NEW DRUG APPROVALS

**Myalept for Lipodystrophy**

The FDA has approved metreleptin injection (Myalept, Amylin Pharmaceuticals) as replacement therapy to treat complications of leptin deficiency, in addition to diet, in patients who have congenital or acquired generalized lipodystrophy (GD).

GD is associated with a lack of fat tissue. Patients with congenital GD are born with little or no fat tissue. Patients with acquired GD generally lose fat tissue over time. Because fat tissue makes leptin, GD patients have very low levels of this hormone, which regulates food intake and other hormones, such as insulin.

Patients with both types of GD, an orphan disease, often develop severe diabetes mellitus and hypertriglyceridemia (including diabetes mellitus, hypertriglyceridemia) or with metabolic disease (including diabetes mellitus and hypertriglyceridemia) without concurrent evidence of GD.

Metreleptin is available only through the Myalept Risk Evaluation and Mitigation Strategy (REMS) Program.

The FDA is requiring seven postmarketing studies for metreleptin, including a long-term prospective observational study (product exposure registry) of patients treated with the drug, a study to assess metreleptin’s immunogenicity, and an assessment and analysis of spontaneous reports of potential serious risks related to the use of metreleptin. Eight additional studies are being requested as postmarketing commitments.

Source: FDA, February 24, 2014

**Vimizim for Morquio A Syndrome**

Elosulfase alfa (Vimizim, BioMarin Pharmaceutical) has become the first FDA-approved treatment for mucopolysaccharidosis type IVA (Morquio A syndrome). Morquio A syndrome is a rare, autosomal-recessive lysosomal storage disease caused by a deficiency in N-acetylgalactosamine-6-sulfate sulfatase (GALNS).

Elosulfase alfa is intended to replace the missing GALNS enzyme involved in an important metabolic pathway. Absence of this enzyme leads to problems with bone development, growth, and mobility. There are approximately 800 patients with Morquio A syndrome in the U.S.

Elosulfase alfa was granted priority review and was the first drug to receive the rare pediatric disease priority review voucher, which aims to encourage the development of new drugs and biologics for the prevention and treatment of rare pediatric diseases.

The safety and effectiveness of eolosulfase alfa were established in a clinical trial involving 176 participants with Morquio A syndrome ranging from 5 to 57 years old. Participants treated with eolosulfase alfa showed greater improvement in a six-minute walk test than participants given placebo. On average, patients treated with eolosulfase alfa walked 22.5 meters farther in six minutes than patients who received placebo.

The most common side effects in patients treated with eolosulfase alfa during clinical trials included fever, vomiting, headache, nausea, abdominal pain, chills, and fatigue. The safety and effectiveness of eolosulfase alfa have not been established in patients less than 5 years old.

Elosulfase alfa is being approved with a boxed warning that includes the risk of anaphylaxis. During clinical trials, life-threatening anaphylactic reactions occurred in some patients during eolosulfase alfa infusions.

Source: FDA, February 24, 2014

**Northera for Neurogenic Orthostatic Hypotension**

The FDA has approved droxidopa (Northera, Chelsea Therapeutics) for the treatment of neurogenic orthostatic hypotension (NOH).

NOH is a rare, chronic, and often debilitating drop in blood pressure upon standing that is associated with Parkinson’s disease, multiple-system atrophy, and pure autonomic failure. Symptoms of NOH include dizziness, lightheadedness, blurred vision, fatigue, and fainting upon standing.

The labeling for droxidopa includes a boxed warning about the risk of supine hypertension, a common problem that affects people with primary autonomic failure and can cause stroke. The most common adverse events associated with droxidopa in clinical trials were headache, dizziness, nausea, hypertension, and fatigue.

Droxidopa’s effectiveness was shown through two weeks in two clinical studies in subjects with NOH. Subjects taking droxidopa reported a decrease in dizziness, lightheadedness, feeling faint, or feeling as if they might black out compared with those taking placebo. The
durability of the improvement in patient symptoms beyond two weeks has not been demonstrated.

Source: FDA, February 18, 2014

**Aveed for Hypogonadism**

The FDA has approved testosterone undecanoate (Aveed, Endo Pharmaceuticals) injection for the treatment of adult men with hypogonadism that is associated with a deficiency or absence of the male hormone testosterone.

Testosterone undecanoate is indicated to produce serum testosterone levels in the normal range by administration of a single 3-mL (750-mg) intramuscular injection given once at initiation of therapy, at four weeks, and every 10 weeks thereafter.

The approval was based on data from a pivotal 84-week phase 3 trial in hypogonadal U.S. men. Participants had an average age of 54 years and a serum total testosterone level of less than 300 ng/dL. Treatment with testosterone undecanoate increased mean serum testosterone levels, maintaining them for up to 10 weeks at steady state (between weeks 14 and 24).

Testosterone undecanoate injection is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired). The drug has a boxed warning for serious pulmonary oil microembolism (POME) reactions and anaphylaxis. It should be used for patients in whom the benefits of the product outweigh the serious risks of POME and anaphylaxis.

Testosterone undecanoate is available as a single-use vial. Dosage titration is not necessary. The drug has been approved with a risk evaluation and mitigation strategy (REMS) requiring prescriber education and certification as well as restricted product distribution.

In 2009, the FDA issued a complete response letter stating that testosterone undecanoate could not be approved because of the agency’s concern about the risk of POME and anaphylaxis occurring immediately after injection. Endo submitted another new drug application that presented additional information from a review of clinical and postmarketing databases to identify and characterize all cases of POME and anaphylaxis associated with testosterone undecanoate.

According to the FDA briefing document compiled by Endo, testosterone undecanoate provides hypogonadal men with a new testosterone-replacement formulation that achieves normal testosterone levels in most patients (94% of subjects in the pivotal phase 3 trial). As an injectable, it does not risk transference, which may endanger children and women who inadvertently come into contact with men using topical testosterone gel products. The drug also does not exceed supraphysiological testosterone levels like short-acting injectables, require a surgical procedure like pellets, or result in gum irritation like buccal preparations.

Sources: Endo Pharmaceuticals, March 6, 2014, and FDA, April 18, 2013

**Generic Approvals**

**Raloxifene Hydrochloride**

The FDA has approved Teva Pharmaceuticals’s 60-mg tablets of raloxifene hydrochloride, the first generic version of Eli Lilly’s Evista, after determining the two medications to be therapeutically equivalent.

Raloxifene hydrochloride is an estrogen agonist/antagonist indicated for treatment and prevention of osteoporosis in postmenopausal women, reduction of invasive breast cancer risk in postmenopausal women with osteoporosis, and reduction of invasive breast cancer risk in postmenopausal women at high risk for invasive breast cancer.

Raloxifene hydrochloride carries a boxed warning of an increased risk of deep vein thrombosis and pulmonary embolism, as well as an increased risk of death due to stroke in postmenopausal women with documented coronary heart disease or at increased risk for major coronary events.

Source: FDA, March 4, 2014

**Ibandronate Sodium Injection**

The FDA has approved Sun Pharmaceutical Industries’ generic version of Boniva injection for the treatment of osteoporosis in postmenopausal women.

The agency found that Sun’s ibandronate sodium injection, 1 mg (base)/mL, packaged in 3-mL single-dose vials, was therapeutically equivalent to Roche’s Boniva injection. Ibandronate sodium is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The recommended dosage is 3 mg every three months.

