3 clinical program in conjunction with completed phase 1 and 2 studies.

Source: Pharma e-track, November 27, 2013

VRS-317 for Growth Hormone Deficiency

VRS-317 (Versartis, Inc.) is a drug candidate that is intended to be used once monthly for patients with growth hormone deficiency. This fusion protein consists of recombinant human growth hormone and the all-natural hydrophilic amino acids, referred to XTEN. This product should promote better compliance and convenience, fewer adverse effects, and enhanced administration of a liquid formulation via a fine-gauge needle.

Source: Versartis and Pharma e-Track, December 18, 2013

MG01CI for Fragile X Syndrome

Sustained-release metadotexine (MG01CI, Alcobra Ltd.) is used to treat cognitive dysfunction in patients with Fragile X syndrome. Positive results in cognitive and social functioning were achieved in a preclinical study of an animal model. The study was funded in part by the FRAXA Research Foundation.

Source: Pharma e-Track, December 18, 2013

OMS721 for Prevention Of Thrombotic Microangiopathy

OMS721 (Omeros) Corp.) is a human monoclonal antibody that targets mannamin-binding lectin-associated serine protease-2 (MASP-2), the key regulator of the lectin pathway of the immune system. Given by subcutaneous injection, the medication is designed to prevent complement-mediated thrombotic microangiopathies (e.g., atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura). By targeting MASP-2, OMS721 blocks the lectin pathway.

Source: Pharm e-Track, December 18, 2013

IMMU-132 for Small-Cell Lung Cancer


IMMU-132 contains the humanized anti-TROP-2 antibody, hRS7, conjugated by a pH sensitive linker to SN-38. TROP-2 is expressed by many human tumors but with only limited expression in normal human tissues. hRS7 internalizes into cancer cells following binding to TROP-2, making it a suitable candidate for the delivery of cytotoxic drugs.

SN-38 is the active metabolite of irinotecan (Camptosar, Pfizer), a standard therapy for patients with metastatic colorectal cancer, but it is associated with gastrointestinal and hematological toxicity.

By attaching SN-38 to tumor-targeting antibodies, delivery of SN-38 to the tumor may be increased several-fold while lessening systemic toxicity.

Source: Immunomedics, Inc., December 4, 2013

Emricasan in Liver Transplantation

Emricasan (Conatus Pharmaceuticals) is designed to treat liver transplant recipients with re-established fibrosis to delay the progression to cirrhosis and end-stage liver disease. This first-in-class, orally active caspase protease inhibitor is intended to reduce the activity of enzymes that mediate inflammation and cell death in patients with chronic liver disease.

Source: Pharma e-Track, December 3, 2013

KX02 for Brain Gliomas

Kinex Pharmaceuticals is testing KX02 for the treatment of gliomas, an aggressive form of brain cancer. A dual src/
pre-tubulin inhibitor, KX02 is a small-molecule drug that has potent inhibitory activity against a broad panel of brain tumor cell lines, including those that are resistant to temozolomide (Temodar, Merck, T98G).

Temozolomide is the most widely used chemotherapy for malignant gliomas. In an animal model, KX02 eliminated brain tumors in 30% to 60% of animals after 4 weeks of therapy, induced more necrosis, and generated an immune response to the glioblastoma tumor cells. KX02 is absorbed orally and has 76% penetration into brain tissue from plasma.

A phase 1 trial is planned.
Source: Kinex, December 4, 2013

**Infectious Disease Product Designation Isavuconazole for Aspergillosis**

The FDA has designated isavuconazole (isavuconazonium sulfate, Astellas) as a Qualified Infectious Disease Product (QIDP) for the treatment of invasive aspergillosis. QIDP status provides priority review and a 5-year extension of market exclusivity if a product receiving this designation is approved in the U.S.

The possibility of a 5-year extension is in addition to the potential 7-year exclusivity based on isavuconazole’s FDA orphan drug designation in invasive aspergillosis. In the U.S., isavuconazole also received an orphan drug designation for the treatment of zygomycosis.

Isavuconazole is a once-daily IV and oral broad-spectrum antifungal agent with potential for treating severe invasive and life-threatening fungal infections. Isavuconazole is being co-developed with Basilea Pharmaceutica Ltd.

