NEW DRUG APPROVALS

Invokamet for Type-2 Diabetes

The FDA has approved Invokamet (Janssen Pharmaceuticals), a fixed-dose combination of canagliflozin and metformin hydrochloride in one tablet, for the treatment of adults with type-2 diabetes.

Canagliflozin (Invokana, Janssen) was the first sodium glucose co-transporter 2 (SGLT2) inhibitor available in the U.S., while metformin is commonly prescribed early in type-2 diabetes treatment. Invokamet is the first FDA-approved fixed-dose combination of an SGLT2 inhibitor with metformin.

Invokamet is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes who are not adequately controlled by treatment that includes either canagliflozin or metformin, or who are already being treated with both canagliflozin and metformin as separate medications. Invokamet should not be used in patients with type-1 diabetes or diabetic ketoacidosis, and it is not known whether the treatment is safe and effective in children younger than 18 years of age.

Studies showed that the administration of Invokamet was equivalent to the co-administration of corresponding individual doses of canagliflozin and metformin.

Invokamet will be available in tablets with canagliflozin 50 mg or 150 mg and metformin 500 mg or 1,000 mg. The recommended dosing is twice daily. Invokamet’s prescribing information includes a boxed warning of the potential for lactic acidosis.

The co-administration of canagliflozin and metformin as individual agents was evaluated in six phase 3 clinical studies that enrolled 4,732 patients with type-2 diabetes. The studies showed that the combination of canagliflozin and metformin lowered blood sugar and was associated with significant reductions in body weight and systolic blood pressure.

In two studies comparing canagliflozin plus metformin to current standard treatments plus metformin—one using sitagliptin and one using glimepiride—regimens with canagliflozin 300 mg provided greater reductions in hemoglobin A1c and body weight than either comparator.

The most common adverse reactions due to the initiation of metformin included diarrhea, nausea/vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.

Canagliflozin can increase the risk of hypoglycemia when combined with insulin or with a medication that increases insulin levels, such as a sulfonylurea. A lower dose of insulin or an insulin-increasing medication may be required to minimize the risk of hypoglycemia when used in combination with canagliflozin.

Source: Janssen Pharmaceuticals, August 8, 2014

Jardiance for Type-2 Diabetes

Empagliflozin (Jardiance, Boehringer Ingelheim) has received FDA approval as an addition to diet and exercise to improve glycemic control in adults with type-2 diabetes.

Empagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, blocks the reabsorption of glucose by the kidney. Its safety and effectiveness were evaluated in seven clinical trials involving 4,480 patients with type-2 diabetes. The pivotal trials showed that empagliflozin improved hemoglobin A1c levels compared with placebo.

Empagliflozin has been studied as a stand-alone therapy and in combination with other type-2 diabetes treatments, including metformin, sulfonylureas, pioglitazone, and insulin. The drug should not be used to treat patients with type-1 diabetes, diabetic ketoacidosis, severe renal impairment, or end-stage renal disease or patients receiving dialysis.

The FDA is requiring four post-marketing studies of empagliflozin:

- Completion of an ongoing cardiovascular outcomes trial
- A pediatric pharmacokinetic/pharmacodynamic study
- A pediatric safety and efficacy study, in which the effect on bone health and development will be evaluated
- A nonclinical (animal) juvenile toxicity study, with a focus on renal development, bone development, and growth

Empagliflozin can cause dehydration, leading to hypotension, which can result in dizziness and/or fainting and a decline in renal function. The elderly, patients with impaired renal function, and patients receiving diuretics to treat other conditions appeared to be more susceptible to this risk. The most common adverse effects of empagliflozin are urinary tract infections and female genital infections.

Source: FDA, August 1, 2014

Zydelig for Three Blood Cancers

The FDA has approved idelalisib (Zydelig, Gilead Sciences) for the treatment of three types of blood cancer.

The drug received traditional approval to treat patients whose chronic lymphocytic leukemia (CLL) has relapsed. In combination with rituximab (Rituxan, Genentech), idelalisib is to be used in patients for whom rituximab alone would not be appropriate because of comorbidities.

Idelalisib received accelerated approval for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) or relapsed small lymphocytic lymphoma (SLL), another type of non-Hodgkin lymphoma. Idelalisib is intended to be used in patients who have received at least two prior systemic therapies.

continued on page 598
The safety and effectiveness ofidelalisib in treating relapsed CLL were established in a clinical trial involving 220 subjects who were randomly assigned to receive idelalisib and rituximab or placebo and rituximab. The trial was stopped for efficacy after the first prespecified interim analysis, which showed that subjects treated with idelalisib and rituximab had the possibility of living at least 10.7 months without disease progression compared with approximately 5.5 months for subjects treated with placebo and rituximab. Results from a second interim analysis continued to show a statistically significant improvement for idelalisib and rituximab compared with placebo and rituximab.

The safety and effectiveness ofidelalisib for the treatment of relapsed FL and relapsed SLL were established in a clinical trial involving 123 subjects with indolent non-Hodgkin lymphomas. All were treated with idelalisib and evaluated for the complete or partial disappearance of their cancer after treatment (i.e., the objective response rate [ORR]). ORR was reported among 54% of the subjects with relapsed FL and 58% of those with SLL.

Idelalisib has a boxed warning about the potential for fatal and serious toxicities, including liver toxicity, diarrhea, colitis, pneumonitis, and intestinal perforation. Common side effects include diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash. Common laboratory abnormalities include neutropenia, hypertriglyceridemia, hyperglycemia, and elevated liver enzyme levels.

Idelalisib is an oral inhibitor of phosphoinositide 3-kinase (PI3K) delta, which plays a role in the activation, proliferation, and viability of B cells. PI3K delta signaling is active in many B-cell leukemias and lymphomas; idelalisib blocks cellular signaling pathways that drive B-cell viability.

Sources: FDA and Gilead Sciences, July 23, 2014

**Plegridy for Multiple Sclerosis**

The FDA has approved peginterferon beta-1a (Plegridy, Biogen Idec) for the treatment of patients with relapsing forms of multiple sclerosis (MS).

Plegridy is the only pegylated beta interferon (IFN) approved for use in relapsing MS. It is dosed once every two weeks and can be administered subcutaneously (SC) with the Plegridy pen (a ready-to-use auto-injector) or a prefilled syringe.

The FDA’s approval is based on the pivotal ADVANCE trial, which involved more than 1,500 MS patients. The two-year, phase 3, placebo-controlled (in year 1) study evaluated the efficacy and safety of Plegridy administered SC. The analyses for all primary and secondary efficacy endpoints occurred at the end of year 1. After the first year, patients receiving placebo were treated with Plegridy for the rest of the study.

In year 1, Plegridy dosed once every two weeks reduced the annualized relapse rate by 36%, reduced the risk of 12-week confirmed disability progression by 38%, reduced the number of new gadolinium-enhancing lesions by 86%, and reduced new or newly enlarging T2-hyperintense lesions by 67%. The most common adverse events included injection-site reactions, flu-like illness, fever, headache, muscle pain, chills, injection-site pain, weakness, injection-site itching, and joint pain.

The IFN beta-1a in Plegridy is pegylated to extend its half-life, allowing less-frequent dosing. The recommended dosage is 125 mcg injected SC every 14 days. Patients should start treatment with 63 mcg on day 1. On day 15, the dose is increased to 94 mcg, reaching the full dose of 125 mcg on day 29.

IFN beta has been associated with severe hepatic injury, depression, suicidal ideation, suicide, seizures, congestive heart failure, cardiomyopathy, decreased peripheral blood counts, autoimmune disorders, and (rarely) anaphylaxis. Injection-site reactions, including injection-site necrosis, can occur with the use of IFN beta given SC.

Sources: Biogen Idec, August 15, 2014, and Plegridy prescribing information

**Orbactiv for Skin Infections**

Oritavancin for injection (Orbactiv, The Medicines Company) has been given FDA approval for the treatment of adults with acute bacterial skin and skin-structure infections (ABSSSIs) caused by susceptible designated gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).

Oritavancin is the only antibiotic approved to treat ABSSSIs in a single administration. Once fully infused over three hours, treatment is complete for patients with skin infections caused by susceptible gram-positive pathogens.

FDA approval was based on the randomized, double-blind SOLO I and SOLO II trials, which evaluated one 1,200-mg intravenous dose of oritavancin for ABSSSIs in 1,987 patients and assessed 405 patients with documented MRSA infections. These studies demonstrated noninferiority for once-only oritavancin infusion compared with seven to 10 days of twice-daily vancomycin (1 g or 15 mg/kg).