Although Sun’s is the first generic version of ibandronate sodium injection to reach the U.S. market, it is unlikely to be the last: Roche’s patent expires on September 2, 2014.

Falling market demand and other generic treatments have already cut Boniva sales sharply, Roche said in its 2012 financial report. The company cited 2012 U.S. Boniva sales of about $82 million—down 77% from 2011.

Source: FDA, February 14, 2014

**Oxybutynin Transdermal System**

The FDA has approved Barr Laboratories’ oxybutynin transdermal system, 3.9 mg/day (extended release). The generic formulation was found to be therapeutically equivalent to the Oxytrol Transdermal System manufactured by Watson Laboratories.

Oxybutynin is an antispasmodic, anticholinergic muscarinic antagonist indicated for the treatment of overactive
bladder with symptoms of urge urinary incontinence, urgency, and frequency. Users apply the skin patch twice weekly to dry, intact skin on the abdomen, hip, or buttocks, selecting a new application site with each new patch to avoid re-application to the same site within seven days.

Source: FDA, March 4, 2014

**Dutasteride and Tamsulosin**

The FDA has approved a generic formulation of dutasteride and tamsulosin hydrochloride capsules, 0.5 mg/0.4 mg, for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate.

Anchen Pharmaceuticals’ formulation was found to be therapeutically equivalent to GlaxoSmithKline’s Jalyn capsules, which combine dutasteride, a 5-alpha-reductase inhibitor, and tamsulosin, an alpha-adrenergic antagonist. Dutasteride shrinks the enlarged prostate and tamsulosin relaxes muscles in the prostate and neck of the bladder.

Source: FDA, February 26, 2014

**Rifabutin**

Lupin Pharmaceuticals’ generic version of 150-mg rifabutin capsules USP has been approved by the FDA, which found the formulation therapeutically equivalent to the 150-mg Mycobutin marketed by Pharma- cia and Upjohn. Rifabutin, a semisynthetic ansamycin antibiotic, is indicated for the prevention of disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection.

Source: FDA, February 24, 2014

**Telmisartan and Hydrochlorothiazide**

Mylan Pharmaceutical’s generic formulations of telmisartan and hydrochlorothiazide tablets USP, 40 mg/12.5 mg, 80 mg/12.5 mg, and 80 mg/25 mg, have been approved for treatment of hypertension by the FDA. The FDA found the medications to be therapeutically equivalent to Micardis HCT tablets marketed by Boehringer Ingelheim.

Telmisartan is an orally active angiotensin II antagonist acting on the AT1 receptor subtype, and hydrochlorothiazide is a diuretic. Combination therapy is generally recommended only after a patient has failed to achieve the desired effect with monotherapy.

Source: FDA, February 25, 2014

**Moxifloxacin HCl**

The FDA has approved Teva Pharmaceuticals’s generic 400-mg tablet formulation of the fluoroquinolone antibiotic moxifloxacin hydrochloride. The agency found the medication to be therapeutically equivalent to the 400-mg Avelox tablets marketed by Bayer HealthCare Pharmaceuticals.

Source: FDA, February 18, 2014

**Lamivudine and Zidovudine Tablets**

The FDA has approved a generic fixed-dose combination of lamivudine and zidovudine tablets USP, 150 mg/300 mg, manufactured by Hetero Labs Limited of Hyderabad, India. The medications are indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection.

The FDA determined that the generic formulation is therapeutically equivalent to Combivir, a GlaxoSmithKline product.

Source: FDA, February 3, 2014

**Ketorolac Tromethamine Ophthalmic Solution**

Akorn has received FDA approval to produce ketorolac tromethamine ophthalmic solution, 0.45%, packaged in single-use vials. The agency determined the product was therapeutically equivalent to Aller- gan’s Acuvail Ophthalmic Solution, 0.45%, a nonsteroidal, anti-inflammatory agent indicated for the treatment of pain and inflammation following cataract surgery.

Source: FDA, February 10, 2014

**NEW INDICATIONS**

**Kalydeco for More Mutations That Cause Cystic Fibrosis**

The FDA has approved a supplemental new drug application (sNDA) for ivacaftor (Kalydeco, Vertex Pharmaceuticals) for people ages 6 years and older with cystic fibrosis (CF) who have one of eight additional mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Ivacaftor was approved in January 2012 for people ages 6 and older with CF who have at least one copy of the G551D mutation. With the approval of the sNDA, Kalydeco is now approved for use in people with CF with the following nine mutations: G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D. In the U.S., approximately 150 people ages 6 and older have one of the additional eight mutations for which the treatment is now approved.

CF is caused by defective or missing CFTR proteins that result from mutations in the CFTR gene. The defective function or absence of CFTR proteins results in poor flow of salt and water into and out of cells in several organs, including the lungs. Ivacaftor facilitates increased chloride transport by potentiating the “channel open” probability (gating) of the CFTR protein. Ivacaftor is the first medication to treat the underlying cause of CF in people with specific mutations in the CFTR gene. Known as a CFTR potentiator, the oral treatment aims to help the CFTR protein function more normally once it reaches the cell surface in the lungs, to help hydrate and clear mucus from the airways.

Source: Vertex Pharmaceuticals, February 21, 2014

**NEW FORMULATIONS**

**Lower-Dose NSAID, Tivorbex, For Adults’ Acute Pain**

The FDA has approved indomethacin (Tivorbex, Iroko Pharmaceuticals) cap-
sules, a nonsteroidal anti-inflammatory drug (NSAID), at 20-mg and 40-mg doses for the treatment of mild to moderate acute pain in adults.

Tivorbex was approved at dosage strengths that are 20% lower than the 25-mg and 50-mg indomethacin products already on the market. The FDA’s approval was based on data from two phase 3 placebo-controlled trials that demonstrated significant improvements in pain relief in patients with postsurgical acute pain who were treated with the new indomethacin formulation compared with patients receiving placebo.

Tivorbex contains indomethacin as submicron particles that are approximately 20 times smaller than their original size. The reduction in particle size provides an increased surface area, leading to faster dissolution, according to Iroko.

In October 2013, the FDA approved Iroko’s Zorvolex (diclofenac) capsules, also developed using this technology, for the treatment of mild to moderate acute pain in adults. Zorvolex is now available in the U.S.

Source: Iroko Pharmaceuticals, February 24, 2014

**DRUG NEWS**

**Fast Track Designations**

**C. Difficile Treatment: Cadazolid**

The FDA has designated cadazolid as a qualified infectious disease product (QIDP) and a “fast track” development program for the treatment of *Clostridium difficile*-associated diarrhea (CDAD).

Among other incentives, the QIDP designation means that the Actelion antibiotic will receive a nine-month priority review upon successful completion of the ongoing phase 3 IMPACT (International Multicenter Program Assessing Cadazolid Treatment) program. In IMPACT, two phase 3 studies are comparing the efficacy and safety of cadazolid (250 mg administered orally twice daily for 10 days) with that of vancomycin (125 mg administered orally four times daily for 10 days) in CDAD patients.

The studies are designed to determine whether the clinical response after the administration of cadazolid is noninferior to that of vancomycin in subjects with CDAD, and whether the administration of cadazolid is superior to vancomycin in terms of a sustained clinical response. The program is expected to enroll approximately 1,280 subjects.