Source: Astellas, December 3, 2013

**New Vials For Acetylcysteine Solution**

Fresenius Kabi USA has launched Acetylcysteine Solution, USP, 20% in 10-mL vials for inhalation as a mucolytic agent or as an oral medication to be used as an antidote for acetaminophen. This solution, USP, has been on the FDA’s and the American Society of Health-System Pharmacists’ drug shortage lists since 2011.

In 2012, Fresenius Kabi introduced a 20% concentration in 30-ml vials, and earlier this year, the company also launched acetylcysteine injection, the therapeutic equivalent to Cumberland’s Acetadote.

Acetylcysteine is used as adjuvant therapy for patients with abnormal mucous secretions in such conditions as chronic and acute bronchopulmonary disease, pulmonary complications of cystic fibrosis, and atelectasis caused by mucous obstruction. It is also used in tracheotomy care, in pulmonary complications of surgery, during anesthesia, in diagnostic bronchial studies, and in post-traumatic chest conditions.

Source: Pharma e-Track, December 16, 2013

**Evolocumab Lowers LDL-Cholesterol Levels**

Positive results have been reported for Amgen’s evolocumab from a phase 3 study called MENDEL-2 (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2). Patients in the trial experienced reduced levels of low-density lipoprotein-cholesterol (LDL-C).

Evolocumab is an investigational human monoclonal antibody designed for the treatment of hyperlipidemia. The drug inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), a protein that reduces the liver’s ability to remove LDL-C from the blood.

According to the Centers for Disease Control and Prevention (CDC), more than 71 million adults in the U.S. have high levels of LDL-C, which is considered a major risk factor for cardiovascular disease.

Source: Amgen, December 17, 2013

**A Negative BRCA Test May Still Suggest Breast Cancer Risk**

Women who have relatives with BRCA2 genetic mutations, but who test negative for the family-specific BRCA2 mutations themselves, may be at greater risk for the development of breast cancer compared with women in the general population who do not have family members with the mutation.

Women with certain mutations in their BRCA1 or BRCA2 genes are at increased risk for breast cancer. If a woman whose relatives have the mutated BRCA gene has negative test results for her family-specific BRCA mutation, her risk for breast cancer has been considered to be the same as someone in the general population. The new study, however, suggests women who test negative for family-specific BRCA2 mutations have more than four times the risk for breast cancer than those in the general population.

According to Dr. Gareth Evans from the United Kingdom, it is likely that these women inherit genetic factors other than BRCA-related genes that increase their risk. He explained that about 77 single nucleotide polymorphisms (SNPs), or genetic variations that can help track the inheritance of disease genes within families, are linked to the risk.

Identifying additional SNPs is necessary to understand why some of the BRCA-negative women from BRCA families are at higher risk.

The authors suggested that specialists use caution when informing a woman that her risk is the same as that of the general population after a negative genetic test. The National Institute for Health Research funded the study.

Source: American Association for Cancer Research, Cancer Epidemiol Biomarkers Prev, November 27, 2013

*continued on page 32*
ADHD Drugs and Priapism

The FDA has warned that methylphenidate, a type of stimulant drug used to treat attention-deficit/hyperactivity disorder (ADHD), may in rare instances cause prolonged penile erections (priapism). The agency has updated the drug labels and patient medication guides to include information about this risk. Patients who develop erections lasting longer than 4 hours should seek medical treatment right away to prevent permanent damage to the penis.

In the FDA’s review, the median age of patients who took a methylphenidate product and experienced priapism was 12.5 years (range, 8 to 33 years). Priapism also occurred after the dose was increased and at other times.

The non-stimulant drug atomoxetine (Strattera) has also been associated with priapism in young children, teenagers, and adults. Priapism appears to be more common with atomoxetine than with methylphenidate.

The FDA has also received reports of priapism in four patients taking an amphetamine product. However, it is not clear whether the amphetamine products caused the priapism, because all of these patients had been taking other drugs that could have caused it.

Source: FDA, December 18, 2013

Vaccine Improves Survival In Patients With Brain Cancer

In a phase 2 study, more than 90% of patients with glioblastoma multiforme who received a vaccine called Prophage Series G-200 (Agenus, Inc.) were alive 6 months after surgery and 30% of patients were alive at 12 months. Median overall survival was approximately 11 months.