The most common side effects included headache, nausea, vomiting, the formation of skin and soft-tissue abscesses on arms and legs, and diarrhea. The product labeling includes a warning regarding interference with coagulation tests and interaction with warfarin.

Oritavancin for injection is indicated for the treatment of ABSSSIs caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*),
and Enterococcus faecalis (vancomycin-susceptible isolates only).

Sources: FDA and The Medicines Company, August 6, 2014

**Targiniq ER Oxycodone**

The FDA has approved oxycodone hydrochloride and naloxone hydrochloride extended-release tablets (Targiniq ER, Purdue Pharma) to treat pain that is severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

The medication has properties that are expected to deter, but not eliminate, abuse of the oxycodone component by snorting and injection. When it is crushed and snorted, or crushed, dissolved, and injected, the naloxone in Targiniq ER blocks the euphoric effects of oxycodone, so abusers like it less than oxycodone alone. Naloxone is commonly used to reverse the effects of opioid overdose.

Targiniq ER is not approved for and should not be used for as-needed pain relief. Given its risks for abuse, misuse, and addiction, it should be prescribed only to people for whom alternative treatment options are ineffective, are not tolerated, or would otherwise be inadequate to provide sufficient pain management.

The safety and effectiveness of Targiniq ER were evaluated in a clinical study involving 601 subjects with chronic low back pain. The safety database supporting approval included more than 3,000 subjects treated with Targiniq ER. Data from in vitro and in vivo abuse-liability studies demonstrated the abuse-deterrent features of Targiniq ER as they relate to snorting and injection. The most common side effects of treatment with Targiniq ER are nausea and vomiting.

The FDA is requiring post-marketing studies to assess the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with use beyond 12 weeks. The FDA is also requiring post-marketing studies to further assess the effects of the drug’s abuse-deterrent features on the risk for abuse. Targiniq ER is part of the Extended Release/Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy.

Source: FDA, July 23, 2014

**Belsomra for Insomnia**

Suvorexant (Belsomra, Merck, Sharp & Dohme Corp.) has received FDA approval for use as needed to treat insomnia. Suvorexant is the first in a new class of drugs called orexin receptor antagonists. Orexins help regulate the sleep–wake cycle and play a role in keeping people awake. Suvorexant alters orexin signaling in the brain.

The FDA approved suvorexant in 5-, 10-, 15-, and 20-mg strengths. Using the lowest effective dose can reduce the risk of side effects. The total dosage should not exceed 20 mg once a night, taken within 30 minutes of going to bed and at least seven hours before the planned waking time.

Drowsiness was the most common adverse event in clinical trials. Medications that treat insomnia can impair next-day alertness, even among people who feel fully awake.

The FDA asked Merck to study next-day driving performance in people who had taken suvorexant. The testing showed impaired driving performance in men and women who took the 20-mg strength. Patients using the 20-mg strength should be cautioned against next-day driving or activities requiring full mental alertness. Patients taking lower doses should be made aware of the potential for next-day driving impairment because of individual variation in sensitivity to the drug.

In three clinical trials involving more than 500 participants, patients taking suvorexant fell asleep faster and spent less time awake at night compared with subjects taking a placebo.

There is a risk with suvorexant of sleep-driving and other complex behaviors while not being fully awake. Chances of such activity increase among people who consume alcohol or take other medicines that make them sleepy.

Belsomra will be dispensed with a patient medication guide that provides instructions for its use and important safety information. Belsomra is a controlled substance (schedule IV) because of the potential for abuse or dependence.

Source: FDA, August 13, 2014

**Striverdi Respimat for COPD**

The FDA has approved once-daily olodaterol inhalation spray (Striverdi Respimat, Boehringer Ingelheim) to treat patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, who are experiencing airflow obstruction.

Olodaterol is a long-acting beta-adrrenergic agonist (LABA) that helps the muscles around the airways in the lungs stay relaxed to prevent symptoms. The safety and effectiveness of olodaterol were evaluated in 3,104 subjects diagnosed with COPD. Subjects treated with olodaterol showed improved lung function compared with those given placebo.

The drug’s labeling includes a boxed warning that LABAs increase the risk of asthma-related death. The safety and effectiveness of olodaterol in people with asthma have not been established, and it is not approved to treat asthma. The drug should not be used as a rescue therapy to treat acute bronchospasm.

Olodaterol should not be used in patients with acutely deteriorating COPD and may cause serious side effects in them, including paradoxical bronchospasm and cardiovascular effects.

The most common adverse effects associated with olodaterol in the clinical study included nasopharyngitis, upper respiratory tract infection, bronchitis,
cough, urinary tract infection, dizziness, rash, diarrhea, back pain, and arthralgia.
Source: FDA, July 31, 2014

Ruconest for Hereditary Angioedema
The FDA has approved the C1 esterase inhibitor, recombinant (Ruconest, Salix Pharmaceuticals/Pharming Group) 50 IU/kg for the treatment of acute angioedema attacks in adults and adolescents with hereditary angioedema (HAE).

Ruconest can be administered by a patient who has received training from a health care provider. Because of the limited number of patients with laryngeal attacks, the effectiveness of the drug in this setting was not established.

HAE attacks are caused by a deficiency of the C1 inhibitor protein in the blood. HAE is a rare inherited genetic condition that is often not properly diagnosed until later in life because the symptoms of an attack can mirror an allergic reaction. Severe, painful swelling can occur at any time.

FDA approval was based on the results of a phase 3, randomized, double-blind, placebo-controlled trial (RCT) that included an open-label extension (OLE) phase. This study was supported by results from two additional RCTs and two additional OLE studies. The pivotal trials evaluated 44 subjects who experienced 170 HAE attacks. A statistically significant difference in the time to the beginning of symptom relief was observed in the intent-to-treat population for Ruconest compared with placebo ($P = 0.031$). The median time to the beginning of symptom relief was 90 minutes for Ruconest and 152 minutes for placebo.
Source: Salix Pharmaceuticals, July 17, 2014

Acticlate for Infections
The tetracycline-class antibacterial doxycycline hyclate (Acticlate, Aqua Pharmaceuticals) has received FDA approval to treat a number of infections, including severe acne as adjunctive therapy.

The film-coated, round 75-mg tablets and oval-shaped, dual-scored 150-mg tablets are designed to be smaller and perhaps easier to swallow than other available scored doxycycline tablets. Doxycycline hyclate should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.
Source: Aqua Pharmaceuticals, July 28, 2014

Generic Approvals
Ropivacaine Hydrochloride Injection
The FDA has approved Navinta LLC’s ropivacaine hydrochloride injection USP, 0.5% (5 mg/mL) packaged in 150 mg/30 mL single-dose vials and 1% (10 mg/mL) packaged in 200 mg/20 mL single-dose vials—the first generic version of the anesthetic Naropin Injection, manufactured by Fresenius Kabi USA.
Source: FDA, July 17, 2014

Methoxsalen
Strides Arcolab’s 10-mg methoxsalen soft gelatin capsules have received FDA approval as the first generic version of Oxsoralen-Ultra capsules. Methoxsalen is indicated for the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other therapy, with a diagnosis supported by biopsy. Methoxsalen is administered in conjunction with controlled doses of long-wave ultraviolet radiation.
Sources: FDA, June 5, 2014, and Oxsoralen-Ultra prescribing information

Argatroban Injection
The FDA has approved generic argatroban injection, 100mg/mL in 250mg/2.5mL single-dose vials, manufactured by Par Sterile Products, LLC, and Mylan Institutional, LLC. Argatroban (the generic version of Pfizer’s Acova Injection) is a direct thrombin inhibitor indicated for prophylaxis or treatment of thrombosis in adults with heparin-induced thrombocytopenia (HIT) and as an anticoagulant in adults with or at risk for HIT undergoing percutaneous coronary intervention.
Sources: FDA, June 30, 2014, and Acova prescribing information

Codeine Sulfate
The opioid analgesic codeine sulfate in 15-mg, 30-mg, and 60-mg tablets manufactured by Lannett Company Inc. has received FDA approval as the generic version of Roxane’s Codeine Sulfate tablets.
Source: FDA, June 13, 2014

NEW INDICATIONS
Avastin for Cervical Cancer
The FDA has approved bevacizumab (Avastin, Genentech) in combination with paclitaxel and cisplatin or paclitaxel and topotecan for the treatment of women with persistent, recurrent, or metastatic cervical cancer. Bevacizumab now has U.S. approval to treat five tumor types.

