NEW DRUG APPROVALS

Xpovio for Heavily Pretreated Refractory Multiple Myeloma

The FDA has granted accelerated approval to selinexor tablets (Xpovio, Karyopharm Therapeutics) in combination with dexamethasone for the treatment of adults with relapsed refractory multiple myeloma (RRMM) who have received at least four prior therapies. The indication specifies patients whose disease is resistant to several other forms of treatment, including at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

In a study of 83 RRMM patients who were treated with selinexor plus dexamethasone, the overall response rate was 25.3%, the median time to first response was four weeks, and the median duration of response was 3.8 months. The efficacy evaluation was supported by additional information from an ongoing, randomized trial in multiple myeloma patients.

Common side effects in patients taking selinexor with dexamethasone include leukopenia, neutropenia, thrombocytopenia, and anemia. Patients also reported vomiting, nausea, fatigue, diarrhea, fever, decreased appetite and weight, constipation, upper respiratory tract infections and hyponatremia. Patients should avoid taking selinexor with medications that may cause dizziness or confusion, and they should avoid situations in which dizziness might be a problem. Pregnant or breastfeeding women should not take selinexor, which must be dispensed with a patient medication guide.

The FDA granted this application fast track and orphan drug designations. Because selinexor received an accelerated approval, further clinical trials will be required to verify and describe its clinical benefit.

Source: FDA, July 3, 2019

Vyleesi for Hypoactive Sexual Desire Disorder

The FDA has approved bremelanotide (Vyleesi, AMAG Pharmaceuticals) to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women.

HSDD is characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a coexisting medical or psychiatric condition, problems in the relationship, or the effects of a medication or other drug substance. Acquired HSDD develops in patients who previously had no problems with sexual desire. Generalized HSDD occurs regardless of the type of sexual activity, situation, or partner.

Bremelanotide activates melanocortin receptors, but the mechanism by which it improves sexual desire and related distress is unknown. Patients inject bremelanotide under the skin of their abdomen or thigh at least 45 minutes before anticipated sexual activity and may decide on the optimal time to use the drug based on how they experience the duration of benefit and any side effects, such as nausea. Patients should not use more than one dose within 24 hours or more than eight doses per month. Patients should discontinue treatment after eight weeks if sexual desire and associated distress do not improve.

Bremelanotide was studied in two 24-week, randomized, double-blind, placebo-controlled trials in 1,247 premenopausal women with acquired, generalized HSDD. Most patients used bremelanotide two or three times a month and no more than once a week. There was no difference between treatment groups in the change in the number of satisfying sexual events. Bremelanotide does not enhance sexual performance.

Bremelanotide's most common side effects are nausea and vomiting, flushing, injection-site reactions, and headache. Around 40% of patients in trials experienced nausea, most commonly with the first bremelanotide injection, and 13% needed medication to treat the nausea. About 1% of bremelanotide patients reported darkening of the gums and parts of the skin, which did not go away in about half of the patients after they stopped treatment. Patients with dark skin were more likely to develop this side effect.

In trials, bremelanotide increased blood pressure after dosing, which usually resolved within 12 hours. Because of this, bremelanotide should not be used in patients who have uncontrolled high blood pressure or known cardiovascular disease.

Source: FDA, June 21, 2019

Polivy for Diffuse Large B-Cell Lymphoma

The FDA has awarded accelerated approval to polatuzumab vedotin-piiq (Polivy, Genentech), combined with bendamustine and a rituximab product (a combination known as BR), for the treatment of adults with diffuse large B-cell lymphoma (DLBCL) that has progressed or returned after prior therapy.

Each year, more than 18,000 people in the U.S. are diagnosed with DLBCL, a quick-growing cancer that can spread from the lymph nodes to the bone marrow, spleen, liver, or other organs. Although it is curable, approximately 30% to 40% of patients relapse.

Polatuzumab vedotin-piiq is an antibody that is attached to a chemotherapy drug. After binding to CD79b, a protein that is found only on B cells, polatuzumab vedotin-piiq releases the chemotherapy drug into those cells.

The new therapy was evaluated in a study of 80 patients with relapsed/refractory DLBCL who were randomized to receive either polatuzumab vedotin-piiq plus BR or BR alone.

The most common side effects with polatuzumab vedotin-piiq plus BR include neutropenia, thrombocytopenia, and anemia; peripheral neuropathy; fatigue; diarrhea; fever; decreased appetite; and pneumonia. Patients should be monitored for infusion-related reactions, low blood counts, fatal and/or serious infections, tumor lysis syndrome, hepatotoxicity, and progressive multifocal leukoencephalopathy. The drug is not recommended for pregnant or breastfeeding women.

The FDA granted polatuzumab vedotin-piiq breakthrough therapy, orphan drug, and priority review designations.

Source: FDA, June 10, 2019

Zirabev, an Avastin Biosimilar

The FDA has approved bevacizumab-bvzr (Zirabev, Pfizer Inc.), a biosimilar to Avastin, for the treatment of metastatic colorectal cancer; unresectable, locally advanced, recurrent, or metastatic non-squamous non–small-cell lung cancer (NSCLC); recurrent glioblastoma; metastatic renal cell carcinoma; and persistent, recurrent, or metastatic cervical cancer.

FDA approval was based on a comprehensive data package that demonstrated the biosimilarity of bevacizumab-bvzr to Avastin. This included results from REFLECTIONS B7391003, a comparative study, which found clinical equivalence and no clinically significant differences between bevacizumab-bvzr and Avastin in patients who had advanced non-squamous NSCLC.

Bevacizumab-bvzr inhibits angiogenesis by specifically recognizing and binding to the vascular endothelial growth factor protein.

Bevacizumab-bvzr is the second biosimilar to Avastin (Genentech, Inc.), which was approved in February 2004. The FDA approved bevacizumab-awwb (Mvasi, Amgen Inc.) in September 2017.

Sources: Pfizer Inc., June 28, 2019; FDA, July 3, 2019

Kanjinti, a Herceptin Biosimilar

The FDA has approved the biosimilar trastuzumab-anns (Kanjinti, Amgen Inc. and Allergan plc) for all the approved indications of Herceptin (Genentech): the treatment of HER2-overexpressing adjuvant and metastatic breast cancer and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.

Trastuzumab-anns was shown to be highly similar and to have no clinically meaningful differences to Herceptin based on extensive comparative analytical, pharmacokinetic, and clinical data. At the time of its approval, trastuzumab-anns was the only trastuzumab biosimilar to incorporate the evaluation of a single transition in the clinical study, demonstrating similar safety and immunogenicity in patients who were previously taking Herceptin.

Trastuzumab is a recombinant DNA-derived, humanized, monoclonal immunoglobulin G1 kappa antibody. Trastuzumab and its biosimilars have boxed warnings relating to cardiomyopathy, infusion reactions, and pulmonary toxicity.

Trastuzumab-anns is the fifth biosimilar to Herceptin that has been approved by the FDA.

Sources: Amgen Inc. and Allergan plc, June 13, 2019; FDA, July 3, 2019

Generic Approvals

Diclofenac Sodium Injection

Mylan Laboratories has received FDA approval to market diclofenac sodium injection, 37.5 mg/mL single-dose vials, the first generic version of the now-discontinued Dyloject (Javelin Pharmaceuticals). Diclofenac is indicated for the management of mild-to-moderate pain and moderate-to-severe pain either alone or in combination with opioid analgesics.