Glioblastoma multiforme is the most common and most aggressive form of primary brain cancer. Prophage Series vaccines are currently being studied in both newly diagnosed and recurrent forms of the cancer.

The vaccines are made using a patient’s own tumor after surgical removal. Each vaccine contains the antigenic “fingerprint” of the patient’s specific cancer and is designed to activate the patient’s immune system to target and destroy cancer cells bearing this fingerprint. Prophage Series G-200 is a heat-shock protein–based therapeutic vaccine.

The phase 2 trial enrolled 41 patients with surgically resectable recurrent high-grade glioblastoma multiforme. Patients underwent surgery to remove at least 90% of the tumor. After surgery, eligible patients received the vaccine once weekly for 4 weeks, followed by biweekly injections until the vaccine was depleted. No serious adverse events were associated with the vaccine’s administration.

Sources: Neuro-Oncology, December 12, 2013 (online); Agenus, December 16, 2013

FDA and EMA Launch Joint Initiative for Generic Drugs

The FDA and the European Medicines Agency (EMA) plan to work together on a joint initiative to share information on inspections of bioequivalence studies submitted in support of generic drug approvals. This collaborative effort provides a way to conduct joint facility inspections for both agencies.

Studies submitted for generic drug applications must prove that a generic drug performs in the same manner as a brand-name drug. The FDA and the regulatory authorities in the European Union (EU) inspect facilities conducting these studies to ensure that the data submitted to the agencies are reliable.

Taking part in this initiative are the EMA and the EU member states France, Germany, Italy, the Netherlands, and the United Kingdom. Streamlining the inspection process for generic drug applications should help consumers gain access to safe and effective generic drugs.

Source: FDA, December 18, 2013

Optimal Antimicrobial Dosages For Heavier Patients

Does a patient’s weight affect the efficacy of antimicrobial drugs? Weight can affect hydrophilic drugs such as vancomycin (Vancocin), for instance, because adipose tissue is 30% water. Moreover, giving the right dose may be even more important in overweight patients, who may be at a higher risk for nosocomial infections, compromised healing, and impaired circulation.

Researchers at Creighton University in Omaha, Nebraska, and at Methodist Hospital in Rochester, Minnesota, point out that clinical studies often exclude patients who are overweight or obese, a practice that limits the amount of pharmacokinetic and pharmacodynamic information available. This omission makes choosing the best dose for patients with serious infections much more difficult.

The researchers analyzed results from two clinical trials of 1,079 patients with complicated skin and skin-structure infections (cSSSIs) or nosocomial pneumonia. The patients were randomly assigned to receive a fixed dose of intravenous (IV) linezolid or weight-based vancomycin (15 mg/kg every 12 hours). They were divided into quartiles according to weight (Q4 for the highest, 97 to 295 kg for the cSSSI cohort, and 88 to 215 for the NP cohort).

Overall, linezolid was safe and effective at 600 mg orally or IV every 12 hours for both cSSSIs and nosocomial pneumonia caused by methicillin-resistant Staphylococcus aureus (MRSA), regardless of the patient’s weight. Success rates were similar for vancomycin-treated patients in all weight quartiles. However, clinical suc-
cess rates for vancomycin patients with cSSSIs were significantly lower compared with linezolid in the highest-weight quartile (70% vs. 86%) but remained similar among patients with nosocomial pneumonia.

The mean vancomycin trough concentrations at day 3 were higher in the heaviest patients, compared with the lower quartiles, and trough concentrations were higher at day 7 compared with day 3 for all quartiles. Other than the second quartile at day 3, vancomycin levels were within the therapeutic range recommended by the Infectious Diseases Society of America. Those data suggest that the weight-associated decline in efficacy with vancomycin was not related to a decrease in drug concentrations.

Among the patients with pneumonia, the highest vancomycin trough was in the higher-weight quartiles, reaching the higher threshold at day 6; however, the outcome in the top quartile, compared with the bottom quartile, did not differ significantly. This suggests that the weight-based algorithm might have a threshold of effectiveness related to weight; that is, lower-weight patients might be receiving insufficient doses, or actual weight might not be the most effective dosing parameter.