The latest approval was based on the GOG-0240 study, which assessed the efficacy and safety of bevacizumab plus chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) in women with persistent, recurrent or metastatic cervical cancer.

Overall survival (OS) rose 26% in women who received bevacizumab plus chemotherapy compared with those who received chemotherapy alone (16.8 months vs. 12.9 months, respectively). Women who received bevacizumab plus chemotherapy had a significantly higher objective response rate compared to chemotherapy alone (45% vs. 34%). In bevacizumab-containing regimens compared with chemotherapy alone, there were more reports of grade 2 or higher hypertension (29% vs. 6%), grade 3 or higher thrombosis (8.3% vs. 2.7%), and gastrointestinal-vaginal fistulas (8.2% vs. 0.9%).
In July, the FDA granted priority review to an application for an additional indication for bevacizumab plus chemotherapy for the treatment of women with recurrent platinum-resistant ovarian cancer. In the phase 3, randomized, open-label AURELIA trial, 361 women with platinum-resistant recurrent epithelial ovarian primary peritoneal or fallopian tube cancer who had received no more than two prior anticancer regimens were assigned to one of six arms (paclitaxel, topotecan, or liposomal doxorubicin with or without bevacizumab).

Bevacizumab plus chemotherapy increased progression-free survival (PFS) by 52% compared with chemotherapy alone (6.7 months vs. 3.4 months). No statistically significant difference was seen in OS (16.6 months vs. 13.3 months). Women treated with bevacizumab plus paclitaxel experienced 54% longer PFS compared with those on chemotherapy alone (10.4 months vs. 3.9 months) and a 35% improvement in OS (22.4 months vs. 13.2 months).

Bevacizumab interferes with tumors’ blood supplies. It is also approved, in certain circumstances or combinations, for treatment of colorectal cancer, non–small-cell lung cancer, and renal-cell carcinoma.

Source: Genentech, August 14, 2014, and July 21, 2014

**Ibrutinib Use for CLL Expanded**

The FDA has expanded the approved use of ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) to treat patients with chronic lymphocytic leukemia (CLL) who carry a deletion in chromosome 17 (17p deletion), which is associated with poor responses to standard treatment for CLL. Ibrutinib had received a breakthrough therapy designation for this use.

The FDA also approved new labeling to reflect that ibrutinib’s clinical benefit in treating CLL has been verified. In February 2014, ibrutinib received accelerated approval to treat CLL based on its effect on the overall response rate. New clinical trial results examining progression-free survival (PFS) and overall survival (OS) have confirmed the drug’s clinical benefit. A type of non-Hodgkin lymphoma, CLL is a rare disease of the blood and bone marrow that usually worsens slowly over time, causing a gradual increase in B lymphocytes.

The FDA approvals were based on a clinical study of 391 previously treated patients, who were randomly assigned to receive ibrutinib or ofatumumab until disease progression or side effects became intolerable. The study was stopped early for efficacy after a preplanned interim analysis showed that ibrutinib-treated participants experienced increases of 78% in PFS and 57% in OS. Among the 127 participants who had CLL with the 17p deletion, those treated with ibrutinib experienced a 75% reduction in the risk of disease progression or death.

The most common side effects with ibrutinib included thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, upper respiratory tract infection, rash, nausea, and fever.

Source: FDA, July 28, 2014

**Velcade for Retreatment Of Multiple Myeloma**

Bortezomib (Velcade, Millennium/Takeda) has received FDA approval for the retreatment of adult patients with multiple myeloma (MM) who had responded to bortezomib therapy and had relapsed at least six months after the completion of prior bortezomib treatment.

The labeling update includes dosing guidelines as well as safety and efficacy findings for the use of bortezomib as a single agent or in combination with dexamethasone in patients previously treated with bortezomib. Bortezomib retreatment may be started at the last tolerated dose.

The phase 2 RETRIEVE trial showed a 38.5% overall response rate in MM patients who had been treated with a bortezomib-based regimen (a median of two prior lines of therapy) and had previously achieved a partial response or better. The safety profile with bortezomib retreatment was consistent with the known safety profile of intravenous bortezomib in relapsed MM; no cumulative toxicities were observed during retreatment. The most common adverse reaction was thrombocytopenia in 52% of the patients.

RETRIEVE, a single-arm, open-label trial, enrolled 130 patients ages 18 years and older who had previously responded to bortezomib-based therapy and who had relapsed at least six months before treatment with bortezomib.

Bortezomib is approved for the treatment of MM patients and mantle cell lymphoma patients who have received at least one prior treatment.

Source: Millennium, August 8, 2014

**Octagam for Immune Thrombocytopenic Purpura**

The FDA has approved immune globulin intravenous (human) 10%, 100 mg/mL liquid preparation (Octagam 10%, Octapharma USA) for the treatment of adults with chronic immune thrombocytopenic purpura (ITP), a platelet disorder that can result in easy or excessive bruising and bleeding.

Since 2004, immune globulin intravenous (human) 5%, 50 mg/mL liquid preparation (Octagam 5%) has been marketed for the treatment of primary humoral immunodeficiency.

The FDA’s approval was based on the results of a clinical trial that evaluated the safety and efficacy of Octagam 10% in 66 patients with chronic ITP. The study found that 82% of patients attained a clinical response (i.e., a platelet count of at least 50 x 109/L within seven days of dosing) that was significantly higher than the predicted responder rate of 70%. Further, 78% of patients who had bleeding
at baseline reported no bleeding seven days after treatment.

The most common treatment-related adverse events associated with Octagam 10% included headache, fever, and increased heart rate. The most serious adverse event was a moderate headache.

Octagam 10% is indicated for the treatment of chronic ITP in adults to rapidly increase platelet counts to control or prevent bleeding. Octagam 10% is a solvent/detergent-treated, sterile preparation of highly purified immunoglobulin G derived from large pools of human plasma. The product is a solution for infusion to be administered intravenously.

The labeling for Octagam 10% includes a boxed warning regarding the potential for thrombosis, renal dysfunction, and acute renal failure.

Sources: Octapharma USA, July 15, 2014, and Octagam 10% prescribing information

**Lumizyme for All Pompe Disease**

The FDA has expanded the indication for alglucosidase alfa (Lumizyme, Genzyme) in patients with Pompe disease. Lumizyme (manufactured at the 4,000-L scale) is now indicated for all Pompe patients of any age or phenotype.

Previously, in the U.S., Lumizyme had been approved only for patients with late-onset Pompe disease. In the U.S., alglucosidase alfa is manufactured at two production scales. Alglucosidase alfa manufactured at the 160-L scale (initial pilot scale) has a brand name of Myozyme, and alglucosidase alfa manufactured at the 4,000-L scale (final manufacturing scale) has a brand name of Lumizyme. In the rest of the world, only alglucosidase alfa manufactured at 4,000 L is available. Based on biochemical and clinical data, the FDA concluded that alglucosidase alfa manufactured at both scales in the U.S. (i.e., Lumizyme and Myozyme) is comparable.

Pompe disease is a rare, progressive, debilitating, and often fatal neuromuscular disease caused by a genetic deficiency or dysfunction of the lysosomal enzyme acid alpha-glucosidase. This enzymatic defect results in the accumulation of glycogen, primarily in muscle tissues, which leads to muscle weakness, loss of respiratory function, and often premature death.

Specific updates to the Lumizyme product label include the removal of the Risk Evaluation and Mitigation Strategies (REMS) program and an update to the boxed warning to include an infantile-onset-specific warning regarding fluid overload. The current boxed warning includes the potential for anaphylaxis, hypersensitivity, immune-mediated reactions, or cardiopulmonary failure.

Source: Genzyme, August 1, 2014

**Eylea for Diabetic Macular Edema**

The FDA has approved aflibercept (Eylea, Regeneron Pharmaceuticals) for the treatment of diabetic macular edema (DME). The recommended dosage is 2 mg every eight weeks after five initial monthly injections; additional efficacy was not demonstrated when the product was dosed every four weeks.

FDA approval was based on one-year data from two ongoing phase 3 trials—VISTA-DME and VIVID-DME—involving 862 patients. These studies compared aflibercept 2 mg every four weeks, aflibercept 2 mg every eight weeks (after five initial monthly injections), or macular laser photocoagulation (at baseline and then as needed). Across both trials, patients in the aflibercept dosing groups gained, on average, the ability to read approximately two additional lines on an eye chart compared with almost no change in the control group.