Source: FDA, June 18, 2019

Dapiprazole HCl Ophthalmic Solution

The FDA has given Baradaina, LLC, permission to market dapiprazole hydrochloride ophthalmic solution, 0.5%, formerly produced by Fera Pharmaceuticals. Dapiprazole is a treatment for iatrogenically induced mydriasis due to adrenergic (phenylephrine) or parasympatholytic (tropicamide) agents.

Source: FDA, May 29, 2019

Micafungin for Injection

Fresenius Kabi USA has received FDA approval to sell micafungin for injection, 50 mg/vial and 100 mg/vial single-dose vials, the first generic versions of these formulations of Mycamine For Injection (Astellas). Micafungin is indicated for treating candidemia, acute disseminated candidiasis, candida peritonitis, and abscesses. It is also indicated for the treatment of esophageal candidiasis and prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplantation.

Source: FDA, May 17, 2019

Mesalamine Delayed-Release Capsules

The FDA has granted Teva Pharmaceuticals permission to market mesalamine delayed-release capsules, 400 mg, the first generic version of Delzicol (Apil). Mesalamine is used in the treatment of mild-to-moderately active ulcerative colitis in patients aged 5 years and older, and as maintenance treatment for ulcerative colitis in adults.

Source: FDA, May 9, 2019

Bosentan Tablets

The FDA has approved the marketing of bosentan tablets, 62.5 mg and 125 mg, by Amneal Pharmaceuticals Company GmbH, Sun Pharmaceutical Industries Ltd., Hikma Pharmaceuticals USA Inc., Watson Laboratories, Inc., Natco Pharma Limited, Zydus Pharmaceuticals (USA) Inc., Alvogen Pine Brook LLC, and

Par Pharmaceutical, Inc. They are the first generic versions of these dosages of Tracleer (Actelion Pharms Ltd.), which is used for the treatment of pulmonary arterial hypertension.

Source: FDA, April 26, 2019

NEW INDICATIONS

Soliris for Neuromyelitis Optica Spectrum Disorder

The FDA has approved eculizumab injection (Soliris, Alexion Pharmaceuticals) for intravenous use to treat adults with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive. The central nervous system (CNS) autoimmune disease mainly affects the optic nerves and spinal cord.

Eculizumab is the first FDA-approved treatment for NMOSD, which can lead to attacks of optic neuritis and transverse myelitis. Most attacks occur in clusters—days, months, or years apart—followed by partial recovery during remissions. The disease affects more women than men, and African-Americans are at greater risk. Approximately 4,000 to 8,000 people in the United States are believed to be affected by NMOSD.

Neuromyelitis optica spectrum disorder can be associated with antibodies that bind to the protein AQP4; this binding appears to activate other components of the immune system, causing inflammation and damage to the CNS.

The drug has a boxed warning indicating that life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. Such infections may rapidly become life-threatening or fatal if not recognized and treated early. No cases of meningococcal infection were observed in the clinical trial.

Eculizumab is available only through a risk evaluation and mitigation strategy (REMS). Prescribers must enroll in the REMS program, counsel patients on the risk of meningococcal infection, provide REMS educational materials to patients, and ensure that patients are vaccinated with meningococcal vaccine(s).

The most frequently reported adverse reactions in the trial included upper respiratory infection, nasopharyngitis, diarrhea, back pain, dizziness, influenza, arthralgia, pharyngitis, and contusion.

Approved by the FDA in 2007, eculizumab is indicated for the destruction of red blood cells in adults with paroxysmal nocturnal hemoglobinuria; for adults and children with atypical hemolytic uremic syndrome; and for adults with myasthenia gravis who are anti-acetylcholine receptor antibody positive.

The FDA gave eculizumab an orphan drug designation for its use in NMOSD.

Source: FDA, June 27, 2019

Doptelet for Chronic Immune Thrombocytopenia

The FDA has expanded the indications for avatrombopag (Doptelet, Dova Pharmaceuticals, Inc.) to include the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Avatrombopag is also FDA-approved for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure.

Avatrombopag is an oral thrombopoietin receptor agonist that is administered with food. In the pivotal phase 3 study, avatrombopag administration resulted in a platelet count of at least 50,000 per microliter at Day 8 of therapy in most patients, with efficacy superior to placebo at maintaining platelet counts in the target range during the six-month treatment period.

Safety data for 128 patients with ITP, and more than 1,000 subjects across 24 studies in the avatrombopag clinical development program across multiple indications, support the safety and tolerability of the medication.

Dova is promoting avatrombopag in partnership with Salix Pharmaceuticals.

Source: Dova Pharmaceuticals, Inc., June 27, 2019

New Darzalex Regimen For Multiple Myeloma

Daratumumab (Darzalex, Janssen), in combination with lenalidomide and dexamethasone, has secured FDA approval for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem-cell transplant.

The approval is based on results from MAIA, a randomized open-label, multicenter phase 3 clinical study. At a median follow-up of 28 months, daratumumab in combination with lenalidomide and dexamethasone significantly reduced the risk of disease progression or death by 44% in patients with newly diagnosed multiple myeloma who are transplant-ineligible, compared to lenalidomide and dexamethasone alone.

The most frequent adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea, and cough. Serious adverse reactions included pneumonia, bronchitis, dehydration, neutropenia, lymphopenia, and leukopenia.

Daratumumab binds to the surface protein CD38, which is present in high numbers on multiple myeloma cells, and inhibits tumor cell growth.

The application received approval through the FDA's Real-Time Oncology Review pilot program. Daratumumab was initially approved in November 2015.

Source: Janssen, June 27, 2019

Victoza at Age 10 For Type-2 Diabetes

Liraglutide injection (Victoza, Novo Nordisk) has been approved to treat patients aged 10 years or older with type-2 diabetes (T2D). Liraglutide is the first noninsulin drug approved to treat T2D in pediatric patients since metformin's approval in 2000.

Although T2D occurs primarily in patients older than 45 years, its prevalence among younger patients has been rising dramatically in the U.S. The Centers for Disease Control and Prevention estimates that more 5,000 new cases of T2D are diagnosed each year among people younger than 20 years of age.

Liraglutide, a glucagon-like peptide-1 receptor agonist, was approved to treat adults with T2D in 2010. It slows digestion, prevents the liver from making too much glucose, and helps the pancreas produce more insulin when needed. Liraglutide is not a substitute for insulin and it is not indicated for patients with T1D or diabetic ketoacidosis. Liraglutide is indicated to reduce the risk of major adverse cardiovascular events in adults with T2D and established cardiovascular disease, but it is not indicated for this use in children.

Liraglutide has a boxed warning about the increased risk of thyroid C-cell tumors. For this reason, patients with a personal or family history of medullary thyroid carcinoma should not use liraglutide, nor should patients who have multiple endocrine neoplasia syndrome type 2. The most common side effects with liraglutide are nausea, diarrhea, vomiting, decreased appetite, indigestion, and constipation.

The FDA granted this application a priority review.

Source: FDA, June 17, 2019

Keytruda for Small-Cell Lung Cancer

The FDA has given accelerated approval to pembrolizumab (Keytruda, Merck) for patients with metastatic small-cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

Pembrolizumab's efficacy was investigated in 83 patients with SCLC who had disease progression on or after two or more prior lines of therapy, who were enrolled in one of two multicenter, multicohort, nonrandomized, open-label trials: KEYNOTE-158 or KEYNOTE-028. The overall response rate was 19% (complete response rate, 2%). Of the 16 responding patients, responses were durable for six months or longer in 94%, 12 months or longer in 63%, and 18 months or longer in 56%.