The Q1 patients (weight, 40 to 63 kg) with pneumonia had the least clinical success with vancomycin. Lower weight could be a proxy for other factors, such as older age and overall debilitation; evidence is mounting that low weight may be a risk factor for acquiring infections and having poorer outcomes.

Adverse events were consistent with the known safety profiles of each drug regardless of weight quartile.

Limitations to this analysis included a lack of data on patient height. The researchers also could not not able to calculate body mass index (BMI), compare body mass, or distinguish fat mass from lean. Yet they wrote that guidance was scarce regarding a standardized dosing regimen and the parameters to consider for patients with varying weights (e.g., lean body weight, total body weight, BMI).

The weight analysis also did not consider sex differences. Despite the limitations, the team concluded that their analysis provided added evidence about the impact of weight on treatment outcomes.

Source: Clin Ther 2013;35:1557–1570 (November)

Misuse of Antiarrhythmic Drugs

More than one-third of the antiarrhythmic drugs that are prescribed for cardiac disease are not being used according to guideline recommendations, say researchers from Duke Clinical Research Institute in Durham, North Carolina.

Commercial health claims were used to categorize patients into guideline-established groups based on their most serious concurrent heart disease: heart failure, coronary artery disease (CAD), hypertension, and no heart disease.

Of 78,877 patients with a prescription for at least one antiarrhythmic agent, most received one drug, 12% received two drugs, and 2% received three or more drugs. The median time from the first inpatient or outpatient encounter for the diagnosis of atrial fibrillation (AF) to the first prescription claim for an antiarrhythmic drug was 29 days (range, 9–89 days).

In the patients with heart failure and CAD, 45% and 31% of antiarrhythmic drugs were inconsistent with first-line or second-line recommendations, respectively. Only 55% of these agents, such as amiodarone (Cordarone, Pfizer) and dofetilide (Tikosyn, Pfizer), when used in patients with AF and heart failure conformed to recommendations. The use of sotalol (e.g., Betapace [Berlex/Bayer; Sotalex and Sotacor [Bristol-Myers Squibb]), dronedarone, propafenone (Rythmol, GlaxoSmithKline), and flecainide (Tambocor, 3M) did not conform to the recommendations.

Among patients with CAD, only 40% of antiarrhythmic drug use (sotalol, dronedarone, and dofetilide) conformed to first-line recommendations. Propafenone and flecainide, which are not recommended for patients with CAD, accounted for 31% of antiarrhythmic drug use.

Among patients with hypertension, all high-use antiarrhythmic drugs were consistent with guidelines. Of the 81,891 patients with AF who did not have heart failure, CAD, or hypertension, 19% received these drugs (usually flecainide, propafenone, and sotalol), all of which are acceptable according to clinical practice guidelines.

The study raised several concerns, such as the high use of dronedarone. As the first study to address how dronedarone, introduced in 2009, is being used in the U.S., it provides an early picture of a drug that has since been reported to have safety problems. Dronedarone was available only for the first third of the study period, but it accounted for 9% of all antiarrhythmic drug use in patients with heart failure or CAD, 8% in patients with hypertension, and 6% in patients without the selected cardiac diseases.

Although this study provides only a snapshot of antiarrhythmic drug use based on claims data, the high rates of nonconformity are a concern. Much of the recent focus has been on evaluating and comparing a rate-control versus rhythm-control strategy, with relatively little attention given to comparing the specific drugs used in those strategies. The authors concluded that the extensive use of potentially inappropriate antiarrhythmic drugs highlights the need for more detailed analyses, especially for patients with concomitant heart failure and CAD.

Source: Am Heart J 2013;166:871–878 (November)
NSAIDs May Reduce Depression

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to treat the pain and inflammation of osteoarthritis, but they may have another effect: relieving depression.

Depression is two to three times more prevalent in patients with osteoarthritis. Recent research has suggested that NSAIDs—via an association between cytokine release and prostaglandin synthesis in depression—may have a role to play. For instance, studies have shown a benefit of NSAIDs as augmentation therapy in patients taking concurrent antidepressant therapy.