Aflibercept had a similar incidence of adverse events across treatment groups compared with the control group. The most common included conjunctival hemorrhage, eye pain, cataract, vitreous floaters, hypertension, and nasopharyngitis.

Aflibercept, a vascular endothelial growth factor (VEGF) inhibitor formulated as an injection for the eye, is designed to block the growth of new blood vessels and to decrease vascular permeability in the eye by blocking VEGF-A and placental growth factor, both of which are involved in angiogenesis.

Source: Regeneron, July 29, 2014

**NEW FORMULATIONS**

**Rasuvo for Arthritis, Psoriasis**

The FDA has approved a subcutaneous injectable methotrexate (Rasuvo, Medac Pharma) for the treatment of patients with rheumatoid arthritis (RA), polyarticular-course juvenile idiopathic arthritis (pJIA), or psoriasis. The product will be available in 10 dosage strengths, ranging from 7.5 mg to 30 mg in 2.5-mg increments.

Methotrexate is the most commonly used drug for treating RA. Oral forms have been associated with highly variable absorption rates and inconsistent bioavailability, according to Medac. The subcutaneous mode of delivery was designed to improve bioavailability.

Methotrexate inhibits dihydrofolate reductase, thereby interfering with DNA synthesis, repair, and cellular replication.

Subcutaneous methotrexate is a folate analog metabolic inhibitor indicated for the management of patients with severe, active RA or pJIA who are intolerant of or had an inadequate response to first-line therapy. Rasuvo is also indicated for symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. It is not approved for the treatment of neoplastic diseases.

The labeling for Rasuvo includes a boxed warning regarding the potential for severe toxic reactions, including embryofetal toxicity and death.

Sources: Medac Pharma, July 14, 2014, and Rasuvo prescribing information
Ryanodex for Malignant Hyperthermia

The FDA has approved dantrolene sodium for injectable suspension (Ryanodex, Eagle Pharmaceuticals) for the treatment of malignant hyperthermia (MH), along with appropriate supportive measures. MH is an inherited, potentially fatal disorder triggered by certain anesthesia agents in genetically susceptible individuals.

The FDA designated Ryanodex as an orphan drug in August 2013 and granted priority review status in March 2014.

According to Eagle Pharmaceuticals, Ryanodex allows anesthesiologists to deliver a therapeutic dose of dantrolene sodium—the only antidote for MH—in a more expedient manner than is possible with other intravenous (IV) dantrolene products.

Ryanodex provides a therapeutic loading dose of dantrolene sodium in a single vial. Dantrolene 250 mg is mixed with 5 mL of sterile water and administered to the patient in less than one minute. Other dantrolene sodium formulations require multiple 20-mg vials reconstituted in large volumes of sterile water; it can take 15 to 20 minutes to mix, reconstitute, and administer them.

Ryanodex should be administered by continuous rapid IV push, beginning with a loading dose of 2.5 mg/kg and continuing until symptoms subside.

MH can be triggered when genetically susceptible individuals come in contact with certain inhaled (volatile) anesthetics or the muscle relaxant succinylcholine. These patients can experience tachycardia, elevated blood pressure, raised carbon dioxide levels, and a very high body temperature. If not treated immediately, the hypermetabolic episode can be fatal.

Source: Eagle Pharmaceuticals, July 23, 2014

CD19 proteins. After they have been reprogrammed, the T cells are reintroduced into the patient’s blood. They proliferate and bind to the targeted CD19-positive cancer cells, destroying them.

In one study, 22 pediatric patients with relapsed or refractory ALL received a targeted T-cell dose range of 107 to 108 cells/kg, with a transduction efficiency (TE) of 11% to 45%, and five adult patients received a target dose of 5 x 109 total cells divided over three days, with a TE of 6% to 31%.

Among the pediatric patients, 19 (86%) achieved complete remission (CR), but five later relapsed. All five of the first adult ALL patients treated with CTL019 experienced CRs, the longest of which continued six months after treatment.

Source: Novartis, July 7, 2014, and December 7, 2013

Pirfenidone for Pulmonary Fibrosis

The investigational antifibrotic agent pirfenidone (InterMune, Inc.) has been designated a breakthrough therapy by the FDA for the treatment of patients with idiopathic pulmonary fibrosis (IPF).

Pirfenidone is an orally active, antifibrotic agent that inhibits the synthesis of transforming growth factor-beta, a chemical mediator that controls many cell functions, including proliferation and differentiation, and that plays a key role in fibrosis. Pirfenidone also inhibits the synthesis of tumor necrosis factor-alpha, a cytokine that is known to have an active role in inflammation.

IPF is an irreversible and ultimately fatal disease characterized by progressive loss of lung function due to fibrosis, which hinders the ability of the lungs to absorb oxygen. IPF inevitably causes shortness of breath, and a deterioration in lung function and exercise tolerance.

Source: InterMune, Inc., June 17, 2014

DRUG NEWS

Breakthrough Therapy Status

Vaccine Combo for Pancreatic Cancer

The FDA has granted a breakthrough therapy designation for an investigational pancreatic cancer combination treatment consisting of GVAX Pancreas and CRS-207 immunotherapies (Aduro Biotech, Inc.).

In a randomized, controlled, phase 2 trial among 93 patients with metastatic pancreatic cancer who had failed or refused prior therapy, the median overall survival (OS) of patients receiving the combination of the two vaccines was 6.1 months compared with 3.9 months for those receiving GVAX Pancreas vaccine alone (hazard ratio, 0.59; P = 0.0172).

A phase 2b clinical trial (ECLIPSE) in 240 patients with metastatic pancreatic cancer who have progressed after at least one line of therapy will evaluate the safety, immune response, and efficacy of combination immunotherapy with GVAX Pancreas and CRS-207 compared with chemotherapy or CRS-207 alone.

The GVAX Pancreas vaccine is derived from human cancer cell lines that are genetically modified to secrete granulocyte-macrophage colony-stimulating factor, an immune-stimulatory cytokine. The CRS-207 vaccine is based on a live-attenuated, double-deleted Listeria monocytogenes immunotherapy platform, which induces an innate and T-cell-mediated immune response. Both vaccines express the tumor-associated antigen mesothelin.

Source: Aduro Biotech, Inc., July 21, 2014

CTL019 for ALL

The FDA has granted breakthrough therapy status to CTL019 (Novartis), an investigational chimeric antigen receptor therapy for the treatment of pediatric and adult patients with relapsed or refractory acute lymphoblastic leukemia (ALL).

CTL019 reprograms a patient’s own T cells to “hunt” cancer cells that express...
FDA Priority Reviews
Simeprevir/Sofosbuvir for HCV
The FDA has given a priority review designation to a supplemental new drug application for the use of once-daily simeprevir (Olysio, Medivir/Janssen), an NS3/4A protease inhibitor, in combination with sofosbuvir (Sovaldi, Gilead Sciences), an NS5B polymerase inhibitor, for 12 weeks of treatment in adults with genotype-1 chronic hepatitis C virus (HCV) infection.

The application was supported by data from the phase 2 COSMOS trial, which included treatment-naïve patients with advanced fibrosis and prior null-responders with all stages of liver fibrosis. In this study, 93% of the patients achieved a sustained virological response 12 weeks after the end of treatment (SVR12). The addition of ribavirin did not improve SVR rates, and consistent responses for both treatment arms were seen across HCV genotype subgroups after 12 weeks. The most common adverse events were fatigue, headache, nausea, anemia, pruritus, dizziness, rash, and photosensitivity.

Sources: Medivir, July 15, 2014, and April 12, 2014

Ruxolitinib for Polycythemia Vera
A supplemental new drug application for ruxolitinib (Jakafi, Incyte Corp.) as a potential treatment for patients with polycythemia vera (PV) who have shown an inadequate response to or are intolerant of hydroxyurea will receive priority review from the FDA, with an action date of December 5, 2014.

Ruxolitinib is the first FDA-approved treatment for patients with intermediate- or high-risk myelofibrosis (MF), including primary MF, post-PV MF, and post–essential thrombocythemia MF. Ruxolitinib is also the first JAK1/ JAK2 inhibitor to demonstrate efficacy in a phase 3 study of patients with PV. If approved, it would be the first JAK1/ JAK2 inhibitor available to U.S. patients with PV, a myeloproliferative neoplasm characterized by an overproduction of normal red blood cells, white blood cells, and platelets that leads to an increased risk of thrombosis.

