NEW DRUGS

Tanzeeum for Type-2 Diabetes

The FDA has approved albiglutide (Tanzeeum, GlaxoSmithKline) subcutaneous injection as a once-weekly treatment to improve glycemic control, along with diet and exercise, in adults with type-2 diabetes.

The safety and effectiveness of albiglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, were evaluated in eight clinical trials involving more than 2,000 patients with type-2 diabetes, who showed an improvement in HbA1c levels.

Albiglutide has been studied as monotherapy and in combination with other therapies, including metformin, glimepiride, pioglitazone, and insulin. It should not be used to treat people with type-1 diabetes or diabetic ketoacidosis, or as first-line therapy for patients who can’t be managed with diet and exercise.

Albiglutide has a boxed warning noting that thyroid C-cell tumors have been observed in rodent studies with some GLP-1 receptor agonists, but it is unknown whether albiglutide causes such tumors, including medullary thyroid carcinoma (MTC), in humans. Albiglutide should not be used in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2.

Albiglutide is administered using an injector pen supplied with a 5-mm 29-gauge thin-walled needle.

The FDA is requiring these post-marketing studies:

- A clinical trial to evaluate dosing, efficacy, and safety in pediatric patients
- An MTC case registry for at least 15 years to identify any increase in MTC incidence related to the drug
- A cardiovascular outcomes trial to evaluate the cardiovascular risk of albiglutide in patients with high baseline risk of cardiovascular disease

In clinical trials, the most common side effects observed with albiglutide were diarrhea, nausea, and injection-site reactions. Albiglutide has a risk evaluation and mitigation strategy (REMS).

Sources: FDA and GlaxoSmithKline, April 15, 2014

Oralair to Treat Allergic Rhinitis

The FDA has approved Oralair (Stallergenes S.A.) to treat allergic rhinitis with or without conjunctivitis that is induced by certain grass pollens in people ages 10 through 65 years. It was the first sublingual allergen extract approved in the U.S.

Allergic rhinitis with or without conjunctivitis is often caused by sensitivity to grass pollen. Those affected may suffer from repetitive sneezing, nasal itching, runny nose, nasal congestion, and itchy and watery eyes.

Oralair is a once-daily tablet that rapidly dissolves after it is placed under the tongue. Treatment begins four months before the start of the grass pollen season and continues throughout the season. The first dose is administered at the health care provider’s office, where the patient is observed for at least 30 minutes for potential adverse reactions. Afterward, the product can be taken at home.

The treatment contains a mixture of freeze-dried extracts from the pollens of five grasses: Kentucky Blue Grass, Orchard, Perennial Rye, Sweet Vernal, and Timothy. Its safety and effectiveness were evaluated in studies involving approximately 2,500 people in the U.S. and Europe who received Oralair or placebo. The subjects reported their symptoms and any additional medications they needed to get through allergy season.

During treatment for one grass pollen season, subjects taking Oralair experienced a 16% to 30% reduction in symptoms and in the need for medications compared with those who received placebo.

The product has a boxed warning about the possibility of severe allergic reactions (including life-threatening anaphylaxis). The most common adverse reactions were itching in the ears and mouth, itching of the tongue, swelling of the mouth, and throat irritation among adults and itching and swelling in the mouth and throat irritation among children.

Source: FDA, April 2, 2014

Grastek for Grass Pollen Allergy

Timothy grass pollen allergen extract (Grastek, Merck) has received FDA approval for sublingual use as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis.

The product is approved for use in persons 5 through 65 years of age with pollen-specific immunoglobulin E antibodies for Timothy grass or cross-reactive grass pollens confirmed by a skin test or in vitro testing. It is not indicated for the immediate relief of allergic symptoms.

The prescribing information includes a boxed warning about severe allergic reactions. The product is contraindicated in patients with severe, unstable, or uncontrolled asthma; a history of any severe systemic allergic reaction; a history of any severe local reaction after taking any sublingual allergen immunotherapy; a history of eosinophilic esophagitis; or hypersensitivity to any of the product’s inactive ingredients.