Common adverse reactions included fatigue, decreased appetite, cough, nausea, and constipation. Serious adverse reactions occurred in 31% of patients; the most frequent were pneumonia and pleural effusion.

The FDA granted pembrolizumab orphan drug and priority review designations for SCLC.

Source: FDA, June 18, 2019

Keytruda for Metastatic/ Unresectable Recurrent HNSCC

Pembrolizumab (Keytruda, Merck) has been approved for the first-line treatment of metastatic or unresectable, recurrent head and neck squamous-cell carcinoma (HNSCC). The new indications specify that pembrolizumab can be used as monotherapy in patients whose tumors express programmed death ligand-1 (PD-L1) with a combined positive score (CPS) of at least 1 based on an FDA-approved test, or in combination with platinum and fluorouracil chemotherapy regardless of PD-L1 expression.

Approval was based on KEYNOTE-048, a randomized, open-label, active-controlled trial in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease, or who had recurrent disease and were considered incurable by local therapies.

An interim analysis found a statistically significant improvement in median overall survival (OS) in the overall population for patients using pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy (13.0 months vs. 10.7 months). In patients expressing PD-L1, OS improved significantly with pembrolizumab as a single agent compared with cetuximab plus chemotherapy (12.3 months vs. 10.3 months with CPS ≥ 1, and 14.9 months vs. 10.7 months with CPS ≥ 20). For the overall population, there was no significant difference in OS for pembrolizumab as a single agent versus cetuximab plus chemotherapy.

The most common adverse reactions among patients who received pembrolizumab as a single agent were fatigue, constipation, and rash. The most common adverse reactions in patients who received pembrolizumab with chemotherapy were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, and cough.

The FDA granted pembrolizumab a priority review.

Source: FDA, June 11, 2019

Emgality for Cluster Headaches

The FDA has approved galcanezumab-gnlm injection solution (Emgality, Eli Lilly) for the treatment of episodic cluster headache in adults.

The effectiveness of galcanezumab-gnlm was demonstrated in a trial comparing the drug to placebo in 106 patients. The trial measured the average number of cluster headaches per week for three

weeks and compared the average changes from baseline in the groups. Patients taking galcanezumab-gnlm experienced 8.7 fewer weekly attacks than they did at baseline, compared to 5.2 fewer attacks for patients taking placebo.

Galcanezumab-gnlm use carries a risk of hypersensitivity reactions, and treatment should be discontinued if reaction occurs. Hypersensitivity reactions can occur days after administration and can be prolonged. The most common side effect reported by trial participants was injection-site reactions.

Galcanezumab-gnlm injection is self-administered. It was approved by the FDA in September 2018 for the preventive treatment of migraine in adults.

The FDA granted this application priority review and breakthrough designations.

Source: FDA, June 4, 2019

Zerbaxa for HABP, VABP

The FDA has approved a new indication for ceftolozane/tazobactam injection (Zerbaxa, Merck) for the treatment of adults who have hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). Potentially fatal, HABP and VABP are the second most common type of hospital-acquired infections in the U.S.

A multinational, double-blind study compared ceftolozane/tazobactam to another antibacterial drug in 726 adult patients with HABP/VABP. Mortality and cure rates proved similar between ceftolozane/tazobactam and the comparator. The most common adverse reactions in patients treated with ceftolozane/tazobactam were elevated liver enzyme levels, renal impairment or failure, and diarrhea.

The FDA granted qualified infectious disease product and priority review designations to ceftolozane/tazobactam for the treatment of HABP/VABP. The drug combination was initially approved in 2014 to treat complicated intra-abdominal infections and complicated urinary tract infections.

Source: FDA, June 3, 2019

Dupixent for Nasal Polyps With Chronic Rhinosinusitis

Regeneron Pharmaceuticals' Dupixent (dupilumab) has been approved for adults with nasal polyps accompanied by prolonged sinus and nasal cavity inflammation. It is the first approved treatment for inadequately controlled chronic rhinosinusitis with nasal polyps, which can lead to loss of smell.

Two studies evaluated dupilumab in 724 adults with chronic rhinosinusitis and nasal polyps who were symptomatic with intranasal corticosteroid use. At 24 weeks in both studies, dupilumab patients had 57% and 51% improvement in nasal congestion and obstruction severity, compared with 19% and 15% improvement with placebo patients. Nasal polyp scores fell 33% and 27% with dupilumab, but rose 7% and 4% with placebo. Loss of smell improved by 52% and 45% with dupilumab compared to 12% and 10% with placebo.

Serious allergic reactions and eye problems can occur with dupilumab, including conjunctivitis and keratitis. The most commonly reported side effects were injection-site reactions and eye/eyelid inflammation, including redness, swelling, and itching. Also, patients taking dupilumab should avoid live vaccines.

Dupilumab was approved in 2017 for patients aged 12 years and older with eczema that is inadequately controlled by topical therapies or when such therapies are inadvisable. In 2018, it was approved as add-on maintenance treatment for patients aged 12 years and older with moderate-to-severe eosinophilic asthma or oral corticosteroid-dependent asthma.

Sources: FDA and Regeneron, June 26, 2019

Symdeko for Cystic Fibrosis From Age 6

The FDA has expanded the indication for tezacaftor/ivacaftor tablets (Symdeko, Vertex Pharmaceuticals) to include the treatment of patients 6 years of age and older with cystic fibrosis (CF) who have certain genetic mutations. In 2018, the drug had been approved for patients aged 12 years and older with those mutations.

Cystic fibrosis, a genetic disorder that creates a buildup of thick mucus in the lungs, digestive tract, and other parts of the body, is caused by a defective protein resulting from mutations in the CF transmembrane conductance regulator (*CFTR*) gene. There are approximately 2,000 known *CFTR* mutations. Tezacaftor/ivacaftor is used in patients with two copies of the most common mutation—F508del—or with at least one of the mutations that responds to the drug's active ingredients.

The drug's efficacy in patients with CF aged 12 years and older was evaluated in three double-blind, placebo-controlled phase 3 trials. Subjects showed improvements in lung function and other important measures, including a reduction in exacerbations. Tezacaftor/ivacaftor's safety in patients aged 6 to under 12 years was supported by data from a 24-week, open-label treatment period with 70 patients, which had similar results to trials in older patients.

The most common side effects with tezacaftor/ivacaftor include headache, nausea, sinus congestion, and dizziness.

Source: FDA, June 21, 2019

Botox for Pediatric Upper Limb Spasticity

OnabotulinumtoxinA (Botox, Allergan Inc.) has received FDA approval for the treatment of upper limb spasticity in pediatric patients (2–17 years old).

The approval is based on two phase 3 studies evaluating the safety and effi-

cacy of onabotulinumtoxinA in more than 200 pediatric patients with upper limb spasticity. The trials included a 12-week, double-blind study and a one-year open-label extension study.

Treatment with onabotulinumtoxinA is not meant to replace existing physical therapy or other rehabilitation that may have been prescribed.

OnabotulinumtoxinA has a boxed warning about the spread of toxin effects.

The FDA gave this application a priority review.