Cadazolid inhibits *C. difficile* protein synthesis, which leads to the suppression of toxin and spore formation. In preclinical studies, the antibiotic showed *in vitro* activity against *C. difficile* clinical isolates and a low propensity for the development of resistance. In a human gut model of CDAD, cadazolid had a limited effect on the normal gut microflora.

Source: Actelion, February 27, 2014

**ER Morphine and Oxycodone**

The FDA has granted “fast track” status to Egalet-001, an oral morphine formulation, and Egalet-002, an oral oxycodone formulation—two abuse-deterrent, extended-release drugs in development for the treatment of moderate to severe pain.

The drugs’ developer, Egalet Corporation, plans to submit a new drug application (NDA) for Egalet-001 in late 2014 or early 2015. The NDA submission for Egalet-002 is scheduled for 2016.

According to Egalet, both medications have been developed in the form of tablets that are specifically designed to deter abuse by physical and chemical manipulation while providing the ability to tailor the release of the active pharmaceutical ingredient.

Source: Egalet Corporation, February 27, 2014

**Pracinostat for AML**

The FDA has granted orphan drug designation to marizomib, a proteasome inhibitor being developed by Triphase Accelerator Corporation, for the treatment of multiple myeloma.

An intravenous (IV) formulation of marizomib has been evaluated in more than 230 patients across four phase 1 and 2 studies, either as a single agent or in combination with dexamethasone or a histone deacetylase inhibitor. An ongoing phase 2 clinical trial is testing the IV formulation in combination with dexamethasone in a highly refractory multiple myeloma population. Marizomib is also being tested in a phase 1/2 study in combination with pomalidomide and dexamethasone in relapsed and refractory multiple myeloma. An oral formulation is in development.

Source: Triphase Accelerator Corporation, February 27, 2014

**Antidepressant GLYX-13**

The FDA has granted “fast track” designation to investigation of GLYX-13 (Naurex), a rapid-acting antidepressant in phase 2 clinical development, as adjunctive therapy in major depressive disorder.

In a single-dose phase 2a clinical study in subjects who had failed treatment with existing agents, GLYX-13 produced statistically significant reductions in depression scores within 24 hours that lasted several days. Naurex describes safety results as “excellent.”

Source: Naurex, March 3, 2014

**Orphan Drug Designations**

**Marizomib for Multiple Myeloma**

The FDA has granted orphan drug designation to marizomib, a proteasome inhibitor being developed by Triphase Accelerator Corporation, for the treatment of multiple myeloma.

Among other incentives, the QIDP designation to the investigational drug pracinostat (MEI Pharma) for the treatment of acute myeloid leukemia (AML). Pracinostat is an orally available histone deacetylase (HDAC) inhibitor that has been tested in a number of phase 1 and 2 clinical trials in advanced hematologic disorders and solid tumor indications in both adult and pediatric
patients. Pracinostat has been generally well tolerated in more than 200 patients to date, with manageable side effects such as fatigue.

Source: MEI Pharma, February 28, 2014

**Gallium-68 DOTATATE for GEP-NETs**

The FDA and the European Medicines Agency have approved orphan drug designation for the radiopharmaceutical Gallium-68 DOTATATE (Advanced Accelerator Applications) as a diagnostic agent for management of gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Used in positron emission tomography and computed tomography imaging of GEP-NETs, the product will be prepared using a kit that is reconstituted in hospital radiopharmacies without the use of a radiochemistry module—making the product available to hospitals that lack fully equipped production radiopharmacy units.

Available data indicates that Gallium-68 DOTATATE has greater sensitivity and specificity for tumor detection than the current standard and is expected to significantly reduce radiation doses received by patients.

Source: Advanced Accelerator Applications, March 4, 2014

**FDA Rejects Empagliflozin For Type-2 Diabetes**

The FDA has rejected the new drug application (NDA) for empagliflozin (Boehringer Ingelheim/Eli Lilly), an investigational sodium glucose co-transporter-2 (SGLT2) inhibitor.

The agency’s complete response letter referred to previously observed deficiencies at a Boehringer Ingelheim facility where empagliflozin will be manufactured. The FDA said these deficiencies must be resolved before the application can be approved.

Empagliflozin is being investigated for the reduction of blood glucose levels in adults with type-2 diabetes. The emerging SGLT2 inhibitor class removes excess glucose through the urine by blocking glucose reabsorption by the kidney.

The FDA for empagliflozin was based on results from clinical programs involving more than 13,000 people.

In June 2013, Eli Lilly announced positive results from a pooled analysis of four pivotal phase 3 trials of empagliflozin in a total of 2,477 people with type-2 diabetes. Those treated with empagliflozin achieved significant reductions in hemoglobin A1c, fasting plasma glucose, weight, and blood pressure compared with those given placebo after 24 weeks.

Sources: Eli Lilly, March 5, 2014, and June 22, 2013

**Vitamins’ Heart and Cancer Benefits Questioned**

There isn’t enough evidence to determine the effectiveness of taking vitamins and minerals to prevent cardiovascular disease or cancer, according to the U.S. Preventive Services Task Force (USPSTF).

Many people take vitamins and mineral supplements to improve or maintain overall health. However, this USPSTF recommendation is limited to the use of vitamin, mineral, and multivitamin supplements specifically for the prevention of cardiovascular disease and cancer.

“Cardiovascular disease and cancer have a significant health impact in America, and we all want to find ways to prevent these diseases,” said USPSTF Chair Virginia Moyer, MD, MPH. “However, we found that there is not enough evidence to determine whether taking single or paired nutrients or a multivitamin helps to prevent cardiovascular disease or cancer.”

In addition, the task force recommends against using two vitamins: beta-carotene and vitamin E. “The evidence shows that there is no benefit to taking vitamin E and that beta-carotene can be harmful because it increases the risk of lung cancer in people who are already at increased risk for the disease,” said USPSTF Co-chair Michael LeFevre, MD, MSPH.

“Due to the uncertain benefit of vitamin supplements to prevent cardiovascular disease and cancer, health care professionals should use their best judgment and consider their patient’s health history, values, and preferences when having conversations about nutritional supplements,” Dr. LeFevre added.

For most people, the best way to get nutrients essential for health is through a balanced diet, the task force says. Eating a diet rich in fruits, vegetables, whole grains, low-fat dairy products, and seafood has been associated with a reduced risk of cardiovascular disease and cancer.

Some health care providers continue to endorse supplements as well as diet for cardiovascular health, including hypertension. To learn more about that viewpoint, see the article on page 291.

Source: USPSTF, February 25, 2014

**NDA for Peramivir**

The FDA has accepted for review a new drug application (NDA) for intravenous peramivir for prevention of influenza. The FDA assigned a standard review time, with an action date of December 23, 2014.

The NDA includes results from more than 2,700 subjects in 27 clinical trials. The drug’s developer (BioCryst Pharmaceuticals) is preparing to make peramivir available in the U.S. during the 2014–2015 flu season, provided FDA approval is granted in time.

Peramivir is an investigational antiviral agent that inhibits the interactions of influenza neuraminidase, an enzyme that is critical to the spread of the influenza virus within a host. In laboratory tests, the drug has shown activity against multiple influenza strains, including H7N9 and pandemic H1N1 swine flu viral strains.