Five trials enrolled 1,497 patients with osteoarthritis who were taking NSAIDs. Each trial was 6 weeks long, double-blind, and placebo-controlled. Patients were randomly assigned to receive placebo, ibuprofen 800 mg three times daily, naproxen (e.g., Naprosyn or Anaprox) 500 mg twice daily, or celecoxib (Celebrex, Pfizer) 200 mg daily. All patients were screened at baseline for depression using the Patient Health Questionnaire-9 (PHQ-9) and were assessed at weeks 2 and 6. The outcome measured was a change in PHQ-9 scores at week 6 or early termination.

At baseline and week 6, median PHQ-9 scores were similar in all three groups (for placebo, ibuprofen and naproxen, and celecoxib). After 6 weeks of treatment, there was a significant trend toward lower scores among patients taking ibuprofen or naproxen (~0.31) and celecoxib (~0.61). There was also a trend toward significant treatment effect of all NSAIDs compared with placebo.

Although the findings are intriguing and suggest a connection between depression and inflammation, the researchers do not recommend routine population-based screening for depression and the prophylactic use of NSAIDs in individuals at high risk. However, they do underscore the importance of NSAIDs in osteoarthritis, especially because the benefits may go beyond reducing inflammation.

Source: *Am J Med* 2013;126:1017.e11–1017.e18 (November)

Drugs That Improve Cognition

There’s no gold standard list of drugs that affect cognition in cognitively normal older adults, say researchers from St. Louis, Missouri. This means that physicians and pharmacists must rely on prescribing guides, such as the Beers criteria, which are based on consensus but lack supporting data. As a first step in addressing this lack of knowledge, the researchers examined the long-term effects of the top 100 medications used by 4,414 participants in the National Alzheimer’s Coordinating Center database. They found that roughly 10% of those drugs were associated with long-term changes in cognition.

The researchers divided the patients into four groups: Group 1 did not take the drug at visit 1 but took it at visit 2, Group 2 stopped taking the drug, Group 3 did not take it, and Group 4 took the drug at both visits. Composite scores were constructed from 10 psychometric tests. The researchers looked at change in cognition from the baseline visit to the follow-up visit, as well as changes in, or maintenance of, the use of each medication. The average time between assessments was 1.2 years.

Nine drugs were associated with a statistically significant difference between at least two of the four study groups. Naproxen (e.g., Naprosyn, Anaprox), calcium with vitamin D, ferrous sulfate, potassium chloride, flax, and sertraline (Zoloft, Pfizer) were all associated with improved psychometric performance. Bupropion (Buspar, Bristol-Myers Squibb), oxybutynin (Oxytrol, Actavis), and furosemide (Lasix, Sanofi) were associated with declines. Ferrous sulfate was associated with changes in attention, processing speed and episodic memory. The other eight drugs were associated mainly with changes in attention and processing speed.

Medications that improved cognition did so by a variety of proposed mechanisms. Naproxen might have improved scores by relieving pain, which can impede performance. Vitamin D deficiency is linked to reduced cognition in older adults, and ferrous sulfate is used to treat anemia; correcting those deficiencies may have helped cognition.

Potassium chloride is used to treat or prevent hypokalemia, which can lead to confusion and cognitive problems. In this study, those stopped taking potassium showed drops in change scores compared with those who continued taking it.

Flax was an outlier; the researchers were puzzled by its connection to better cognition. They did note, however, that people taking flax seed were also usually taking a calcium–vitamin D supplement. They speculated the patients taking potassium might also be taking other medications or supplements that improve cognition.

Sertraline has been shown to improve immediate and delayed verbal recall in older adults and to have better effects on cognition compared with other selective serotonin reuptake inhibitors (SSRIs).

Some findings were new, such as the potential positive effects of ferrous sulfate. Similarly, bupropion had not previously been linked to negative effects on cognition in older adults. Such data deserve more examination, the investigators say. Future studies may also show whether those drugs could delay the onset of incident dementia.


**DEVICE NEWS**

**Approvals**

**Microcyn HydroGel for Scars**

A therapy for raised and red scars has
received a 510(k) approval by the FDA. Microcyn Scar Management HydroGel is made by Quinnova Pharmaceuticals, a dermatology partner of Oculus U.S. The product is intended to manage old and new hypertrophic and keloid scarring resulting from burns, surgical procedures, and trauma wounds. The gel is scheduled to be available in the first half of 2014.