Source: Allergan PLC, June 21, 2019

Dextenza for Inflammation After Ophthalmic Surgery

The FDA has approved an additional indication for dexamethasone ophthalmic insert, 0.4 mg (Dextenza, Ocular Therapeutix, Inc.)—the treatment of ocular inflammation following ophthalmic surgery.

The intracanalicular insert delivers medication to the surface of the eye without any need for eye drops. A single administration of the preservative-free, resorbable hydrogel insert delivers 0.4 mg of the corticosteroid dexamethasone to treat postsurgical ocular inflammation and pain for up to 30 days. The drug was previously approved in November 2018 for the treatment of ocular pain following ophthalmic surgery.

The new approval is supported by data from three randomized, vehicle-controlled phase 3 trials in patients who had just undergone cataract surgery. In all three trials, dexamethasone ophthalmic insert had a statistically significant higher proportion of patients who were pain-free on post-operative day 8, compared with vehicle.

The most common ocular adverse reactions were anterior chamber inflammation, including iritis and iridocyclitis; increased intraocular pressure; reduced visual acuity; cystoid macular edema; corneal edema; eye pain; and conjunctival hyperemia. The most common non-ocular adverse event was headache.

Source: Ocular Therapeutix, Inc., June 21, 2019

Emflaza for Duchenne Muscular Dystrophy In Children Aged 2–5 Years

The indication for deflazacort (Emflaza, PTC Therapeutics, Inc.) has been expanded to include patients with Duchenne muscular dystrophy (DMD) between 2 and 5 years of age. The FDA approved deflazacort in February 2017 for the treatment of DMD in patients aged 5 and older.

Duchenne muscular dystrophy is a rare childhood genetic disorder that causes progressive, irreversible muscle deterioration and weakness. Starting deflazacort at the time of diagnosis is the standard of care, according to PTC Therapeutics. The company believes that treating patients as young as possible, when they still have a substantial amount of muscle, will have the greatest benefit for patients aged 2 years and older.

Source: PTC Therapeutics, Inc., June 7, 2019

Nucala Self-Administration

The FDA has approved two new methods for administering mepolizumab (Nucala, GlaxoSmithKline)—an auto-injector and a pre-filled safety syringe. Patients or caregivers can self-administer the medication for severe eosinophilic asthma (SEA) or eosinophilic granulomatosis with polyangiitis once every four weeks after a healthcare professional decides it is appropriate.

The approval is supported by positive data from two open-label, single-arm, phase 3a studies evaluating the real-world use of mepolizumab administered via the new options in clinics and at home by patients with SEA or by their caregivers. Both studies showed that patients were able to successfully self-administer treatment with both the auto-injector and pre-filled syringe after appropriate training (89–95% and 100%, respectively). Most patients preferred the at-home self-administration option to the in-clinic administration.

An additional open-label, parallel-group, single-dose study confirmed that the pharmacokinetic and pharmacodynamic profile of mepolizumab administered via pre-filled syringe or auto-injector was comparable to the originally approved lyophilised formulation, which remains available for administration by healthcare professionals.

Source: GlaxoSmithKline, June 6, 2019

NEW FORMULATIONS

Slynd, a Contraceptive

The FDA has approved an estrogen-free oral contraceptive containing drospirenone 4 mg (Slynd, Exeltis USA, Inc.) that has a 28-day dosing regimen (24 active tablets and 4 inactive tablets) and a 24-hour missed-pill window.

Drospirenone is a synthetic form of the progesterone that has a similar pharmacological profile to natural progesterone. In clinical trials, the drug showed no instances of thromboembolic events. Slynd was approved with no boxed warning but is contraindicated for women who have conditions that predispose them to hyperkalemia.

Source: Exeltis, June 6, 2019

Thiola EC for Cystinuria

The FDA has approved 100-mg and 300-mg tablets of enteric-coated tiopronin (Thiola EC, Retrophin, Inc.), a new formulation of tiopronin for the treatment of cystinuria.

The new formulation allows patients to take tiopronin with or without food and reduce the number of tablets they need. In clinical studies, the average dose of

tiopronin was approximately 1,000 mg, or 10 of the original 100-mg pills per day, which should be taken at least one hour before or two hours after meals.

Cystinuria is a rare inherited disorder that causes a buildup of cystine levels in the urine, resulting in the formation of recurring cystine kidney stones.

Source: Retrophin, Inc., June 28, 2019

FDA REVIEW ACTIVITIES

Breakthrough Therapy Status

Avexitide for Post-Bariatric Hypoglycemia

The FDA has given a breakthrough therapy designation to Eiger BioPharmaceuticals for avexitide, a treatment for post-bariatric hypoglycemia (PBH).

Approximately 150,000 to 200,000 bariatric surgeries are performed each year in the United States. As that number has increased, so has PBH, with symptoms typically developing a year or more after surgery. Severe hypoglycemia can result in neuroglycopenic outcomes (e.g., altered mental status, loss of consciousness, seizures, coma). Recurrent episodes of severe hypoglycemia can be debilitating, and there is no approved treatment.

Avexitide is a targeted, first-in-class, glucagon-like peptide-1 (GLP-1) antagonist. It selectively targets and blocks GLP-1 receptors, normalizing insulin secretion by the pancreas and reducing postprandial hypoglycemia.

Source: Eiger BioPharmaceuticals, June 17, 2019

Aliqopa for Marginal Zone Lymphoma

Bayer has received a breakthrough therapy designation for copanlisib (Aliqopa) for the treatment of adults with relapsed marginal zone lymphoma (MZL) who have received at least two prior therapies.

MZL, an indolent form of non-Hodgkin's lymphoma (iNHL), accounts for approximately 10% of all NHL in the U.S. Typically, the treatment is chemotherapy, immunotherapy, or both. Although initial therapies often succeed, there is an unmet need for relapsed (advanced) MZL.

Copanlisib is an intravenous phosphatidylinositol-3 kinase (PI3K) inhibitor that is predominantly active against the PI3K-alpha and PI3K-delta isoforms expressed in malignant B cells.

In the MZL subgroup of the phase 2 CHRONOS-1 study, copanlisib showed preliminary efficacy in iNHL patients, including 23 with relapsed or refractory MZL who had received at least two prior therapies. An 18-month follow-up analysis showed an overall response rate (ORR) of 60.6% and, in the MZL histology, an ORR of 78.3%.

Bayer is conducting two additional phase 3 studies—CHRONOS-3 and CHRONOS-4—to evaluate copanlisib in combination with other therapies for people with iNHL (including MZL) who have relapsed following one or more prior therapies.

Source: Bayer, May 29, 2019

SEP-363856 for Schizophrenia

Sunovion Pharmaceuticals Inc. and PsychoGenics Inc. have received an FDA breakthrough therapy designation for SEP-363856 for the treatment of schizophrenia.

Schizophrenia affects approximately 2.4 million people in the United States. There have been few major advances in treatment since the advent of antipsychotic pharmacotherapy in the 1950s.

SEP-363856 is a psychotropic agent with a novel mechanism of action that is distinct from currently marketed antipsychotics. SEP-363856 does not bind to dopamine 2 or serotonin 2A receptors, which are thought to mediate the effects of currently available antipsychotic medicines. Although the exact mechanism of action is unknown, SEP-363856 is believed to activate trace amine-associated receptor 1 in addition to serotonin 1A receptors.