The recommended dose is one tablet daily placed under the tongue, where it will dissolve. The first dose should be administered in a health care setting under the supervision of a physician experienced in the diagnosis and treatment of allergic diseases. The physician should observe the patient for at least 30 minutes after he or she takes the first dose to watch for signs or symptoms of a severe systemic or local allergic reaction.

A patient who tolerates the first dose may take subsequent doses at home. The physician should prescribe auto-injectable epinephrine and train the patient on its use. Children must use the product under
adult supervision. Treatment is initiated at least 12 weeks before the expected onset of grass pollen season and continued throughout the season.

The efficacy of Timothy grass pollen allergen extract was supported by data from three pivotal studies involving 2,479 patients. Those treated with Timothy grass pollen allergen extract showed significant reductions in nasal and ocular symptoms and reduced use of symptom-relieving allergy medication. The decrease in the total combined score for grass pollen seasons for Timothy grass pollen allergen extract compared with placebo ranged from –3% in a one-year study to –41% in the second year of a five-year study.

Source: Merck, April 14, 2014

**Alprolix for Hemophilia B**

The FDA has approved coagulation factor IX (recombinant), Fc fusion protein (Alprolix, Biogen Idec), the first recombinant, DNA-derived hemophilia B therapy with prolonged circulation in the body.

Alprolix is indicated for the control and routine prophylaxis in adults and children with hemophilia B. It has been shown to reduce bleeding episodes with prophylactic infusions starting at least a week apart. Biogen Idec says the product’s approval marks the first significant advance in hemophilia B treatment in more than 17 years.

Treatments for hemophilia B can be administered either on a schedule to help prevent or reduce bleeding episodes (prophylaxis) or to help control a bleeding episode when it occurs (on demand). According to National Hemophilia Foundation guidelines, traditional therapy for hemophilia B requires prophylactic infusions twice a week or more.

The FDA’s approval is based on results from the phase 3 B-LONG study, as well as on interim pharmacokinetic and safety data from the ongoing phase 3 Kids B-LONG study.

B-LONG was a global, open-label study that evaluated the efficacy, safety, and pharmacokinetics of prevention or reduction of bleeding episodes with prophylactic infusions in 123 males ages 12 years and older with hemophilia B. Adults and adolescents with severe hemophilia B achieved prevention or reduction of bleeding episodes with prophylactic infusions at least a week apart.

The study included two prophylaxis regimens—a weekly arm and an individualized-interval arm, in which the dosing interval started at once every 10 days. The overall median dosing interval with individualized-interval prophylaxis was 12.5 days. More than 90% of all bleeding episodes were controlled by a single infusion.

The overall median annualized bleeding rates reported in the study were 3.0 for weekly prophylaxis, 1.4 for individualized-interval prophylaxis, and 17.7 for the on-demand treatment. No B-LONG participants developed neutralizing antibodies, vascular clots, or serious allergic reactions.

Across the routine prophylaxis and on-demand therapy arms, 8.4% of participants reported adverse reactions, including headache, oral paresthesia, dizziness, dysgeusia, breath odor, fatigue, infusion-site pain, palpitations, obstructive uropathy, and hypotension.

Source: Biogen Idec, March 28, 2014

**Otezla for Psoriatic Arthritis**

Apremilast (Otezla, Celgene Corporation) has received FDA approval for the treatment of adults with active psoriatic arthritis (PsA). It is the only FDA-approved oral treatment for PsA.

The drug’s approval was based on safety and efficacy results from three randomized, double-blind, placebo-controlled trials—PALACE 1, 2, and 3—conducted in adults with active PsA who were adequately controlled by disease-modifying anti-rheumatic drugs (DMARDs) and/or biologics.

Treatment with apremilast versus placebo (with or without concomitant DMARDs) resulted in greater improvement in the signs and symptoms of PsA, as demonstrated by the proportion of patients with a 20% improvement in American College of Rheumatology criteria (ACR20) at week 16. In PALACE 1, 38% of patients treated with apremilast 30 mg twice daily achieved ACR20 at week 16 compared with 19% of those given placebo. Similar results were achieved in PALACE 2 and PALACE 3. Higher ACR50 and ACR70 responses (indicating 50% and 70% improvement, respectively) were seen at week 16 across the three studies.