Sources: Oculus and Reuters, December 4, 2013

**Stimulator Zaps Migraine Pain**

The Cerena Transcranial Magnetic Stimulator (TMS), made by eNuera Therapeutics, has been approved for people 18 years of age and older. This is the first device designed to relieve pain caused by migraine headaches that are preceded by an aura.

The device is used after the onset of pain associated with a migraine. Using both hands to hold the device against the back of the head, the user presses a button to release a pulse of magnetic energy to stimulate the occipital cortex in the brain, which may stop or lessen the pain.

The FDA reviewed the data for the Cerena TMS through the de novo premarket review pathway, which is indicated for low-risk to moderate-risk medical devices that are not substantially equivalent to an already legally marketed device.

In a randomized controlled clinical trial of 201 patients, with auras preceding at least 30% of their migraines, almost 38% of those using the device were pain-free 2 hours later compared with about 17% of controls. After 24 hours, nearly 34% of the Cerena TMS users were pain-free compared with 10% of those in the control group.

Adverse events, although rare, included sinusitis, aphasia, and vertigo. Dizziness has also been reported.

Patients should not use the stimulator if they have metal implants in the head, neck, or upper body; if they have or are thought to have epilepsy; or if they have a personal or family history of seizures.

The device should not be used more often than once per 24 hours.

Source: FDA, December 16, 2013

**Recalls**

**Glucose Test Strips**

Abbott Laboratories acknowledged that 20 lots of its glucose test strips may produce inaccurate low blood glucose results when they are used with certain older meters. As a safety precaution, the company voluntarily recalled the strips.

The recall involves FreeStyle and FreeStyle Lite blood glucose test strips shipped for use in the U.S. The meters are from lots that expire between May 2014 and March 2015.

The problem relates to the presence of both old and new glucose meter technology in the marketplace. If the test strips are used with the FreeStyle and FreeStyle Flash meters, the strips could produce erroneously low values, even though both meters have not been in production since 2010 (however, many are still in use). The newer-model FreeStyle Freedom, Lite, and Freedom Lite meters have not shown problems with the glucose test strips in question. The company is offering free replacement strips.

The FreeStyle InsuLinx uses its own InsuLinx test strips. InsuLinx might not be affected by this recall, but there were problems with the device in 2013. In April, Abbott announced that it was pulling FreeStyle InsuLinx blood glucose meters off the market in the U.S. because of a risk of inaccurate readings at very high blood glucose levels.

Sources: Abbott, November 20, 2013; FDA and Medscape, November 27, 2013

**da Vinci Robot**

Intuitive Surgical has issued a recall of the da Vinci robot. The arms may be producing too much friction in some surgical systems. If this occurs, the da Vinci robot can briefly stop working during surgery.

The company sent out an Urgent Medical Device Recall to affected customers on November 11. With the da Vinci system costing about $1.5 million per unit, this recall affects 1,386 of the robot system arms around the globe.

The da Vinci S, Si, and Si-e systems were affected. The company has taken steps to address problems with the instrument arm (the da Vinci Patient Side Manipulator) and plans to repair or replace the arms as needed.

Of the more than 55,000 procedures completed with this group of instrument arms, there was one reported instance of interrupted motion resulting in an imprecise cut; there were also two additional instances of perceived resistance. No patient complications were reported in association with these three instances.

The company clarified that only the device arms, not the systems themselves, were affected.

Source: FierceMedical Devices, December 4, 2013

**Safety of HeartStart Defibrillators Questioned**

Some HeartStart automated external defibrillator (AED) devices made by Philips Medical Systems may be unable to deliver needed defibrillator shock in a cardiac emergency situation. The FDA has issued a safety communication including recommendations on improving the inspection and monitoring of the readiness of these devices, as well as steps to follow if a recalled device must be used in an emergency.

The FDA advises keeping all of these recalled devices in service until customers obtain a replacement from Philips Healthcare or another manufacturer even if the device indicates it has detected an error during a self-test. The FDA con-
siders the benefits of attempting to use an AED in a cardiac arrest emergency greater than the risk of not attempting to use the defibrillator.