The designation for SEP-363856 is based on data from the phase 2 SEP361-201 study, in which hospitalized patients with acute exacerbation of schizophrenia who were treated with SEP-363856 showed statistically significant, clinically meaningful improvement in the Positive and Negative Syndrome Scale (PANSS) total score compared to patients treated with placebo after four weeks of treatment. They also showed improvement in the overall severity of illness and in all major PANSS subscales.

SEP-363856 was generally well tolerated, with similarities to placebo treatment in discontinuation rates; proportion of patients experiencing extrapyramidal symptoms or akathisia; and change in metabolic parameters such as weight, lipids, glucose, and prolactin.

Source: Sunovion Pharmaceuticals and PsychoGenics, May 10, 2019

Fast-Track Designations

TRQ-1501 for Relapsed or Refractory Solid Tumors

The FDA has granted a fast-track designation for Torque's first deep-primed T-cell immunotherapy program, TRQ-1501 (Deep IL-15 Primed T cells). The designation is for the treatment of relapsed or refractory solid tumors and lymphomas that express any of five tumor-associated antigens: PRAME, WT-1, SSX2, Survivin, and NY-ESO-1.

TRQ-1501 is an investigational immune-cell therapy produced from a patient's own T cells, primed to target the five tumor-associated antigens and loaded with deep IL-15 (a multimer of IL-15 cytokine) anchored to the cells' surface.

Deep-primed T cells pharmacologically activate an immune response with anchored cytokines. The process does not require genetic engineering of the T cells,

so it preserves the natural T-cell receptor for delivering a regulated immune response, with the potential for a high margin of safety. Immunomodulators are tethered to the surface of deep-primed T cells—initially IL-15 and IL-12 cytokines, and Toll-like receptor agonists—that activate both innate and adaptive immunity. Administering these immunomodulators systemically can cause lethal toxicity by activating immune cells throughout the body. By loading precise doses of cytokines onto the surface of T cells, deep priming focuses the immune response to target the tumor, without systemic exposure.

A phase 1/2 clinical trial in solid cancers and lymphoma is enrolling patients and will evaluate TRQ-1501 as a single agent and in combination with the anti–programmed death-1 therapy pembrolizumab (Keytruda, Merck).

Source: Torque, June 18, 2019

Momelotinib for Myelofibrosis

Sierra Oncology, Inc. has been granted a fast-track designation for momelotinib, a Janus kinase 1 (JAK1), JAK2, and activin A receptor type 1 inhibitor.

Momelotinib is intended for the treatment of patients with intermediate to high-risk myelofibrosis who have previously received a JAK inhibitor. These patients typically suffer from uncontrolled constitutional symptoms, progressively worsening anemia that often results in transfusion dependency, and enlarged spleens.

Sierra plans to launch the phase 3 MOMENTUM trial in the fourth quarter of 2019, enrolling patients with myelofibrosis who are symptomatic and anemic and who have been treated previously with a JAK inhibitor. Patients will receive either momelotinib or danazol, which is used to ameliorate anemia in patients with myelofibrosis. After 24 weeks of treatment, patients on danazol will be allowed to cross over to receive momelotinib.

Source: Sierra Oncology, June 5, 2019

Jardiance for Chronic Heart Failure

The FDA has given a fast-track designation to Boehringer Ingelheim and Eli Lilly and Company for empagliflozin (Jardiance) to reduce the risk of hospitalization and death in people with chronic heart failure (CHF).

This designation is for the ongoing EMPEROR program, consisting of the EMPEROR-Reduced and EMPEROR-Preserved studies, which will evaluate the effect of empagliflozin on cardiovascular death and hospitalization for heart failure in adults with CHF with reduced or preserved ejection fraction, respectively. The two phase 3 studies include more than 8,500 people with CHF.

Empagliflozin is a once-daily tablet used with diet and exercise to lower blood sugar in adults with type-2 diabetes (T2D), and to reduce the risk of cardiovascular death in adults with T2D and known cardiovascular disease.

Source: Boehringer Ingelheim and Eli Lilly and Company, June 26, 2019

ZW25 for Gastroesophageal Adenocarcinoma

The FDA has given Zymeworks Inc. a fast-track designation for ZW25, a novel Azymetric bispecific antibody, for the first-line treatment of patients with HER2-overexpressing gastroesophageal adenocarcinoma in combination with standard-of-care chemotherapy.

ZW25 is being evaluated in phase 1 and phase 2 trials across North America and South Korea. It can simultaneously bind two non-overlapping epitopes of HER2, which is known as biparatopic binding. This unique design results in multiple mechanisms of action, including dual HER2 signal blockade, increased binding and removal of HER2 protein from the cell surface, and potent effector function, which leads to encouraging antitumor activity in patients.

Zymeworks is developing ZW25 as a HER2-targeted treatment option for patients with any solid tumor that expresses HER2. Zymeworks has also received an orphan drug designation for ZW25 for the treatment of gastric and ovarian cancers.

Source: Zymeworks Inc., May 29, 2019

IMR-687 for Sickle Cell Disease

Imara, Inc.'s IMR-687 was given a fast-track designation from the FDA for the treatment of sickle cell disease.

IMR-687 is an oral, highly potent, selective phosphodiesterase 9 inhibitor. Preclinical data demonstrate that it reduces both sickling and blood vessel occlusion. In a phase 1 clinical trial in healthy volunteers, IMR-687 was well tolerated. It is now being evaluated in a multinational phase 2a clinical trial in adults.

Source: Imara, Inc., May 29, 2019

PD-0325901 for Neurofibromatosis Type 1

SpringWorks Therapeutics, Inc. has received a fast-track designation for PD-0325901, an oral, small-molecule inhibitor of mitogen-activated protein kinase 1 (MEK1) and MEK2, for the treatment of patients aged 2 years and older who have neurofibromatosis type 1–associated inoperable plexiform neurofibromas (NF1-PNs) that are progressing or causing significant morbidity.

These neurofibromas are characterized by mutations in the MAPK pathway that lead to the growth of peripheral nerve sheath tumors that cause significant pain, disfigurement, and morbidity. The MAPK pathway, a key signaling network that regulates cell growth and survival, is highly relevant in multiple oncology and rare disease indications.

Neurofibromatosis type 1 affects an estimated 100,000 patients in the United States. Typically, NF1-PNs are diagnosed in the first two decades of life and are characterized by aggressive tumor growth, which tends to be more rapid during childhood. There are no approved therapies. Most patients are treated with surgery, and sometimes require amputation; however, surgery has variable success rates and a high rate of recurrence has been observed because of the aggressive nature of the tumors.

PD-0325901 has been evaluated in several phase 1 and phase 2 clinical trials, with more than 200 subjects receiving treatment. A phase 2 trial evaluated PD-0325901 in 19 adolescents and adults with inoperable and symptomatic or growing PN, and the results demonstrated an objective response in 42% of participants (defined as a ≥ 20% or greater reduction in tumor volume).

SpringWorks is evaluating PD-0325901 as monotherapy for the treatment of patients with NF1-PN, and in combination with other anticancer agents across a range of solid tumors. The company expects to initiate a phase 2b single-arm, open-label study of PD-0325901 in pediatric and adult patients with NF1-PN in the third quarter of 2019.

Source: SpringWorks Therapeutics, June 3, 2019

Priority Review Status

Invokana for Chronic Kidney Disease

Janssen has been granted a priority review for its supplemental new drug application for canagliflozin (Invokana) to reduce the risk of end-stage kidney disease and renal or cardiovascular death in adults with type-2 diabetes (T2D) and chronic kidney disease (CKD). Canagliflozin would be the first diabetes medicine to treat CKD in patients with T2D.