Erythrocytosis is the most prominent clinical manifestation of PV. Patients with uncontrolled PV have an increased risk of cardiovascular complications, such as stroke, pulmonary embolism, deep vein thrombosis, and heart attack.

Source: Incyte Corp., August 5, 2014

Fast Track Designation to Pacritinib for Myelofibrosis
CTI BioPharma Corp.’s pacritinib has been granted fast track designation by the FDA for the treatment of intermediate- and high-risk myelofibrosis (MF). Treatment could include (but is not limited to) patients with disease-related thrombocytopenia, patients experiencing treatment-emergent thrombocytopenia on other JAK2 therapy, or patients who are intolerant to or whose symptoms are suboptimally managed on other JAK2 therapy.

Pacritinib, an oral tyrosine kinase inhibitor with dual activity against JAK2 and FLT3, is being evaluated in two phase 3 clinical trials for MF patients. PERSIST-1, with approximately 320 patients, is a randomized, open-label, multicenter trial comparing the efficacy and safety of pacritinib with that of best available therapy, other than JAK inhibitors, in patients with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF, without limitations on blood platelet counts. The PERSIST-2 trial will evaluate pacritinib compared to best available therapy, including approved JAK2 inhibitors that are dosed according to the product label, in up to 300 patients with MF whose platelet counts are less than or equal to 100,000/uL.

Source: CTI BioPharma, August 7, 2014

FDA Committees to Address Testosterone Product Safety
The FDA has scheduled a September 17 joint meeting of its Bone, Reproductive, and Urologic Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee to discuss the appropriate indicated population for testosterone replacement therapy and the potential for adverse cardiovascular outcomes associated with this use.

In January, the FDA announced that it was investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. The agency decided to reassess the issue based on the publication of two studies that suggested an increased risk of cardiovascular events among men prescribed testosterone therapy.

An observational study published in the Journal of the American Medical Association in November 2013 found a 30% increased risk of stroke, heart attack, and death among men in the Veteran Affairs health system who had been prescribed testosterone therapy. The men had low serum testosterone and were undergoing coronary angiography to assess for coronary artery disease. Some of the men received testosterone treatment, while others did not. On average, the men in the study were about 60 years old; many had underlying cardiovascular disease.

A second observational study reported an increased risk of heart attack in older men, as well as in younger men with preexisting heart disease, who filled a prescription for testosterone therapy. This study reported a twofold increase in the risk of heart attack among men 65 years of age and older in the first 90 days following the first prescription. Among men younger than 65 years old with a pre-existing history of heart disease, the study reported a twofold to threefold increased risk of heart attack in the first 90 days following a first prescription. Younger men...
without a history of heart disease who filled a prescription for testosterone did not have an increased risk of heart attack.

Testosterone is essential to the development of male growth and masculine characteristics. Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition, such as failure of the testicles to produce testosterone because of genetic problems, chemotherapy, or other problems.


**The High Cost of HCV Drugs**

Americans will pay a steep price for treating people infected with the hepatitis C virus (HCV), according to two new estimates.

Average Medicare Part D premiums could rise by up to 8.6% in 2015 as a result of costly new HCV drugs, according to a report by the actuarial firm Milliman that was released by the Pharmaceutical Care Management Association (PCMA). Milliman projects that the drugs will increase Part D spending by $2.9 billion to $5.8 billion next year.

Milliman bases its projections on the assumption that 15% to 30% of the Part D population estimated to be infected with HCV will receive an $84,000 course of treatment in 2015.

Meanwhile, a commentary in the *Journal of the American Medical Association (JAMA)* speculates that treating HCV “could add $200 to $300 per year to every insured American’s health insurance premium for each of the next five years.” CVS Caremark Chief Medical Officer Troyen A. Brennan, MD, and Chief Scientific Officer William Shrank, MD, write that the pool of eligible U.S. patients may be as high as 3 million.

By reducing costs associated with HCV disease progression, Drs. Brennan and Shrank say, “these newer expensive medications may represent a relatively good ‘deal’ by typical cost-effectiveness thresholds.” Still, they add, expensive specialty medications with large potential pools of targeted patients require more effective cost-control approaches that “ensure broad, equitable, and appropriate use of these new interventions in an already stressed health care system.”

Sources: PCMA, July 29, 2014, and *JAMA*, August 21, 2014

**Boxed Warning for Linzess**

A new boxed warning for linaclotide (Linzess, Forest Laboratories) states that the medication is contraindicated in pediatric patients up to 6 years of age.

Linaclotide, a guanylate cyclase-C (GC-C) agonist, is used in adults for treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation. In neonatal mice, increased fluid secretion as a consequence of GC-C agonism caused dehydration deaths within the first 24 hours. Because of increased intestinal expression of GC-C, children under 6 years of age may be more likely than older children and adults to develop significant diarrhea.

The boxed warning also advises providers to avoid use of Linzess in patients 6 through 17 years of age, as the medication’s safety and efficacy have not been established in patients less than 18 years of age.

Source: FDA, July 2014

**Antibiotics May Raise Warfarin Bleeding Risks**

Regular monitoring becomes even more important for patients using warfarin if they’re taking certain antibiotics, according to a study of 22,272 Veterans Affairs (VA) patients. The study by researchers from St. Louis VA Medical Center and Washington University included veterans who were prescribed warfarin for 30 days or more without interruption between 2002 and 2008.

Antibiotics were grouped based on their known interaction with warfarin. Those known to increase bleeding risk were labeled “high risk,” including trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, levofloxacin, metronidazole, fluconazole, azithromycin, and clarithromycin. “Low-risk” antibiotics included clindamycin and cephalaxin.

High-risk antibiotics increased the risk of serious bleeding as a primary diagnosis by nearly 50% compared with low-risk antibiotics. Among the 8,194 patients on low-risk antibiotics, 36 had a bleeding event, compared with 93 of the 14,078 patients on high-risk antibiotics. When serious bleeding was listed as a primary or secondary reason for admission, TMP/SMX, ciprofloxacin, levofloxacin, azithromycin, and clarithromycin doubled or nearly doubled the risk of serious bleeding compared with low-risk antibiotics.

Among warfarin users who received high-risk antibiotics, 7.8% had international normalized ratio (INR) elevations of more than 4 and less than or equal to 6. Metronidazole, fluconazole, and receipt of two or more high-risk antibiotics were also associated with elevated INR. Compared with low-risk antibiotics, fluconazole and metronidazole increased INR significantly, with 9.7% and 4.9% of patients, respectively, having elevations of 6 or higher. INR evaluation within three to 14 days of antibiotic co-prescription reduced the risk of serious bleeding by 39%.

Source: *American Journal of Medicine*, July 2014

**Vitamin D Deficiency and Orthostatic Hypotension**

Low levels of vitamin D may contribute to orthostatic hypotension (OH) in older patients, Turkish researchers say. Their study of 546 patients found 32% of those with vitamin D levels below 20 ng/mL had continued on page 610
The analysis showed that 150 participants had OH (35% of men and 65% of women). Of those with OH, 17% had a drop in systolic BP; 20% had a drop in diastolic BP; and 9% had a drop in both. Albumin, hemoglobin, calcium, triglyceride, low-density lipoprotein, high-density lipoprotein, thyroid-stimulating hormone, HbA1c, folic acid, and vitamin B12 levels were not significantly different between the groups. Only serum levels of vitamin D were found to be lower in patients with OH compared to patients without OH. The researchers found a significant relation between vitamin D and both reduced systolic and diastolic BP.

OH is closely linked to mortality and morbidity. In this study, patients with OH had lower scores on indexes of activities of daily living. OH can also lead to falls, impaired sleep, depression, and stroke. Approximately one-third of older patients have OH, although they describe no complaints. Thus, the researchers conclude, recording changes in postural blood pressure should be part of the routine exam in older patients.

Source: *Archives of Gerontology and Geriatrics*, July/August 2014

**When Should Men Get Anti-Osteoporosis Drugs?**

Among people older than age 50, men account for about 29% of fractures, which often happen at sites of low bone-mineral density and are considered to be related to osteoporosis.

But when to treat men with drugs to prevent fractures is a matter of debate, in part because the cut-off point for risk is not well defined. The World Health Organization (WHO) and the National Osteoporosis Foundation (NOF) differ. However, in the Multicenter Osteoporotic Fractures in Men study, when criteria were expanded from the female-specific criterion of one skeletal site to a male-specific criterion of three skeletal sites, the prevalence of osteoporosis jumped fourfold.