These devices were made and distributed between 2005 and 2012 under the names HeartStart FRx, HeartStart HS1 Home, and HeartStart HS1 OnSite. In September 2012, Philips Healthcare initiated the recall of HeartStart FRx, HeartStart HS1 Home, and HeartStart HS1 OnSite AEDs because an internal electrical component failed. That recall affected 700,000 devices.

In March 2013, the FDA issued a proposed order that, if finalized, would require manufacturers of AEDs and accessories to submit Premarket Approval Applications that focus on the critical requirements necessary to ensure that AEDs are safe and effective. The main objective of this proposed approach is to improve the reliability of AEDs so that they can continue to save lives.

Source: FDA, December 3, 2013

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Promus Premier Everolimus-Eluting Platinum Chromium Coronary Stent System

Manufacturer: Boston Scientific, Natick, Mass.

Approval Date: November 25, 2013

Purpose: The stent is used to treat patients with coronary artery disease. The placement of a stent in the artery helps to keep it open and allow the blood to flow more freely.

Description: The product features customized platinum chromium alloy stent architecture. Everolimus (Afinitor, Novartis) is an antineoplastic agent and an inhibitor of the mammalian target of rapamycin (mTOR). The stent delivery system is also enhanced.

Benefit: The platinum chromium stent architecture maintains excellent radial strength and flexibility and provides optimal radiopacity and improved longitudinal strength. The system also features low recoil and fracture resistance, and improved axial strength. An enhanced low-profile delivery system features a shorter, more visible tip. A dual-layer balloon and a bi-segment inner lumen catheter promote precise stent delivery in patients with challenging lesions.

Sources: www.bostonscientific.com; www.pharmalive.com

Name: Estrogen Receptor Image Analysis and Digital Read Application

Manufacturer: Ventana Medical Systems, Inc./Roche, Tucson, Ariz.

Approval Date: December 5, 2013

Purpose: The device is used with the Ventana iScan Coreo scanner running Virtuoso2 software for the detection of breast cancer.

Description: The software algorithm is used to semiquantify the estrogen receptor biomarker and to digitally or manually read and score the biomarker using a computer monitor instead of a microscope. The pathologist is able to digitally view a slide on a computer monitor, assign a score, and then provide a diagnosis or opinion, with or without the assistance of an image-analysis algorithm.

All immunohistochemistry (IHC) breast markers in Ventana's portfolio are approved for image-analysis and digital read applications. Along with the image-analysis software, the full breast panel includes HER2 (4B5), PR (1E2), Ki-67 (30-9), and p53 (DO-7) algorithms along with their accompanying Ventana IHC assays.

Benefit: Hormone receptor status is a main factor in planning breast cancer treatment. The presence or absence of estrogen receptor (ER) and progesterone receptor (PR) status in cancer cells, along with HER2 receptor status, helps guide treatment options. The Ki-67 protein test and the p53 genetic mutation test are known to be accurate markers for cellular proliferation.

Ventana is the first company in the industry to offer a comprehensive portfolio of image analysis algorithms for the five key IHC breast markers.

Sources: www.ventana.com

Name: Direxion Torqueable Microcatheter


Approval Date: November 2013

Purpose: The microcatheter is designed to facilitate access and delivery of diagnostic, embolic, and therapeutic materials into the peripheral vasculature. The device has the potential to be used in patients with challenging conditions such as liver cancer and uterine fibroids.

Description: The small-lumen microcatheter has a distal outside diameter of 2.51 French (0.85 mm) and a maximum outside diameter of 2.71 French (0.95 mm). The inside diameter is 0.021 inch (0.5 mm), minimally, in the proximal and distal regions. The lumen is able to accommodate steerable guidewires with diameters 0.018 inch (0.47 mm). A slotted, nitinol hypotube technology is designed to maximize torque transmission in the catheter shaft.

The device is available in six tip configurations. The guidewires have a hydrophilic coating to provide lubricity, which aids in the navigation of distal, tortuous vasculature. The guidewires are radiopaque to allow for visualization under fluoroscopy, and the tips are shapeable.

Benefit: The slotted nitinol hypotube technology provides physicians with excellent handling characteristics. The shaft design of the microcatheter enables good control in hard-to-navigate vessels.

Sources: www.bostonscientific.com; http://cardiovasculardevices.medicaldevices-business-review.com