Source: BioCryst Pharmaceuticals, February 25, 2014
New Eylea Indication Sought

The FDA has accepted for standard review the supplemental biologics license application (sBLA) for injected aflibercept (Eylea, Regeneron Pharmaceuticals) for the treatment of macular edema following branch retinal vein occlusion (BRVO). The target action date is October 2014.

Aflibercept was approved in the U.S. for the treatment of neovascular age-related macular degeneration (AMD) in November 2011 and for macular edema following central retinal vein occlusion (CRVO) in September 2012.

Vascular endothelial growth factor (VEGF), a naturally occurring protein in the body, normally triggers the angiogenesis that supports the growth of the body’s tissues and organs. However, in certain diseases, such as wet AMD, it is also associated with the growth of abnormal new blood vessels in the eye, which exhibit abnormal increased permeability leading to edema. Scarring and loss of fine-resolution central vision often result.

Source: Regeneron Pharmaceuticals, February 24, 2014

Prevnar 13 Helps Prevent Older Adults’ Pneumonia

A study of approximately 85,000 subjects evaluating the efficacy of Prevnar 13 vaccine (Pfizer) in adults 65 years of age and older achieved its primary clinical objective and both secondary clinical objectives.

The primary objective of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) was to demonstrate the efficacy of pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) against a first episode of vaccine-type invasive pneumococcal disease (IPD).

VT-CAP was defined as CAP caused by any Streptococcus pneumoniae serotype included in the vaccine. Nonbactemeric/noninvasive VT-CAP was defined as CAP in which vaccine-type S. pneumoniae caused the pneumonia but was not detected concurrently in the bloodstream or at any other normally sterile site. Vaccine-type IPD was defined as a case in which vaccine-type S. pneumoniae was present in the bloodstream or any other normally sterile site, with or without pneumonia.

The results were presented March 12 at the Ninth International Symposium on Pneumococci and Pneumococcal Diseases in Hyderabad, India.

In the U.S., Prevnar 13 is approved for use in children 6 weeks through 5 years of age for active immunization for the prevention of invasive disease and otitis media caused by S. pneumoniae serotypes; in children 6 through 17 years of age for active immunization for the prevention of invasive disease caused by S. pneumoniae serotypes; and for adults 50 years of age and older for the prevention of pneumonia and invasive disease caused by S. pneumoniae serotypes.

Source: Pfizer, February 24, 2014

FDA Recommends Against Doribax for Pneumonia

The FDA has concluded that doripenem (Doribax, Shionogi), an antibacterial drug that has been used to treat patients who develop pneumonia while on ventilators, carries an increased risk of death and lower clinical cure rates compared with imipenem and cilastatin for injection (Primaxin, Merck). Based on its analysis of data from a three-year clinical trial that was prematurely stopped in 2011 due to these safety concerns, the FDA has approved changes to the Doribax drug label that describe these risks.

Doripenem is not approved to treat any type of pneumonia, and the revised label includes a new warning about this unapproved use. Health care professionals should consider whether the benefits of doripenem treatment are likely to exceed its potential risks in patients who develop pneumonia while on ventilators.

Doripenem is still considered safe and effective for its FDA-approved indications: treatment of adults with complicated intra-abdominal infections and complicated urinary tract infections, including kidney infections called pyelonephritis.

In the clinical trial that was stopped early, patients with ventilator-associated bacterial pneumonia received either seven-day doripenem treatment or 10-day treatment with imipenem and cilastatin. In the intent-to-treat population, the 28-day all-cause mortality was higher in the doripenem arm (23.0%, 31/135) than in the imipenem and cilastatin arm (16.7%, 22/132). Clinical cure rates were also lower in the doripenem arm.

Source: FDA, March 6, 2014

Full Approval for Synribo for CML

The FDA has granted full approval to omacetaxine mepesuccinate (Synribo, Teva Pharmaceutical) for injection.

Omacetaxine mepesuccinate is indicated for adult patients with chronic-phase or accelerated-phase chronic myeloid leukemia (CML) with resistance and/or intolerance to two or more tyrosine kinase inhibitors. It received accelerated approval in October 2012, with additional clinical trial data required to fulfill FDA postmarketing requirements.

Omacetaxine mepesuccinate is the first protein synthesis inhibitor for CML. While the drug’s mechanism of action is unclear, it has been shown to prevent the production of specific proteins (Bcr–Abl and Mcl-1) that are produced by cancerous CML cells and help drive the disease. As a protein synthesis inhibitor,
medactamine mepesuccinate is believed to work in a way that does not directly depend on Bcr–Abl binding.

Source: Teva Pharmaceutical, February 13, 2014

**Teva Launches Generic Capecitabine**

Teva Pharmaceutical has launched its generic capecitabine 150-mg and 500-mg tablets, equivalent to Genentech’s Xeloda. Teva was the first to receive approval of its abbreviated new drug application from the FDA on September 16, 2013.

Capecitabine, a fluoropyrimidine carbamate with antineoplastic activity, is indicated for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated.

Xeloda 150-mg and 500-mg tablets had annual sales of approximately $754 million in the U.S., according to IMS data as of December 2013.

Source: Teva Pharmaceutical, March 7, 2014

**Medication Spending Expected To Rise 5% in 2014**

Total spending on prescription medications has been relatively flat for years, but that trend is expected to end with a 3% to 5% increase in 2014, according to a report from the University of Illinois at Chicago Center for Pharmacoepidemiology and Pharmacoeconomic Research.

The report reviews recent changes in drug costs, identifies factors likely to influence future prescription expenditures, and projects drug spending for the year. It appeared in the March 15 American Journal of Health-System Pharmacy.

“While prescription drugs are considered to be increasingly expensive, the overall rate of increase in drug expenditures has generally declined over the past 15 years,” said lead author Professor Glen Schumock. For the first nine months of 2013, he said, it was a record low 0.4%. The U.S. economic downturn, increased use of generics, and efforts to curb costs under the health care reform law played a role.

But costs may rise this year, he said, because of increased access to pharmaceuticals with the expanded insurance coverage under the Patient Protection and Affordable Care Act (PPACA). According to the Congressional Budget Office, 14 million previously uninsured Americans are expected to gain coverage in 2014 through Medicaid expansion or insurance exchanges. As a result, U.S. health care expenditures may increase up to 6.1%, reaching $3.09 trillion, or 18.3% of the gross domestic product.

Prescription drugs account for about 11% of overall U.S. health care expenditures, Schumock said. The 3% to 5% increase in overall drug expenditures that the report forecasts includes a 5% to 7% rise in spending for clinic-administered drugs and a 1% to 3% increase in hospital drug expenditures.

Schumock cited a trend toward using drugs that are increasingly complex and more expensive than traditional pharmaceuticals. “This year a company [Gilead Sciences] announced that its new hepatitis C therapy will cost $1,000 per day, or $84,000 for a typical course of therapy,” he said. “A significant amount of effort will be needed to ensure that these drugs are used appropriately.”

Source: University of Illinois at Chicago, March 5, 2014

**Cutting Cancer Costs Without Risk to Patients**

In a review article published in Lancet Oncology, Johns Hopkins experts identify three major sources of high cancer costs and argue that doctors can likely reduce them without harm to patients. The proposals call for changes in routine clinical practice involved in end-of-life care, medical imaging, and drug pricing.