The decision is based on data from the phase 3 CREDENCE study, which evaluated 4,401 patients with T2D and stage 2 or 3 CKD who were receiving standard of care, including an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.

Source: Janssen, May 22, 2019

Ultomiris for Atypical Hemolytic Uremic Syndrome

The FDA has accepted for priority review Alexion Pharmaceuticals' supplemental biologics license application for ravulizumab-cwvz (Ultomiris), a long-acting C5 complement inhibitor for the treatment of atypical hemolytic uremic syndrome (aHUS).

Atypical HUS is a severe chronic disease that can cause progressive damage to vital organs, predominantly the kidneys, leading to organ failure and premature death.

The application is based on results from a phase 3 study of ravulizumab-cwvz in people with aHUS that met the primary endpoint of complete thrombotic microangiopathy response, defined by hematologic normalization and improved kidney function.

The FDA has set a target action date of October 19, 2019.

Source: Alexion Pharmaceuticals, June 20, 2019

Rituxan for Granulomatosis With Polyangiitis and Microscopic Polyangiitis

The FDA has accepted Genentech's supplemental biologics license application and granted a priority review for rituximab (Rituxan), in combination with glucocorticoids, for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children aged 2 years and older.

These rare diseases affect small- and medium-sized blood vessels. Pediatric onset GPA and MPA are associated with severe, potentially life-threatening symptoms.

The application was based on data from the phase 2a, global, open-label, single-arm PePRS study investigating intravenous rituximab in 25 pediatric patients with severe GPA or MPA. The study assessed treatment with four weekly infusions of rituximab in combination with a tapering course of oral glucocorticoids.

Rituximab is currently indicated for GPA and MPA in adults.

Source: Genentech, June 12, 2019

RVT-802 for Pediatric Congenital Athymia

The FDA has accepted a biologics license application and granted a priority review for RVT-802 (Enzyvant), a tissue-based regenerative therapy designed to treat pediatric congenital athymia.

Children with congenital athymia are born without a thymus, which results in severe immunodeficiency due to their inability to produce normally functioning T cells. Approximately 20 infants are born each year in the U.S. with congenital athymia, which is fatal if untreated, typically during the first 24 months of life because of susceptibility to infection. There are no FDA-approved therapies.

In a healthy immune system, T cells that start as stem cells in bone marrow complete development in the thymus. RVT-802 is designed to replicate this process in the absence of a thymus. Derived from infant thymus tissue, RVT-802 is processed and cultured prior to implantation into a patient's quadricep muscle. The patient's bone marrow stem cells migrate to the implanted tissue product, where they are trained to become naïve, immunocompetent T cells. With the renewed ability to generate T cells, immune system function can be restored.

Clinical data demonstrate long-term durability of treatment with RVT-802. At the time the application was filed, 93

patients had received RVT-802 across multiple clinical studies. Survival at year 1 and year 2 post-treatment was 76% and 75%, respectively. For patients surviving 12 months post-treatment, there was a 93% probability of surviving 10 years post-treatment.

Source: Enzyvant, June 5, 2019

Orphengesic Forte for Pain Management

The FDA has received a supplemental abbreviated new drug application and granted a priority review to Galt Pharmaceuticals for Orphengesic Forte, an opioid-free muscle relaxant.

Orphengesic Forte is indicated for the relief of mild-to-moderate pain from acute musculoskeletal disorders, paired with rest and physical therapy. The oral tablets contain 50 mg of orphenadrine citrate, 770 mg of aspirin, and 60 mg of caffeine.

The priority review goal date for approval is August 14, 2019.

Source: Galt Pharmaceuticals, May 30, 2019

Orphan Drug Designations

XWL-008 for Narcolepsy

XW Laboratories Inc. has received an orphan drug designation for XWL-008, a treatment for narcolepsy.

Narcolepsy is a chronic neurological disorder of the sleep–wake cycle, characterized by excessive daytime sleepiness and cataplexy. In the U.S., approximately 1 in 2,000 individuals are affected by this disorder.

Phase 1 studies yielded "robust results" demonstrating favorable safety, tolerability, and pharmacokinetics. XW Laboratories is preparing for late-stage phase 3 clinical research.

Source: XW Laboratories, June 24, 2019

BBT-059 for Acute Radiation Syndrome

The FDA has awarded an orphan drug designation to Bolder BioTechnology, Inc. for its long-acting interleukin-11 (IL-11) analog, BBT-059, for the treatment of acute radiation syndrome (ARS).

Acute radiation syndrome is a collection of illnesses that can follow exposure to high doses of ionizing radiation. Subjects acutely exposed to high-dose radiation typically develop severe neutropenia and thrombocytopenia within days to weeks. Many patients die during this period from infections resulting from a lack of neutrophils or from uncontrolled bleeding caused by a lack of platelets.

BBT-059 stimulates the production of platelets. In animal studies, it protects against the lethal effects of acute, high-dose radiation exposure when administered prior to or following radiation exposure, and accelerates recovery of platelets, red blood cells, and neutrophils.

Source: Bolder BioTechnology, Inc., June 12, 2019

PL-8177 for Noninfectious Uveitis

Palatin Technologies, Inc. has received an orphan drug designation for PL-8177 for the treatment of noninfectious intermediate, posterior, and chronic anterior uveitis and panuveitis.

PL-8177, a selective melanocortin 1 receptor agonist peptide, is a synthetic cyclic heptapeptide with demonstrated efficacy in animal experimental autoimmune uveitis disease models.

Noninfectious uveitis is a group of inflammatory diseases that produce swelling and destroy eye tissue. The disease is caused by inflammatory responses inside the eye, which may be initiated by autoimmune responses, responses to infections or tumors within the eye or other parts of the body, physical injury, or toxins. Uveitis can be associated with several diseases, including autoimmune diseases. Initial noninfectious uveitis symptoms include blurred vision, eye pain, dark floating spots in vision, and light sensitivity. Uveitis can cause vision loss or blindness if left untreated.

Palatin has conducted a single and multiple ascending-dose phase 1 study with PL-8177 and is planning a phase 2 clinical study for 2020. In both animal studies and phase 1 subcutaneous studies, PL-8177 reduced inflammation and restored normal retinal structure.

Source: Palatin Technologies, June 6, 2019

BST-236 for Acute Myeloid Leukemia

Biosight Ltd. has received an orphan drug designation for BST-236, a treatment for acute myeloid leukemia (AML).

BST-236 is a novel antimetabolite, a prodrug of cytarabine, which has been the backbone of AML therapy for the past 40 years. Cytarabine, however, is associated with severe bone marrow, gastrointestinal, and neurological toxicities, which significantly limit its use, especially in older and medically unfit patients. BST-236 is designed to deliver high cytarabine doses to leukemia cells with lower systemic exposure to the free drug and relative sparing of normal tissues.

Data from a completed phase 1/2a study and an ongoing phase 2b study suggest that BST-236 could provide a superior front-line treatment option for AML patients, especially those who are medically unfit to receive standard chemotherapy.

Source: Biosight, June 4, 2019

ARO-APOC3 for Familial Chylomicronemia Syndrome

Arrowhead Pharmaceuticals, Inc. has received an orphan drug designation for ARO-APOC3, a subcutaneously administered RNAi therapeutic targeting apolipoprotein C-III in patients with severe hypertriglyceridemia and familial chylomicronemia syndrome (FCS).