Researchers classified 5,880 men into four groups: those with osteoporosis by WHO criteria alone; osteoporosis by NOF but not WHO criteria; no osteoporosis but high risk; and no osteoporosis and low risk. The researchers used the FRAX tool to predict fracture probability for each group.

Of the entire cohort, 130 (2.2%) were identified as having osteoporosis by WHO criteria, based on a female-specific T score of −2.5 or below at the femoral neck. Applying the NOF definition added another 422 men (based on a male-specific T score of −2.5 or below at the femoral neck, total hip, or lumbar spine), which raised the prevalence to 9.4%.

When the FRAX intervention thresholds (3% for hip fracture and 20% for major osteoporotic fracture as cut-points for starting drug treatment) were applied, 936 men (16%) who did not have osteoporosis were identified as being at high risk of fracture. Thus, the total prevalence of men potentially eligible for drug treatment was 25%. Of those 936 men, 859 (92%) had a male-specific bone-mineral density T score between −1.01 and −2.49.

Nearly all men with no osteoporosis but high risk of fracture had a FRAX 10-year probability of hip fracture of 3% or higher; 65 (7%) had a 10-year probability of major osteoporotic fracture of 20% or higher. Nearly all men with osteoporosis by WHO criteria had a 10-year probability of hip fracture of 3% or higher, but 30 (23%) had a 10-year probability of major osteoporotic fracture of 20% or higher.

During 10 years of follow-up, 177 men (3%) actually fractured a hip, and 429 (7%) had a major osteoporotic fracture.

Expanding the indication for treatment from men with osteoporosis defined by WHO criteria to men who met criteria using FRAX intervention thresholds resulted in a more than 10-fold rise in the proportion of identified candidates for drug treatment. Still, the researchers note that the efficacy of available treatment in preventing fractures in people without osteoporosis has not been shown. In this study, men with osteoporosis according to the more stringent WHO criteria had observed probabilities of clinical fracture that exceeded their FRAX-predicted probabilities. Based on data from trials in women, the researchers say, those men are most likely to benefit from drug treatment.

Source: *BMJ*, July 3, 2014

**Pre-PCI Statins: Useful or Not?**

Guidelines from the American College of Cardiology and the American Heart Association recommend routine use of statins prior to percutaneous coronary intervention (PCI). But is that recommendation followed—and effective?

Researchers from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium evaluated the incidence and in-hospital outcomes associated with statin pretreatment among 80,493 patients in hospitals participating in a quality improvement collaborative. Their key finding: 26,547 patients did not receive guideline-recommended statins before PCI, even if they were hemodynamically stable and had no documented contraindication.
New Drugs

However, patients who did not receive statins had a similar rate of in-hospital mortality (0.43% versus 0.42% in statin users) and periprocedural myocardial infarction (2.34% versus 2.10%). There was no reduction in postprocedural myocardial infarction and no difference in the rates of coronary artery bypass grafting, cerebrovascular accident, or contrast-induced nephropathy.

Finally, the researchers found no statistically significant benefit from statins on mortality at 36 months’ follow-up.

Source: American Heart Journal, July 2014

ACIP Recommends Prevnar 13 Vaccine for Older Adults

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) has recommended Prevnar 13 (pneumococcal 13-valent conjugate vaccine [diphtheria CRM197 protein] [PCV13], Pfizer) for routine use to help protect adults 65 years of age and older against pneumococcal disease, including pneumonia caused by the 13 serotypes in the vaccine.

ACIP recommended the following:

• Adults 65 years of age or older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23 (pneumococcal polysaccharide vaccine [Pneumovax, Merck]).

• Adults 65 years of age or older who have not previously received PCV13 and who have previously received one or more doses of PPSV23 should receive a dose of PCV13.

• The recommendations for routine PCV13 use among adults 65 years of age and older (if approved by ACIP and the CDC’s director) should be re-evaluated in 2018.

However, Medicare would have to change its rules to cover Prevnar 13 for patients who have already received Pneumovax, and its evaluation would likely extend until January 2016.

The recommendations will be forwarded to the director of the CDC and to the U.S. Department of Health and Human Services for review and approval.

Pneumococcal disease refers to a group of illnesses caused by S. pneumoniae bacteria. Among adults 50 years of age and older, approximately 440,000 cases of pneumococcal pneumonia occur each year in the U.S.

Sources: Pfizer and Reuters, August 13, 2014

FDA Warns of Sterile Drugs From Downing Labs

Health care professionals should not use purportedly sterile drugs produced by Downing Labs LLC, says the FDA, which found a variety of problems during an inspection of the Dallas company.

At Downing (also known as NuVision Pharmacy), FDA investigators observed unsanitary conditions that result in a lack of sterility assurance of purportedly sterile drug products. These inspections found sterility failures in several lots of drug products intended to be sterile, recurring environmental contamination problems, and poor sterile production practices.

On July 11, 2014, the FDA issued a formal request to Unique Pharmaceuticals to recall all nonexpired, purportedly sterile drug products. The FDA also requested that the firm cease sterile compounding operations. Unique Pharmaceuticals has agreed to the recall and is ceasing sterile compounding operations until sufficient corrections are made at its facility.

Source: FDA, July 23, 2014

Nine Lots of Cubicin

Cubist Pharmaceuticals, Inc., recalled nine lots of Cubicin (daptomycin for injection) 500 mg after complaints of foreign particulate matter in reconstituted vials. Affected lot numbers and expiration dates are: CDC203, December 2015; CDC207, January 2016; CDC213, February 2016; CDC217, March 2016; CDC226, April 2016; CDC234, May 2016; CDC235, May 2016; CDC243, July 2016; and CDC246, July 2016. The lots shipped between July and December 2013. Health care professionals with medical questions may contact Cubist Medical Information at 877-282-4786, 8 a.m. to 5:30 p.m.

Recalls

“Sterile” Drug Products Recalled

Unique Pharmaceuticals Ltd., of Temple, Texas, has recalled all nonexpired drug products produced for sterile use, including lot 86513, N-Acetyl Cysteine 20%. The FDA warns that the products may be contaminated.

Unique Pharmaceuticals distributed these products nationwide. Most of the product labels include: Unique Pharmaceuticals, Temple TX USA 76502.

Two recent FDA inspections of the Unique Pharmaceuticals facility revealed unsanitary conditions that resulted in a lack of sterility assurance of drug products. These inspections found sterility failures in several lots of drug products intended to be sterile, recurring environmental contamination problems, and poor sterile production practices.

Source: FDA, July 18, 2014
**Mislabeled Ibuprofen Tablets**

American Health Packaging recalled lot 142588 of ibuprofen tablets, USP, 600 mg, in a hospital unit dose presentation that may contain individual blistered doses labeled as oxcarbazepine tablets, 300 mg, lot 142544, which the company also recalled. Mislabeled inner unit dose blister packaging could result in patients receiving ibuprofen (an analgesic) instead of oxcarbazepine (a seizure medication).

These hospital unit dose products were distributed nationwide beginning June 20, 2014. Consumers should discontinue use and contact Genco Pharmaceutical Services at 855-419-4608 from 7 a.m. to 5 p.m. Central time for instructions on returns.

Source: American Health Packaging, July 18, 2014

**Baxter IV Solutions**

Baxter International Inc. recalled four lots of intravenous (IV) solutions that were found to contain cellulose fibers and/or plastics. The products, lots, and expiration dates are: 0.9% Sodium Chloride, 100 mL (Quad Pack), P298190, August 2014; 0.9% Sodium Chloride, 100 mL Mini-Bag Plus, P308650, October 2014; 0.9% Sodium Chloride, 50 mL (Single Pack), P309187, October 2014; and Highly Concentrated Potassium Chloride Injection, 20 mEq/50 mL, Viaflex Plus Container, P309476, October 2014.

To arrange returns, call the 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 Inc., July 14, 2014

**Baxter Peritoneal Dialysis Solution**

Baxter International Inc. recalled lots C940700 and C940841 of Dianeeal Low Calcium (2.5 mEq/L) Peritoneal Dialysis Solution with 2.5% Dextrose 5,000 mL (Ambu-Flex II) due to the presence of oxidized stainless steel, garment fiber, and PVC particulate identified during manufacturing. The lots were distributed between May 30, 2014, and July 9, 2014. For returns, health care providers should contact the 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 Inc., August 13, 2014

**Baxter 0.9% Sodium Chloride Injection**

Baxter International Inc. is recalling lot C931923 of 0.9% Sodium Chloride Injection, USP 1,000 mL, as a result of particulate matter found near the administration port. Part of this lot was distributed between February 27, 2014, and March 1, 2014. To arrange returns, contact the Baxter Healthcare Center for Service at 1-888-229-0001, Monday through Friday, from 7 a.m. to 6 p.m. Central time.