Source: University of Michigan, February 27, 2014

**Are New Diabetes Drugs Worth the Cost?**

Two newer classes of drugs that treat adult-onset diabetes may be no more effective than an old standby, yet they cost significantly more over the course of a patient’s disease, according to a National Science Foundation–funded study by researchers at the University of Michigan, Mayo Clinic, and North Carolina State University.

Based on a simulation model that used 15 years’ worth of data from more than 37,000 patients, the researchers found that the newer drugs cost patients and insurance companies $1,600 to $2,400 more from the time a person is diagnosed until he or she develops heart or circulatory complications or dies.

The simulation model compared the newer diabetes drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists with an older treatment, sulfonylureas. These agents have different mechanisms for stabilizing blood sugar levels.

DPP-4 inhibitors include sitagliptin (Januvia, Merck), saxagliptin (Onglyza, Bristol-Myers Squibb/AstraZeneca), and linagliptin (Tradjenta, Boehringer Ingelheim/Lilly). GLP-1 agonists include exenatide (Byetta, Bristol-Myers Squibb/AstraZeneca) and liraglutide (Victoza, Novo Nordisk).

Since the newer drugs were introduced, many physicians have shifted to prescribing them—partly because they don’t have the risk of hypoglycemia and weight gain that sulfonylureas can have. But the shift is partially to blame for a rise in the cost of diabetes medications and management, the study concludes.

Source: University of Michigan, February 27, 2014
The authors say the biggest opportunities for safe and ethical cost-cutting rest on caring for patients with metastatic cancer, not on new surgical or radiation treatments, clinical trials, curative care, or pediatric care. For example, the authors suggest that improving end-of-life care with better decision-making and planning could reap large savings by reducing hospitalizations in the last month of life.

The article says hospice care improves symptoms, helps caregivers, and costs less, with equal or better survival for patients, yet only half of cancer patients use hospice in their final month. The authors recommend that patients with poor prognoses have better and earlier discussions with their oncologists about chemotherapy use at the end of life, as well as transitions to hospice. The American Society of Clinical Oncology endorses decision aids spanning these topics.

Expensive imaging poses another opportunity to limit costs, the authors say. Positron emission tomography and other scans, for example, are often used to detect cancer recurrence in patients after initial treatments, but studies show that cure rates are just as good when recurrences are found through other examinations.

Finally, the authors suggest that reducing prices of new cancer drugs could help contain cancer costs. One approach, they say, could be to price drugs according to how well they prolong life.

Source: EurekAlert, February 14, 2014

Low-Dose Opioids Safe For COPD Patients

Low-dose opioids are safe for patients with very severe respiratory disease, a team of Swedish, Australian, and American researchers says.

The researchers studied 2,249 patients starting long-term oxygen therapy for chronic obstructive pulmonary disease (COPD). They sought to address concern that benzodiazepines and opioids, alone or combined, cause adverse events in patients with respiratory compromise.

Safety data for benzodiazepines and opioids in patients with severe COPD are limited. However, the researchers say randomized studies have shown that oral sustained-release morphine can relieve chronic refractory breathlessness.

The study’s outcome measures were the effects of benzodiazepines and opioids on hospital admission rates and mortality. During the median 1.1-year follow-up, 1,681 patients were admitted to the hospital and 1,129 died. Benzodiazepines and low-dose opioids (equivalent to 30 mg or less of oral morphine a day) were not associated with increased admission, even when combined. Benzodiazepines were associated with a “modest” increase in mortality. Opioids had a dose–response relationship with mortality.

The study included a large cohort of old, severely ill patients with respiratory failure caused by COPD; many had hypercapnia. Researchers found no evidence that the drugs’ effects were modified by the presence of hypercapnia, comorbid anxiety/depression, previous injury, or being naïve to the drugs.

The lack of associations between low-dose opioids and increased risks of admission or death is consistent with previous data, researchers say. For instance, in a meta-analysis of parenteral opioids in postoperative patients, who are likely to have the highest rates of toxicity, the rate of hypoventilation after 10 mg intramuscular morphine was 0.6%, similar to placebo. Lower-dose benzodiazepines have not been associated with serious adverse events or impaired blood gases in randomized controlled trials, although they have been implicated in an increased risk of admission due to falls.

In this study, the slightly higher mortality risk might relate to concurrent treatment with higher-dose benzodiazepine or opioids, the researchers suggest. The apparent hazards of higher-dose benzodiazepines and opioids might be overestimated, they speculate, because of increased prescriptions and dosages for terminal patients. They suggest sustained-release morphine as a first-line treatment, started at a low dose and titrated upward. Titration up to 30 mg a day might safely improve breathlessness in more than 60% of patients, they conclude.

Benzodiazepines should not be the first-line treatment for breathlessness in those with respiratory failure, say the researchers from Lund University, Lund, Sweden; Blekinge Hospital, Karlskrona, Sweden; Uppsala University Hospital, Uppsala, Sweden; Duke University Medical Center, Durham, North Carolina; and Flinders University, Adelaide, Australia. Source: BMJ 2014;348:g445

Rosuvastatin or Atorvastatin?

Switching patients to newly available generic atorvastatin may not be the best choice, according to a simulation study by researchers from AstraZeneca (maker of Crestor, or rosuvastatin). They concluded patients who were switched could have a higher risk of major adverse cardiovascular events (MACE) and a lower chance of reaching goals for low-density lipoprotein-cholesterol (LDL-C).

Availability of a new generic statin usually leads to migration from branded statins. Anticipating such a transition from rosuvastatin to atorvastatin, the researchers designed a study to estimate its impact. They created a population of 50,038 virtual patients based on real patients in the National Health and Nutrition Examination Survey 1999–2008 database. The researchers designated an adherent population because switching treatments was not relevant to nonadherent patients. The statin treatment models were based on published clinical trials.

Treatment in all arms began with a
washout period during which all lipid-lowering therapies prescribed prior to enrollment were discontinued. The virtual patients were then prescribed an initial dose of 10, 20, or 40 mg of rosuvastatin. Treatments were assigned using an algorithm that matched the population-level distributions of initial dose assignments observed in pharmacy claims data.

At a follow-up visit after six weeks, patients in the experimental arm were switched to atorvastatin at a dose twice that of their rosuvastatin dose (e.g., from rosuvastatin 10 mg to atorvastatin 20 mg). Control patients remained on rosuvastatin. Virtual patients in both arms whose LDL-C levels were higher than their goal were eligible for treatment intensification. If their levels were still high at any point in the next five years, their treatment could be intensified again until they reached the highest dose allowed.

Virtual patients’ biomarkers and outcomes were recorded until 10 years. The primary outcome was MACE, defined as the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes. A secondary outcome was MACE+, defined as the first occurrence of either MACE or revascularization.

The mean reduction from baseline in total cholesterol and HDL-C was 39% when patients remained on rosuvastatin and 35% when patients were switched to atorvastatin. Those changes were maintained from year 1 to year 5. Reduction in LDL-C was 48% at year 1 and 47% at year 5 when patients stayed on rosuvastatin and 43% at years 1 and 5 when they switched to atorvastatin.

After five years, 4.8% fewer virtual patients in the atorvastatin group reached their conservative LDL-C goal: 87%, versus 91% of patients who remained on rosuvastatin.

At five years, the relative risk of MACE was 1.109 for patients taking atorvastatin versus rosuvastatin. At 10 years, the relative risk was 1.115. Trends for MACE+ were similar, but the researchers note the MACE+ results are not as broadly applicable because the prevalence of revascularization is highly dependent on the standard of care.