A phase 1 single- and multiple-dose study is being done to evaluate the safety, tolerability, pharmacokinetics, and phar-

macodynamic effects of ARO-APOC3 in healthy volunteers with elevated triglycerides and in patients with severe hypertriglyceridemia and FCS.

Source: Arrowhead Pharmaceuticals, June 21, 2019

Emixustat for Stargardt Disease

The FDA has awarded an orphan designation to Acucela Inc. for emixustat hydrochloride to treat Stargardt disease, an inherited disease that directly affects the retina of the eye and often results in vision loss.

Stargardt disease affects approximately 1 in 8,000 to 10,000 people worldwide. The most common form is caused by a mutation of the *ABCA4* gene, which leads to the accumulation of toxic vitamin A byproducts in the retina, causing the gradual deterioration of photoreceptors and vision. Symptoms typically appear during childhood or adolescence but may not be identified until later in life.

Emixustat modulates the process by which vitamin A is recycled in the eye by inhibiting a critical enzyme. In animal studies, emixustat was found to stop and reverse the accumulation of A2E and to preserve the integrity of the retina.

Source: Acucela, June 9, 2019

CAD-1883 for Spinocerebellar Ataxia

The FDA has given an orphan drug designation to Cadent Therapeutics for CAD-1883, a treatment for spinocerebellar ataxia (SCA), a genetic disorder characterized by progressive loss of coordination, slurred speech, difficulty controlling eye movements, and cognitive dysfunction. There are no approved treatments.

CAD-1883, a first-in-class selective positive allosteric modulator of SK channels (small-conductance, calcium-activated potassium ion channels), has the potential to regulate neuronal firing and reduce disabilities in patients with SCA and other movement disorders.

Source: Cadent Therapeutics, May 29, 2019

Complete Response Letters

Celiprolol for Vascular Ehlers-Danlos Syndrome

The FDA sent a complete response letter informing Acer Therapeutics Inc. that it cannot approve celiprolol (Edsivo) for the treatment of vascular Ehlers-Danlos syndrome until the company conducts an adequate, well-controlled trial to determine whether celiprolol reduces the risk of clinical events in patients with the disease.

Acer will request a meeting to discuss the FDA's letter and expects to respond to the agency in the third quarter of 2019.

Ten days after disclosing the letter, Acer announced a corporate restructuring. Its headcount has been reduced from 48 to 19 employees and pre-commercial activities on celiprolol have been halted. The restructuring is expected to provide the resources needed for Acer to operate through 2020. Acer's additional pipeline programs remain under way.

Sources: Acer Therapeutics Inc., June 25 and July 5, 2019

Quizartinib for Acute Myeloid Leukemia

Daiichi Sankyo Company Ltd. has received a complete response letter from the FDA about its application for quizartinib for the treatment of adults with relapsed/refractory *FLT3*-ITD acute myeloid leukemia. The company said it is evaluating the letter to determine its next steps but did not disclose the agency's concerns.

Quizartinib is an oral selective type II *FLT3* inhibitor.

Source: Daiichi Sankyo Company Ltd., June 21, 2019

DRUG SAFETY ISSUES

Florida Firm Barred From Selling Stem-Cell Products

A federal judge has ordered a Florida company to stop selling products derived from stem cells—a significant step in the continuing FDA crackdown on a burgeoning illicit practice, the agency says.

U.S. District Judge Ursula Ungaro of the Southern District of Florida issued an order preventing US Stem Cell Clinic LLC, of Weston, Florida; US Stem Cell Inc., of Sunrise, Florida; and their Chief Scientific Officer Kristin Comella, PhD, from the manufacture or distribution of stromal vascular fraction products—adipose tissue-derived stem cell products—until they comply with the law. The court concluded that the defendants adulterated and misbranded their cellular products made from patients' adipose tissue.

Clinics across the country are manufacturing or marketing stem cell products based on the claim that they don't fall under the regulatory provisions for drugs and biological products. But the FDA says the Florida ruling proves that this is not true.

Many companies are deceiving patients with unsubstantiated claims about the potential for stem cell products to prevent, treat, or cure serious diseases—flouting statutes and FDA regulations. This puts patients at risk by delaying legitimate treatment or causing such harmful outcomes as blindness, infection, and even death.

The FDA has vowed to continue its aggressive oversight; in the past year, the agency sent regulatory correspondence to 46 manufacturers and healthcare professionals.

Source: FDA, June 25 and May 30, 2019

Premier Pharmacy Recall

Premier Pharmacy Labs is recalling all unexpired products intended to be sterile—more than 100 lots of 19 drugs—

due to a lack of sterility assurance. The company cited concerns that were raised during the latest FDA inspection, including insufficient environmental controls, potential cross contamination, and lack of product-specific process validations.

Premier Pharmacy Labs has not received any reports of adverse events related to the products. The recall covers all commercially distributed product lots compounded in its Weeki Wachee location in Florida, which the FDA inspected from April 29 to June 12, 2019. Products and lots affected by the recall are listed at https://premierpharmacylabs.com/urgent-product-recall/.

Patients and healthcare providers can contact Premier by calling 800-752-7139 or by emailing recalls@premierpharmacylabs.com.

Source: FDA, June 18, 2019

RXQ Compounding Recall

RXQ Compounding, LLC is recalling all unexpired sterile human and animal products—more than 250 lots—because of a lack of sterility-process assurance. RXQ is also voluntarily ceasing all sterile production at its current location in Athens, Ohio, while it transitions into a new outsourcing facility.

To date, RXQ has not received any reports of adverse events related to the products being recalled, which were distributed to hospitals and practitioners nationwide. A list of drugs and lots is available at https://rxqcompounding.com/Recall-List.pdf.

Consumers who have questions can contact RXQ at 740-331-4202 or email Brian.Post@RXQCompounding.com.

Source: FDA, June 18, 2019

FDA Warns API Repackers

The FDA has issued warning letters to three repackers of active pharmaceutical ingredients (API)—B&B Pharmaceuticals, Inc.; Asclemed USA, Inc., doing business as Enovachem; and Spectrum Laboratory Products, Inc.—for significant violations of current good manufacturing practice requirements.

Generally, repackers take bulk API (usually in powder form) from the original manufacturer's container and place it into a different container without further manipulation of the drug. They then distribute it to drug manufacturers, compounding pharmacies, or outsourcing facilities. The improper repackaging or lack of supply chain oversight of API can cause serious vulnerabilities in the supply chain and may lead to adverse events in patients, the FDA says.

The agency has previously issued separate warning letters to API repackers Vipor Chemicals Private Ltd., Lumis Global Pharmaceuticals Co. Ltd., Sal Pharma, Huron Pharmaceuticals, Inc., and Fagron, Inc.

Source: FDA, July 2, 2019

PharMEDium Hydromorphone

PharMEDium Services, LLC is recalling 45 lots of 0.5 mg/mL hydromorphone hydrochloride in 0.9% sodium chloride 1 mL in 3-mL BD syringes because the company's electronic customer ordering system incorrectly said the product is sulfite-free. The company has distributed 28,140 syringes to six U.S. customers.

Serious adverse reactions could occur in patients with a sulfite allergy who are exposed to hydromorphone containing sulfites. PharMEDium has not received any adverse event reports relating to sulfite reactions or sensitivity.