Source: Baxter International Inc., June 24, 2014

**Hospira Lactated Ringers and 5% Dextrose Injection**

Hospira, Inc., recalled lot 35-118-JT of Lactated Ringers and 5% Dextrose Injection, USP, 1,000 mL, Flexible Container (expiring in November 2015) after particulate matter identified in the solution indicated the presence of mold. Analysis showed that the container had leaked after being punctured. This lot was distributed nationwide from December 2013 through February 2014. Call Stericycle at 1-888-912-8457 from 7 a.m. to 5 p.m. Eastern time, Monday through Friday, to arrange returns.

Source: Hospira, Inc., July 10, 2014

**Hospira Lidocaine HCl Injection**

Hospira, Inc., is recalling lot 25-550-DD of Lidocaine HCl Injection, USP, 2%, 20 mg per mL, 5 mL single-dose vial, preservative-free, due to discolored product with visible particles in the solution and iron oxide embedded in the glass container. This lot, which expires January 1, 2015, was distributed nationwide in June and July 2013. For assistance, call Stericycle at 1-855-827-6586, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Source: Hospira, Inc., July 29, 2014

---

**DEVICE NEWS**

**Approvals**

**Prestige LP Cervical Disc**

The FDA has approved marketing of the Prestige LP Cervical Disc (Medtronic Sofamor Danek USA, Inc.), which can be implanted between two adjacent cervical vertebrae to replace a diseased or bulging disc that causes arm pain, radiculopathy, or myelopathy.

The Prestige LP Cervical Disc, which consists of a titanium-ceramic alloy that fits between the top and bottom surface of the cervical vertebrae, is designed to maintain the distance between the two vertebrae. It is intended for skeletally mature patients to replace a cervical disc from C3 to C7.

Unlike a fusion procedure, the Prestige LP Cervical Disc is designed to allow a range of motion, including bending and rotation. In a study that compared the product to cervical fusion, the overall success rate of the investigational group was 215 of 271 subjects (79.3%) compared with 147 of 220 subjects (66.8%) for the control group at 24 months. The rate of severe and device-related adverse events was comparable between the Prestige LP and control groups. Common adverse events experienced by study patients included neck and/or arm pain, numbness, back and/or leg pain, and difficulty swallowing.

Patients should avoid having surgery with the Prestige LP Cervical Disc if they have a systemic or surgical-site infection, osteoporosis, osteopenia, or a known allergy or sensitivity to materials in the
device, or if they have instability, spondylosis, deformity, or past traumatic damage in the affected area of the cervical spine.

Source: FDA, August 7, 2014

**Donor-Lung Preservation Device**

The FDA has approved the XVIVO Perfusion System (XPS) with STEEN Solution (XVIVO Perfusion Inc.) to preserve donated lungs that do not initially meet the standard criteria for transplantation but may turn out to be transplantable if there is time to evaluate their viability.

Lung transplantation is an option for patients with end-stage chronic lung diseases, such as chronic obstructive pulmonary disease, cystic fibrosis, and idiopathic pulmonary fibrosis. About one in five donated lungs meets the standard criteria for a donor lung and is transplanted into a recipient. In 2012, 1,754 U.S. lung transplants were performed; at the end of that year, 1,616 potential recipients remained on the waiting list.

If more time is needed to determine whether a donated lung meets the standard criteria for lung transplantation, the XPS can warm the donor lungs to near-normal body temperature and continuously flush the lung tissue with a sterile fluid solution (STEEEN Solution) that preserves the lungs and removes waste products. The XPS also ventilates the lungs, which oxygenates the cells and makes it possible for the transplant team to examine the airways with a bronchoscope. Lungs can stay in the machine for up to four hours while the transplant team evaluates their function. Lungs that meet functionality criteria and pass the surgeon’s examination can be transplanted.

Two clinical trials supported the safety and benefit of the device. Both compared the outcomes of lung-transplant patients who received nonideal donor lungs preserved using ex vivo lung perfusion with STEEN Solution with the outcomes of transplant patients who received ideal donor lungs that were preserved using conventional cold-storage techniques. Recipients of the ideal and nonideal lungs had similar rates of survival and organ rejection up to 12 months after transplant.

As a condition of FDA approval, the manufacturer will conduct a post-marketing study of the long-term effects of the device and associated adverse events.

**Stentless Heart Valve**

The FDA has approved the Sorin Freedom Solo Stentless Heart Valve and Solo Smart Stentless Heart Valve (Sorin Group Canada, Inc.).

The Freedom Solo Stentless Heart Valve is an artificial aortic valve made from natural tissue obtained from the sac that surrounds the heart of a cow. It is called “stentless” because the frame does not contain any metals or polymers. The SOLO Smart Stentless Heart Valve is identical to the Freedom SOLO Stentless Heart Valve except that it contains a flexible holder that helps the surgeon sew the valve in place.

A clinical trial found a statistically significant improvement in New York Heart Association functional classification (P < 0.01) in the 572 patients who were followed from the preoperative visit to the one-year visit. More than 85% of the study patients had no regurgitation or trace regurgitation at one year. A comparison of the Freedom SOLO valve hemodynamic data to literature-based hemodynamic data showed hemodynamic performance was similar to other stentless and stented bioprosthetic aortic valves.

The results from in vitro preclinical studies performed for biocompatibility, hydrodynamic performance, and structural performance demonstrate that the Freedom SOLO and the SOLO Smart valves are safe, effective, and suitable for long-term implant.

Source: FDA, June 24, 2014

**Rebel Coronary Stent System**

Boston Scientific Corporation has received FDA approval for the Rebel Platinum Chromium Coronary Stent System, a bare-metal stent for the treatment of coronary artery disease. The Rebel Stent offers the same stent platform as the Promus Premier Drug-Eluting Stent but without the Everolimus drug.

The Rebel Stent System is offered in a matrix of 46 sizes, ranging in diameter from 2.25 mm to 4.50 mm and lengths of 8 mm to 32 mm on a Monorail platform.

Source: Boston Scientific Corporation, July 21, 2014

**DNA Test for Colorectal Cancer**

The FDA has approved Cologuard (Exact Sciences), the first stool-based colorectal screening test that detects the presence of red blood cells and DNA mutations that may indicate the presence of certain abnormal growths that may be cancers, such as colon cancer or precursors to cancer. Patients with positive test results are advised to undergo a diagnostic colonoscopy.

The safety and effectiveness of the test were established in a clinical trial that screened 10,023 subjects. The trial compared the performance of Cologuard with that of the fecal immunochemical test (FIT), which detects blood in the stool. Cologuard detected 92% of colorectal cancers and 42% of advanced adenomas, while FIT detected 74% of cancers and 24% of advanced adenomas. Cologuard correctly gave a negative screening result for 87% of subjects who were negative for colorectal cancer or advanced adenomas, while FIT provided accurate negative screening results for 95%.

Along with the FDA’s approval, the Centers for Medicare and Medicaid Services (CMS) issued a proposed national coverage determination for the Cologuard test—the first product reviewed concurrently under an FDA–CMS pilot project. Source: FDA, August 12, 2014

---

Vol. 39 No. 9 • September 2014 • P&T® 613
program meant to reduce the time between FDA approval of a device and Medicare coverage. CMS proposes to cover the test once every three years for Medicare beneficiaries who are 50 to 85 years old, asymptomatic, and at average risk for colorectal cancer.

Stool DNA testing (also called fecal DNA testing) is not recommended by the U.S. Preventive Services Task Force as a method to screen for colorectal cancer.

Source: FDA, August 11, 2014

**BD Diagnostics STD Assays**

BD Diagnostics has received FDA 510(k) clearance for the BD ProbeTec Chlamydia trachomatis (CT) Qx Amplified DNA Assay and the BD ProbeTec Neisseria gonorrhoeae (GC) Qx Amplified DNA Assay on the BD Viper LT System. The BD Viper LT System is a bench-top molecular platform that automates sample liquid handling, nucleic acid extraction, amplification, detection and result reporting without user intervention. The system is designed to provide low- and mid-volume laboratories with reliable detection of chlamydia and gonorrhea from all genital sample types on an automated platform using primary sample tubes with pierceable caps and ready-to-use reagents.