The increase in absolute risk was greatest among high-risk virtual patients, such as those with prior cardiovascular disease, those who were still above goal, and those with diabetes. Also, of course, unlike real patients, all the virtual patients were 100% adherent.

Source: Clin Ther 2014;36:58–69

Coffee During Pregnancy? New Reason for Caution

Drinking coffee during pregnancy can raise the risk of childhood acute leukemia (AL) by as much as 72%, according to a meta-analysis by researchers from Anhui Medical University in Heifei, China. Even allowing for differences in the type of coffee (e.g., filtered versus boiled) and such variables as ethnic and genetic background, they found a statistically significant association.

The researchers looked at seven studies (five from Europe, one each from Australia and the U.S.) involving 2,090 cases and 3,630 controls. Results indicated that coffee consumption during pregnancy was significantly associated with childhood AL. Compared with women who drank little or no coffee, the risk increased by 22% for women who drank less than two cups a day and 72% for women who drank 10 cups a day or more. The researchers also noted statistically significant associations between maternal coffee consumption and childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), especially for high-level drinkers.

Previous studies have found that caffeine inhibits topoisomerase II (topo II), an important enzyme in the unwinding and regulation of DNA necessary for gene transcription, DNA recombination, and replication. Given the high levels of cell proliferation and topo II present during fetal development, excessive exposure to topo II inhibitors such as coffee during pregnancy may lead to developmental abnormalities in the fetus, they say. Research has also found caffeine can inhibit some genes, such as the tumor suppressor gene, associated with childhood AL.

The researchers found a dose–response association between coffee consumption during pregnancy and childhood AL, including a significant association between drinking one to two cups a day and AL, as well as a link between two to three cups a day and childhood ALL and AML. However, the significant relationship between coffee consumption and childhood AL existed only in Europe. This could be explained in part by differences in amounts and types of coffee consumed there, but the U.S. had one of the highest national coffee-drinking rates. The single U.S. study in the meta-analysis had only 84 cases—possibly too small a number to detect the risk of childhood AL, the researchers say.

Smoking tobacco accelerates caffeine metabolism and reduces exposure to caffeine. The authors of the meta-analysis speculate that coffee consumption might aggravate the accumulation of caffeine in a nonsmoking woman’s body, thus increasing the risks.

Source: Am J Obstet Gynecol 2014;210:151.e1–10

‘Breakthrough’ Designation For Hepatitis C Treatment

The FDA has granted the dual regimen of daclatasvir and asunaprevir (Bristol-Myers Squibb) a “breakthrough therapy” designation for use in the treatment of genotype 1b chronic hepatitis C virus (HCV) infection.

The designation was based on data continued on page 250

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from an ongoing phase 3 clinical trial program evaluating the all-oral combination regimen of daclatasvir, an investigational NSSA replication complex inhibitor, and asunaprevir, an investigational NS3 protease inhibitor, without ribavirin. A breakthrough therapy designation is intended to expedite the development and review of drugs for serious or life-threatening conditions.

Source: Bristol-Myers Squibb, February 24, 2014

FDA to Review 9-Valent HPV Vaccine

The biologics license application (BLA) for V503, an investigational 9-valent human papillomavirus (HPV) vaccine, has been accepted for review by the FDA.

In November 2013, the vaccine’s developer, Merck, announced that vaccination with V503 had prevented approximately 97% of cervical, vaginal, and vulvar precancers caused by HPV types 31, 33, 45, 52, and 58 in a pivotal phase 3 efficacy study. V503 also generated immune responses to HPV types 6, 11, 16, and 18 that were noninferior to those generated by Merck’s Gardasil (human papillomavirus quadrivalent [types 6, 11, 16, and 18] vaccine, recombinant). V503 includes five more HPV types (31, 33, 45, 52, and 58) in addition to the four HPV types (6, 11, 16, and 18) in Gardasil.

Sources: Merck, February 20, 2014, and November 4, 2013

FDA Seeks to Modernize OTC Drug Reviews

The FDA is proposing major changes to its 40-year-old system for approving over-the-counter (OTC) medications to make the system more adaptable to scientific advances.

In a document filed with the Federal Register, the agency said it is interested in overhauling OTC drug regulation to “create a process that is more efficient and more responsive to newly emerging information and evolving science, and to allow for more rapid product innovation where appropriate.”

When the OTC drug review process was established four decades ago, the agency said, “it was generally thought that safety and effectiveness evaluations for the various active ingredients would be fairly straightforward and would not necessarily need continuous re-examination over time.” That is no longer the case, the agency said. It is interested in hearing ideas for changing or even replacing the system.

The FDA scheduled hearings for public comments on March 25 and March 26.

Sources: Reuters and Federal Register, February 21, 2014

Priority Review for IV Antibiotic Oritavancin

The FDA has accepted the filing of a new drug application (NDA) for oritavancin, an investigational intravenous antibiotic, with priority review. The FDA action date is August 6, 2014.

The Medicines Company is seeking approval of oritavancin, administered as a single dose, for the treatment of acute bacterial skin and skin-structure infections (ABSSSIs) caused by susceptible gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).

The NDA submission was based on data from two phase 3 clinical trials (SOLO I and SOLO II), which evaluated the efficacy and safety of a single 1,200-mg dose of oritavancin compared with seven to 10 days of twice-daily vancomycin in adults with ABSSSIs, including MRSA infections. The combined SOLO studies were conducted in 1,959 patients; 405 had an ABSSSI with a documented MRSA infection.

In clinical trials, the most frequently reported adverse events associated with oritavancin were nausea, headache, vomiting, and diarrhea. Hypersensitivity reactions have been reported with the use of antibacterial agents, including oritavancin.

Source: The Medicines Company, February 19, 2014

Expanded Indications Rejected for Xarelto

The FDA has issued complete response letters (CRLs) regarding supplemental new drug applications (sNDAs) for the use of the oral anticoagulant rivaroxaban (Xarelto, Janssen/Bayer HealthCare) to reduce the risk of secondary cardiovascular events—defined as heart attack, stroke, or death—in patients with acute coronary syndrome (ACS) and to reduce the risk of stent thrombosis in the same population, in combination with standard antiplatelet therapy.

Both sNDAs were based on results from the 15,526-patient pivotal phase 3 ATLAS ACS 2 TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to aspirin with/without thienopyridine therapy in Subjects with Acute Coronary Syndrome) trial of rivaroxaban.

The results were published in the *New England Journal of Medicine* in November 2011. An FDA advisory panel concluded in January that clinical data from a single pivotal trial were not strong enough to justify approval to market rivaroxaban to prevent further heart problems, especially since some data were missing.

Rivaroxaban works by blocking a blood-clotting factor (factor Xa). The drug is approved for six indications: reducing the risk of strokes and blood clots in patients with atrial fibrillation not caused by a heart valve problem; treating patients with deep vein thrombosis (DVT); treating patients with pulmonary embolism (PE); reducing the risk of recurrence of DVT or PE following an initial six-month treatment for acute venous thrombo-
embolism; reducing the risk of blood clots in the legs and lungs of patients who have just had knee-replacement surgery; and reducing the risk of blood clots in the legs and lungs of patients who have just had hip-replacement surgery.