Source: FDA, June 28, 2019

DEVICE APPROVALS

ReStore Exo-Suit, a Robotic System for Stroke Therapy

The FDA has cleared the ReStore soft exo-suit system by ReWalk Robotics, Ltd. for sale to rehabilitation centers. ReStore is intended for use in the treatment of stroke survivors with mobility challenges.

ReStore is comprised of a soft, garment-like design that connects to a lightweight waist pack and mechanical cables, which help lift the patient's affected leg in synchronized timing with the natural walking pattern. The system provides targeted assistance to the patient during forward propulsion (plantarflexion) and ground clearance (dorsiflexion), two key phases of the gait cycle. The device also provides physical therapists with extensive data during gait training with ReStore to inform strategies that optimize a patient's treatment and progress.

The company believes that the launch price of $28,900, as well as leasing options, will make ReStore accessible for a broader range of clinics than existing robotic technologies.

The patented exo-suit technology was developed at Harvard University's Wyss Institute for Biologically Inspired Engineering. ReWalk and Wyss entered into a multiyear research collaboration agreement in 2016.

ReWalk expects to publish the results of a multicenter clinical study of the ReStore system later in 2019.

Source: ReWalk Robotics Ltd., June 4, 2019

IB-Stim for IBS Pain

The FDA has allowed marketing of the first medical device to aid in the reduction of functional abdominal pain in patients aged 11 to 18 years with irritable bowel syndrome (IBS), when combined with other therapies for IBS.

The prescription-only IB-Stim (Innovative Health Solutions) is a small, single-use electrical nerve stimulator that is placed behind the patient's ear. It contains a battery-powered chip that emits low-frequency electrical pulses to stimulate branches of certain cranial nerves continuously for five days, at which time it is replaced. Stimulating nerve bundles in

and around the ear is thought to provide pain relief. Patients can use the device for up to three consecutive weeks to reduce functional abdominal pain associated with IBS.

The FDA reviewed data from a published study that included 50 patients aged 11 to 18 years with IBS; 27 were treated with the device and 23 with a placebo device. The study measured change from baseline to the end of the third week in worst abdominal pain, usual pain, and Pain Frequency Severity Duration (PFSD) scores. IB-Stim treatment, compared with placebo, resulted in at least a 30% decrease in usual pain in more patients (52% vs. 30%), at least a 30% decrease in worst pain in more patients (59% vs. 26%), and a greater change in composite PFSD scores.

During the study, six patients reported mild ear discomfort and three patients reported adhesive allergy at the application site.

The FDA reviewed IB-Stim through the *de novo* premarket review pathway.

Previously, the agency granted marketing authorization to similar versions of this device for other uses: the NSS-2 BRIDGE, in 2017, as an aid to reduce symptoms of opioid withdrawal, and the Electro Auricular Device, in 2014, for use in acupuncture.

Source: FDA, June 7, 2019

Hintermann Ankle Replacement

The Hintermann Series H3 Total Ankle Replacement (TAR) System (DT MedTech, LLC) has received FDA premarket approval for use as a noncemented implant to replace a painful arthritic ankle joint caused by primary osteoarthritis, post-traumatic osteoarthritis, or arthritis secondary to inflammatory disease.

The three-piece, mobile-bearing implant was developed by Beat Hintermann, MD, a foot and ankle surgeon in Liestal, Switzerland. It has been implanted in more than 20,000 patients outside of the U.S. since its release in May 2000. Clinical data show that 95.9% of H3 patients were moderately satisfied to very satisfied with the procedure at five years post-implantation, and survivorship at seven years was 88%.

DT MedTech will continue selling the Hintermann Series H2, a two-piece, cemented, semi-constrained TAR that received 510(k) clearance to market in November 2017.

Source: DT MedTech, LLC, June 5, 2019

Quidel Drug Screen

Quidel has received 510(k) clearance from the FDA to market the Quidel Triage TOX Drug Screen 94600, a fluorescence immunoassay for the determination of the presence of drugs and/or metabolites in human urine. The test is to be used with Quidel's Triage MeterPro instrumented system.

The speed and sensitivity of immunoassays have made them the preferred method for detecting drugs in urine. The TOX Drug Screen 94600 uses distinct immunoassays to simultaneously detect drug and/or urinary metabolites of up to nine drug classes. Using monoclonal antibodies that are specific for the metabolites of these drug classes ensures a high level of sensitivity and specificity.

About 15 minutes after the specimen is added, the Quidel Triage MeterPro screen displays results, which are stored in the system's memory to display or print when needed. The results can also be transmitted to the laboratory or hospital information system.

Source: Quidel, June 19, 2019

Nexus Ultrasonic Surgery System

The FDA has awarded 510(k) clearance to Nexus (Misonix, Inc.)—an ultrasonic surgical platform combining the features of Misonix's BoneScalpel, SonicOne, and Sonastar—into a single, fully integrated platform with more power, efficiency, and control.

Nexus will permit physicians to improve tissue resection rates and perform more efficient bone removal procedures using a digital touchscreen display.

Source: Misonix, June 3, 2019

DEVICE SAFETY ISSUES

Endotracheal Tube May Be Linked to Four Deaths

Teleflex Inc. is recalling some Hudson RCI Sheridan Endotracheal Tubes because connectors have detached from the tubes, interrupting breathing support for patients. The problem may have been a factor in four deaths and additional serious injuries.

The products, designed for oral or nasal intubation, are indicated for airway management. The class I recall covers numerous lots of 33 products ranging in size from 6.0 mm to 8.5 mm, distributed between October 2016 and May 2019. Additional information is available at https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/teleflex-incorporated-announces-worldwide-voluntary-recall-select-hudson-rcir-sheridanr-endotracheal.

Teleflex says specific lots of 15-mm Sheridan connectors have become disconnected from endotracheal tubes, detaching patients from the breathing circuit. According to the company, reported complaints involve less than 0.0025% of the distributed products.

Customers should immediately discontinue use of the products and return them to Teleflex or its distributor. Customers can contact the company at 1-866-396-2111 or email recalls@teleflex.com.

Source: FDA, June 25, 2019

Medtronic Insulin Pumps Recalled Over Cybersecurity

The FDA is recalling some Medtronic MiniMed insulin pumps due to potential cybersecurity risks, and recommends that patients using these models switch to pumps that are better equipped to protect against such risks. However, the agency is not aware of any confirmed reports of patient harm relating to this issue.

The potential risks relate to wireless communication between the pumps and devices used with them, such as blood glucose meters, continuous glucose-monitoring systems, the remote controller, and CareLink USB devices. The FDA is concerned that, as a result of cybersecurity vulnerabilities identified in the device, someone other than a patient, caregiver, or healthcare provider could connect wirelessly to a nearby MiniMed insulin pump and change the pump's settings. This could allow a person to overdeliver insulin, which would lead to hypoglycemia, or to stop insulin delivery, which would lead to high blood sugar and diabetic ketoacidosis.

The recall covers Medtronic's MiniMed 508 insulin pump and MiniMed Paradigm series insulin pumps. Medtronic is unable to adequately update these pumps with any software or patch that would address the vulnerabilities. The company is providing alternative insulin pumps to patients with enhanced built-in cybersecurity capabilities. So far, Medtronic has identified 4,000 U.S. patients who are potentially using insulin pumps that are vulnerable to this issue and the company is working to identify additional patients at risk.

Source: FDA, June 27, 2019 ■