At week 16, patients treated with apremilast achieved a reduction in tender and swollen joint counts compared with patients given placebo. Treatment resulted in improvement for each of the seven ACR components measured, compared with placebo, at week 16. Improvements were also seen in disease-related physical functioning. Treatment with apremilast resulted in improvement in dactylitis and enthesitis in patients with these pre-existing symptoms.

In phase 3 trials, adverse reactions reported more often with use of apremilast 30 mg twice daily than placebo for up to 16 weeks were diarrhea, nausea, headache, upper respiratory tract infections, vomiting, nasopharyngitis, and upper abdominal pain.

In the PALACE studies, 10% of patients treated with apremilast reported weight loss of 5% to 10%. It is recommended that patients taking apremilast have their weight checked regularly. Treatment with apremilast was also associated with an increase in reports of depression compared with placebo. The FDA is requiring a pregnancy exposure registry as a post-marketing requirement to assess
the risks to pregnant women related to exposure to apremilast.
Sources: FDA and Celgene Corporation, March 21, 2014

**Neuraceq for Imaging of Beta-Amyloid Plaques**

The FDA has approved florbetaben F18 injection (Neuraceq, Piramal Imaging) for use in positron emission tomography (PET) imaging of the brain to estimate beta-amyloid neuritic plaque density in adults with cognitive impairment who are being evaluated for Alzheimer’s disease (AD) and other causes of cognitive decline.

AD accounts for up to 80% of dementia diagnoses. However, a clinical diagnosis of probable AD is incorrect upon postmortem histological investigation in up to 30% of cases.

The FDA approval of florbetaben F18 injection is based on safety data from 872 patients who participated in clinical trials as well as three studies that examined images from adults with a range of cognitive function, including 205 end-of-life patients who had agreed to participate in a postmortem brain donation program.

Images were analyzed from 82 subjects with postmortem confirmation of the presence or absence of beta-amyloid neuritic plaques. Correlation of the visual PET interpretation with histopathology in these 82 brains demonstrated that florbetaben F18 injection accurately detects moderate to frequent beta-amyloid neuritic plaques. Neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other neurological conditions as well as older people with normal cognition.

For more on advances in AD, see the article by Susan Worley on page 365.
Source: Piramal Imaging, March 20, 2014

**Impavido for Tropical Parasitic Disease**

The FDA has approved miltefosine (Impavido, Paladin Therapeutics) to treat leishmaniasis. Caused by the *Leishmania* parasite, the disease is transmitted to humans through bites from infected sand flies and occurs primarily in the tropics and subtropics. Most U.S. patients acquire leishmaniasis overseas.

Oral miltefosine is approved to treat cutaneous, visceral, and mucosal leishmaniasis in patients 12 years of age and older. It is the first drug approved by the FDA to treat cutaneous or mucosal leishmaniasis.

The safety and efficacy of miltefosine were evaluated in four clinical trials. A total of 547 patients received miltefosine, and 183 patients received either a comparator drug or placebo. The results demonstrated that miltefosine is safe and effective in treating visceral, cutaneous, and mucosal leishmaniasis.

The labeling for miltefosine includes a boxed warning to alert patients and health care professionals that the drug can cause fetal harm and should not be given to pregnant women. Health care professionals should advise women to use effective contraception during and for five months after treatment with miltefosine.

The most common side effects identified in clinical trials were nausea, vomiting, diarrhea, headache, decreased appetite, dizziness, abdominal pain, itching, drowsiness, and elevated levels of liver enzymes (transaminases) and creatinine.

Miltefosine is an alkyl-lysophospholipid analogue drug with *in vitro* activity against the promastigote and amastigote stages of *Leishmania* species.

Cutaneous leishmaniasis (CL) usually presents as one or more skin ulcers at the site of a sand-fly bite. In the U.S., CL may be seen in travelers and soldiers returning from endemic regions. In most cases, the ulcer spontaneously resolves within months, leaving a scar. The goals of therapy are to accelerate healing, decrease morbidity, and decrease relapse.