Source: BD Diagnostics, July 28, 2014

**Recalls**

**Enhancement Medical’s Expression**

Enhancement Medical LLC is recalling all Expression produced through June 27, 2014, because it cannot confirm that the product’s concentration meets specifications. In addition, the FDA has received reports that Expression, which is listed as an intranasal splint, has been used as a dermal filler to smooth facial wrinkles, resulting in adverse events (AEs).

The recall includes 17,875 syringes filled with hyaluronic acid. As an intranasal splint, Expression is intended to minimize bleeding and swelling and to prevent adhesions between the septum and the nasal cavity after surgery or trauma. While most splints are plastic, silicone, or absorbent material, Expression’s hyaluronic acid gel is meant to function as a protective lubricant.

In August 2013, Enhancement Medical asked customers to return some lots of Expression (which it replaced) after complaints of AEs such as swelling, tenderness, firmness, lumps, bumps, bruising, pain, redness, discoloration, itching, and the development of hard nodules. These AEs, associated with subcutaneous injection of Expression, resulted from hyperconcentrated gel. Enhancement Medical has now expanded its 2013 recall.

Expression is considered a low-risk device (class I) as an intranasal splint. Dermal fillers, however, are class III devices, which pose a higher risk and require an FDA review of safety and effectiveness prior to marketing. Expression is not approved as a dermal filler.

One patient developed firm facial masses after being injected with Expression as a dermal filler and was left with an “obvious deformity,” the FDA says. The agency issued a warning letter to Enhancement Medical on June 4, 2014, advising the company of multiple violations that were revealed during an inspection.

Call Enhancement Medical for return instructions at 414-918-4280, Monday through Friday, 8 a.m. to 5 p.m. Central time.

Source: FDA, August 14, 2014, and August 5, 2014

**GE Healthcare Airway Modules**

GE Healthcare, LLC, is recalling its Single-Width Airway Modules (E-MiniC) and Accessories and Extension Modules (N-FC, N-FCREC) because the carbon dioxide detector may fail.

Health care facilities use the Single-Width Airway Modules (serial numbers 6818561 through 6898777) and Extension Modules (serial numbers 6799191 through 6905206) to monitor carbon dioxide and respiration rates in patients weighing more than 11 pounds. Permanent, irreversible impairment or life-threatening changes could result if the carbon dioxide detectors fail or if physicians make decisions based on incorrect values. Patients may experience hyperventilation causing hypercapnia.

The devices were distributed from February 2012 to April 2014. Modules serviced with FRU (Field Replaceable Unit) catalog number M1013204 (miniC Unit, N-FCREC) between February 2012 and May 2014 may also be affected. A complete list of affected serial and model numbers is available at http://tinyurl.com/GERecall. Customers with questions may contact GE Healthcare Technical Support at 1-800-558-7044, Monday through Friday, 8 a.m. to 5 p.m. Central Time.

Source: FDA, July 25, 2014

**IPM Wound Gel**

Wellspring Pharmaceutical Corporation is recalling IPM Wound Gel lot 3P3446 (cartons of four 10-g tubes) because it may be contaminated with the bacteria *Pseudomonas Putida*. The product (used primarily in hospitals for wound care) was distributed between December 2013 and March 2014. Customers with questions may contact the firm at 1-866-337-4500, Monday through Friday, 8:30 a.m. to 4:30 p.m. Eastern time.

Source: FDA, August 12, 2014

**NEW MEDICAL DEVICES**

**Marvin M. Goldenberg, PhD, RPh, MS**

**Name:** Sapien XT Transcatheter Heart Valve

**Manufacturer:** Edwards Lifesciences Corporation, Irvine, California

**Approval Date:** June 16, 2014

**Purpose:** The Sapien XT Transcatheter Heart Valve consists of a catheter-
based artificial aortic heart valve and accessories used to implant the valve without open-heart surgery.

**Description:** The Sapien XT heart valve is compressed and placed on the end of a balloon catheter. The valve, made of cow tissue, is attached to a balloon-expandable, cobalt-chromium frame for support.

The catheter is inserted through the femoral artery in the leg. If the femoral arteries are not suitable, the valve can be inserted through other arteries, the tip of the heart, or the aorta. The catheter is pushed through the blood vessels until it reaches the diseased aortic valve. The valve is then expanded by the balloon and the transcatheter heart valve anchors to the diseased valve. The Sapien XT functions the same way as a normal valve, helping the blood flow properly by opening and closing like a door to force the blood to flow in the correct direction.

**Benefit:** The Sapien XT is used in patients whose aortic heart valve is diseased because of calcium accumulation, which causes aortic stenosis, restricting blood flow through the valve. As the heart works harder to pump enough blood through the diseased smaller opening, the heart eventually weakens, leading to symptoms and life-threatening heart problems such as fainting, chest pain, heart failure, arrhythmias, or cardiac arrest. Once symptoms of severe aortic stenosis occur, over half of patients die within two years if the diseased valve is not replaced.

The Sapien XT should only be used in patients whose cardiologists and surgeons determine that they cannot undergo or would be at high risk in open-heart surgery. In clinical studies, the Sapien XT was shown to be reasonably safe and effective for those patients without the need for open-heart surgery. However, implanting the device also carries the risk of serious complications, such as death, stroke, acute kidney injury, heart attack, bleeding, and complications with the arteries used to insert the valve. For some patients with coexisting conditions or diseases, the risks may be especially high.

**Source:** [www.fda.gov](http://www.fda.gov)

**Name:** Fluency Plus Endovascular Stent Graft

**Manufacturer:** Bard Peripheral Vascular Inc., Tempe, Arizona

**Approval Date:** June 17, 2014

**Purpose:** The Fluency Plus Endovascular Stent Graft opens up a blockage in a previously placed stent on the venous side of the dialysis access circuit. The stent graft is placed inside the stent to reopen it, allowing adequate blood to flow and dialysis to take place.

**Description:** The stent graft is a self-expandable, flexible, metal, tube-shaped stent lined with a plastic graft made from expanded polytetrafluoroethylene (ePTFE). The stent graft is located on the end of a delivery catheter and is held in place by a release mechanism and outer tube (sheath).

A catheter with a deflated balloon at its tip is inserted into a blood vessel. The catheter is advanced through blood vessels to the venous side of the dialysis access circuit to the stent lesion that is disrupting blood flow. The balloon is inflated within the narrowed stent lesion to open it. The balloon and its catheter are then removed.

**Benefit:** The Fluency Plus Endovascular Stent Graft is used to treat instantaneous restenosis, a blockage that has developed inside a previously placed stent in the venous outflow of hemodialysis patients dialyzing by either an arteriovenous (AV) fistula or AV access graft. The stent graft increases blood flow by holding the blood-vessel wall open. The stent graft remains permanently implanted in the blood vessel and acts as a support for the reopened section of the blood vessel.

An AV fistula is a direct connection between an artery and vein, while an AV access graft acts as an artificial blood vessel that goes between an artery and a vein. The AV access graft can be used repeatedly to draw blood with a needle during hemodialysis.

Use of the Fluency Plus Endovascular Stent Graft will restore blood flow to the venous outflow of an AV fistula or AV access graft and keep the area open longer compared to treatment with balloon angioplasty alone.

**Source:** [www.fda.gov](http://www.fda.gov)

**Name:** Endoskeleton TL Fusion System

**Manufacturer:** Titan Spine, Mequon, Wisconsin

**Approval Date:** July 14, 2014

**Purpose:** The Endoskeleton TL is the first lateral fusion device to feature surface technology designed to participate in the fusion process by creating an osteogenic response to the implant’s topography.

**Description:** Large windows and internal volumes allow for bone graft packing, clear CT and MRI imaging, preferred bone graft loading, and the capability of packing additional bone graft material inside the device after implantation.

**Benefit:** The Endoskeleton TL device utilizes Titan’s proprietary roughened titanium surface technology, which has been shown to up-regulate the production of osteogenic and angiogenic factors that are critical for bone growth and fusion.

The Endoskeleton TL device is the first application of surface technology to the lateral approach. The ability to initiate cellular behavior and promote bone growth in response to an interbody device has not been available to the lateral surgeon until now.

**Sources:** [www.titanspine.com](http://www.titanspine.com), [www.cxvascular.com](http://www.cxvascular.com)