Sources: Johnson & Johnson and Reuters, February 14, 2014

**Isavuconazole in Review for Invasive Mucormycosis**

The FDA has designated isavuconazole as a qualified infectious disease product (QIDP) for the treatment of invasive mucormycosis (also known as zygomycosis), a life-threatening invasive fungal infection caused by certain emerging molds.

In 2013, isavuconazole (being developed by Astellas Pharma and Basilea Pharmaceutica) received QIDP designation for the treatment of invasive aspergillosis, a severe fungal infection caused by widespread molds. Isavuconazole is designated an orphan drug for the treatment of zygomycosis and invasive aspergillosis.

Isavuconazole is an investigational once-daily intravenous and oral broad-spectrum antifungal for the potential treatment of severe invasive and life-threatening fungal infections. It is in phase 3 of clinical development.

Source: Astellas Pharma, February 27, 2014

**RECALLS**

**Agila Etmomidate Injection**

Agila Specialties has recalled 10 lots of etomidate injection 2 mg/mL packaged in glass vials in 10 mL and 20 mL volumes. The products were made in Poland by Agila, a subsidiary of Mylan Inc., and carry a Pfizer label.

The product was recalled due to the potential for small black particles, identified as paper shipping labels, to be present in vials; the potential for missing lot numbers and/or expiration dates on cartons; and the potential for illegible or missing lot numbers and expiration dates on vials. The recall involves 20 mL lots 5001012, 5000927, 5000931, 5000936, 5000942, 5001071, and 5001040 and 10 mL lots 5001023, 5000983, and 5000986. Contact Mylan Customer Service with questions at 1-800-848-0462, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Sources: Mylan Inc., February 19, 2014

**Effexor XR**

Pfizer recalled one lot of 30-count and one lot of 90-count Effexor XR (venlafaxine HCl) 150-mg extended-release (ER) capsules and one lot of 90-count Greenstone-branded venlafaxine HCl 150-mg ER capsules after a pharmacist reported that a bottle of Effexor XR contained one capsule of dofetilide (Tikosyn) 0.25 mg in addition to the Effexor XR capsules.

The use of the antiarrhythmic dofetilide by a patient taking the antidepressant venlafaxine HCl ER, where the contraindications and drug-drug interactions have not been considered by the prescribing physician, could cause serious or fatal adverse consequences. Although Pfizer has not received other such reports, these three lots were recalled as a precaution because they were packaged on the same line. Pfizer says there is a very low probability that other bottles of Effexor XR contain a Tikosyn capsule.

The recall involves Pfizer lots V130142 and V130140, which expire in October 2015, and Greenstone lot V130014, which expires in August 2015. Contact Stericycle at 1-888-345-0481, Monday through Friday, 8 a.m. to 5 p.m. Eastern time, for instructions on returns.

Source: Pfizer, March 6, 2014

**BIVIGAM Immune Globulin**

Biotest Pharmaceuticals Corporation (BPC) has recalled 14 lots of BIVIGAM Immune Globulin Intravenous (Human), 10% Liquid, 100 mL, because a very small percentage of vials may exhibit a defect that could result in leakage. The lot numbers are 130009, 130011, 130013, 130019, 130021, 130023, and 130137 (expiration date May 31, 2015); 130029, 130033, 130035, 130037, 130039, and 130041 (expiration date June 30, 2015); and 130043 (expiration date July 31, 2015). Contact BPC to arrange for product return.

Source: Biotest Pharmaceuticals, February 24, 2014

**Dianeal Peritoneal Dialysis Solution**

Baxter International recalled a single lot of Dianeal PD-2 Peritoneal Dialysis Solution with 1.5% Dextrose 6,000 mL (Ambu-Flex II) after receiving complaints of particulate matter, identified as mold, resulting from a leak in the container.

Baxter has received reports of adverse events for lot C903799 (expiration date May 2015), but no causal relationship has been established between the events and the recall. The affected lot was distributed between May 2013 and January 2014. Providers should return it by contacting Baxter Healthcare Center for Service at 1-888-229-0001, Monday through Friday, 7 a.m. to 6 p.m. Central time.

Source: Baxter International, March 5, 2014

**Ben Venue Acetylcysteine Solution 10%**

Ben Venue Laboratories recalled lot 2005479 of Acetylcysteine Solution 10%, USP, (manufactured for Roxane Laboratories, Inc.) 30 mL per vial after discovery of a single visible glass particle in a vial in that lot. For information, contact GENCO Pharmaceutical Services at 1-800-633-1422.

Source: Ben Venue Laboratories, February 14, 2014
**NEW DRUGS**

**DEVICE NEWS**

**Approvals**

**Bydureon Pen for Once-Weekly Diabetes Treatment**

The FDA has approved a pen loaded with exenatide extended-release (ER) injectable suspension 2 mg (Bydureon, AstraZeneca) as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes.

The prefilled, single-use injector eliminates the need for patients to transfer the medication between a vial and a syringe during the self-injection process. The pen contains the same formulation and dose as the original Bydureon single-dose tray, providing the same continuous release of exenatide. The pen can be used at any time of the day with or without meals.

In a 24-week, randomized, open-label trial, once-weekly exenatide ER demonstrated a hemoglobin A1c (HbA1c) reduction of 1.6 percentage points versus 0.9 percentage points for twice-daily exenatide injection (Byetta, Bristol-Myers Squibb/AstraZeneca) at 24 weeks (baseline HbA1c: 8.5% and 8.4%, respectively). In addition, once-weekly exenatide ER demonstrated a mean weight reduction of 2.3 kg versus 1.4 kg with exenatide (baseline: 97 kg and 94 kg, respectively).

The exenatide ER pen should not be used to treat patients with type-1 diabetes or diabetic ketoacidosis and is not recommended as first-line therapy for patients who have inadequate glycemic control with diet and exercise. The concurrent use of the exenatide ER pen with insulin has not been studied and is not recommended.

The pen will be available for patients in the U.S. later this year. The single-dose tray will remain on the market in the U.S. for patients prescribed Bydureon.

Source: AstraZeneca, March 3, 2014

**Monovisc Injections for OA Knee Pain**

The FDA has granted marketing approval for Monovisc, a single-injection supplement to synovial fluid of the osteoarthritic joint designed to treat pain and improve joint mobility in patients with osteoarthritis (OA) of the knee.

Monovisc is a sterile, biocompatible, resorbable, viscoelastic fluid composed of partially cross-linked sodium hyaluronate in phosphate-buffered saline. It is indicated for the treatment of OA pain of the knee in patients who have failed to respond adequately to conservative nonpharmacological therapy and to simple analgesics.

The FDA’s approval was based on positive data from a pivotal randomized, controlled, double-blind study of 369 patients with knee OA in the U.S. and Canada. The patients received either Monovisc or control (saline injection) and were evaluated for improvement in pain, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), at follow-up assessments out to 26 weeks.

According to Reuters, the FDA rejected Monovisc’s original December 2009 filing on grounds that there were deficiencies in the application. Product developer Anika Therapeutics appealed, but the FDA upheld the rejection in December 2012. In January 2013, Anika submitted the amended application that has been approved.

Sources: Anika Therapeutics and Reuters, February 25, 2014

**Safety Advisory for Thoratec LVAS Controller**

Thoratec Corporation issued a safety advisory after some users of its HeartMate II Left Ventricular Assist System (LVAS) experienced difficulty switching from a primary external controller to a backup controller. The problem resulted in four deaths and five reports of lost consciousness or other symptoms of hypoperfusion.

Thoratec has updated labeling and training materials for the HeartMate II LVAS Pocket Controller.

Eight of the nine events occurred in patients who had been converted to the pocket controller after originally being trained on an older model, the EPC System Controller. Two deaths occurred in patients who tried to exchange system controllers while alone and, contrary to the labeling, without contacting the hospital first. Thoratec’s investigations have not revealed any failures of the devices to meet specifications.

Physicians who prescribe the HeartMate II LVAS Pocket Controller should immediately review the updated labeling and training materials provided in the urgent medical device correction letter with all personnel responsible for training patients and caregivers on the controller’s use. Patients and caregivers using the controller should be retrained on its use and given updated patient handbook information.

The pocket system controller was introduced in the U.S. in May 2013. LVAS patients who received it as a replacement for an older system controller model are at a higher risk of experiencing difficulty in the controller exchange process. These patients may not have received adequate training on the differences between the two controllers, Thoratec warns.

This action affects:

- HeartMate II Implant Kit with Pocket Controller: catalog numbers 106015 and 106016
- Pocket Controller: catalog numbers 106762 and 106017
- HeartMate II LVAD Pump and Pocket Controller Kit: catalog number 107801
- Pocket Controllers that have been removed from packaging: model number 105109

Clinicians and patients with questions may contact the company at 1-800-528-2577

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Recalls
Teleflex Tracheal Tubes
Teleflex Medical has recalled its ISIS HVT Tracheal Tube cuffed with subglottic secretion suction port (with and without preloaded stylet). The tubes, manufactured from December 2009 through November 2013 and distributed from March 2010 through December 2013, may kink during patient use. This could deprive the patient of adequate ventilation. Product numbers appear in the recall notification, www.teleflex.com/en/usa/documents/Isis-Customer-Notification.pdf. For questions, call Teleflex at 1-866-804-9881, Monday through Friday, 8 a.m. through 8 p.m. Eastern time.
Source: Teleflex Medical, January 6, 2014, and FDA, February 24, 2014

Philips Respironics Trilogy Ventilators
Respironics, Inc., a Philips Healthcare business, has recalled approximately 600 Philips Respironics Trilogy Ventilators, Models 100, 200, and 202. A potentially defective component on the power management board could affect the function of the device; the ventilator could fail to deliver mechanical breaths and alarm functionality may be reduced. This recall affects devices shipped between December 31, 2013, and January 30, 2014. For replacement, customers may contact their Philips Respironics representative via the Customer Care Center, 1-800-345-6443, at any time.
Source: Philips Healthcare, February 19, 2014

ACME Monaco Guidewire
Medline Industries is recalling ACME Monaco Guidewires designed to fit inside a percutaneous catheter and direct it through a blood vessel. This guidewire (.035x150 3 MMJ TCFC, item number 88241) is used in surgical convenience kits Medline distributed from March through August 2013. The coating could flake off the wire. Product codes in the recall are 054372-1-1A, 054372-1-1B, and 054372-1-2A. Customers should remove the guidewires from the kits, return them to Medline, and use the rest of the kit.
Source: FDA, February 25, 2014

NEW MEDICAL DEVICES
Marvin M. Goldenberg, PhD, RPh, MS

Name: Therapy Cool Flex Ablation Catheter and IBI 1500T9-CP v.1.7 Cardiac Ablation Generator
Manufacturer: St. Jude Medical Company, Irvine, California
Approval Date: January 15, 2014
Purpose: The ablation catheter is used to treat a type of heart arrhythmia called typical atrial flutter by finding the source of the rhythm disturbance and ablating small areas of heart tissue that block the heart’s internal electrical signals that cause the typical atrial flutter. The catheter is removed after treatment.
Description: The Therapy Cool Flex Ablation Catheter is a steerable, deflectable, irrigated catheter. The catheter takes energy from an external source (the IBI 1500T9-CP v.1.7 Cardiac Ablation Generator) to a point in the right side of the heart. The Therapy Cool Flex Ablation Catheter has a laser-cut electrode tip that differs from the previous model of the device. The laser-cut pattern allows the tip to be flexible and provides a more uniform distribution of saline fluid to the ablation site.
Benefit: The Therapy Cool Flex Ablation Catheter is inserted into an artery or vein, usually though a site in the upper leg or neck. The catheter is manually advanced through increasingly larger blood vessels until it reaches the correct location inside the heart. The tip of the catheter can be made into a curve or straightened out by pushing or pulling the handle. This allows the tip of the catheter to reach different areas inside the heart. Once inside the heart, electrodes at the tip of the catheter gather data that identify the location of the faulty tissue in the heart (electrical mapping). Once the site is identified, the device delivers radio-frequency energy to destroy small areas of tissue. The device should not be used in patients who have an active systemic infection, who have a blood clot attached to the inside of the heart, or who have had an incision in the atrium or ventricle in the previous four weeks.
Source: www.fda.gov

Name: CoreValve heart device
Manufacturer: Medtronic Inc., Minneapolis, Minnesota
Approval Date: January 17, 2014
Purpose: The CoreValve heart device is used to replace damaged aortic valves with minimally invasive technology.
Description: The heart valve technology, called transcatheter aortic valve replacement (TAVR), is used to implant new valves through a catheter inserted into a patient’s artery. It is less invasive than open surgery, which can be traumatic. However, open surgery is still considered the safest and most effective option for patients who can withstand it because of TAVR’s increased risk of stroke and other complications.
Benefit: Medtronic estimates that roughly 100,000 people in the U.S. have severe, symptomatic aortic stenosis, and about a third of those are at an extreme risk from surgery. The introduction of the CoreValve heart device, which comes in different sizes than the previously approved Sapien heart device, will provide patients with more choices.

The CoreValve Transcatheter Aortic Valve Platform—including the CoreValve Evolut 23-mm and CoreValve 26-mm,
29-mm, and 31-mm valves—is approved for patients with severe symptomatic aortic stenosis who are at extreme risk for surgical valve replacement.

Sources: www.corevalve.com, www.wsj.com

Name: Advisa DR MRI and Revo MRI SureScan Second Generation Pacing Systems

Manufacturer: Medtronic Inc., Minneapolis, Minnesota

Approval Date: January 24, 2014

Purpose: For use during magnetic resonance imaging (MRI) of any part of the body, including the chest.

Description: The internal circuitry of the SureScan pacemaker is designed to prevent MRI forces from disrupting the device’s function. Highly reduced amounts of ferromagnetic components decrease magnetic attraction between the device and scanner. The lead tips are designed especially to prevent interaction between gradient field energy and radiofrequency energy, lowering the chances that gradient field energy might induce cardiac stimulation.

Benefit: MRI is the most advisable method for soft tissue imaging and is vital for early detection, diagnosis, and treatment. The SureScan Pacing Systems are the first and only pacing systems in the U.S. with such a broad indication. It is estimated that as many as 75 percent of people with pacemakers will need an MRI at some point in their lives. The SureScan pacing systems allow for a broader range of MRI scans for patients with these pacemakers, and will make it easier for them to have chest scans.

Medtronic’s first-generation Revo and second-generation Advisa pacemakers were cleared for use in MRIs excluding the chest area in February 2011 and January 2013, respectively.

Source: www.medtronic.com