In 1% to 10% of patients with CL in the New World, *Leishmania* disseminates from the skin to the naso-oropharyngeal mucosa, resulting in mucosal leishmaniasis and the destruction of nasal and pharyngeal structures. Death may occur due to complicating aspiration pneumonia.

Visceral leishmaniasis is characterized by fever, splenomegaly, and cytopenia.
Sources: FDA, March 19, 2014, and October 18, 2013

**Generic Approvals**

**Atovaquone Oral Suspension**

The FDA has approved the first generic version of Mepron Oral Suspension, 750 mg/5 mL, a GlaxoSmithKline medication used to prevent and treat *Pneumocystis jiroveci* pneumonia (PCP). Amneal Pharmaceuticals’ formulation of atovaquone oral suspension USP, 750 mg/5 mL, was found to be therapeutically equivalent to Mepron.

The antiprotozoal agent is indicated for the prevention of PCP in patients who are intolerant to trimethoprim-sulfamethoxazole (TMP-SMX). It is also indicated for the acute oral treatment of mild-to-moderate PCP in patients who are intolerant to TMP-SMX.

Sources: FDA, March 18, 2014, and Mepron Prescribing Information

**Solifenacin Succinate**

The FDA has approved Teva Pharmaceuticals’ solifenacin succinate tablets, 5 mg and 10 mg—the first generic formulation of VESIcare. The tablets were found to be therapeutically equivalent to the 5-mg and 10-mg VESIcare tablets made by Astellas Pharma. Solifenacin succinate, a muscarinic receptor antagonist, is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Sources: FDA, April 2, 2014, and VESIcare Prescribing Information

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Carbidopa

The FDA has approved Amerigen Pharmaceuticals’ carbidopa 25-mg tablets, a generic equivalent of Valeant’s Lodosyn. Carbidopa is indicated for use with carbidopa-levodopa or levodopa to treat symptoms of idiopathic Parkinson’s disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism. Carbidopa is used with carbidopa-levodopa in patients for whom the dosage of carbidopa-levodopa provides less than adequate daily dosage of carbidopa. It is used with levodopa in patients whose dosage requirement of carbidopa and levodopa necessitates separate titration of each medication.

Sources: Amerigen Pharmaceuticals, March 12, 2014, and Lodosyn Prescribing Information

Procardia

The FDA has approved TWi Pharmaceuticals’ generic nifedipine extended-release tablets, 30 mg, 60 mg, and 90 mg. A calcium channel blocker, nifedipine is indicated for the management of vasospastic angina, chronic stable angina, and hypertension. This is the latest generic version of Pfizer’s Procardia XL, which together with other generic versions of nifedipine has combined annual U.S. sales of about $116 million, according to 2013 IMS data.

Sources: TWi Pharmaceuticals, April 7, 2014, and Procardia Prescribing Information

NEW FORMULATIONS

Oxycodone/Acetaminophen Combination for Acute Pain

The FDA has approved oxycodone hydrochloride and acetaminophen extended-release tablets, CII (Xartemis XR, Mallinckrodt) for the management of acute pain severe enough to require opioid treatment and for patients in whom alternative treatment options (e.g., nonopioid analgesics) are ineffective, not tolerated, or would otherwise be inadequate. This is the first extended-release oral combination of oxycodone and acetaminophen.

The FDA’s approval is based partly on data from a pivotal phase 3 efficacy study conducted in an acute postsurgical pain model. Xartemis XR met the study’s primary endpoint and showed statistically significant improvement in pain scores from baseline to more than 48 hours compared with placebo. The combination was also evaluated in extensive lab testing and in a human abuse-liability study.

The immediate- and extended-release components of Xartemis XR were formulated to provide the onset of pain relief in less than one hour and to allow twice-daily dosing. The medication is not interchangeable with other oxycodone-/acetaminophen products because of differing pharmacokinetic profiles that affect the frequency of administration.

Xartemis XR is indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. Because of the risks of addiction, abuse, misuse, overdose, and death with opioids, even at recommended doses, the product should be reserved for use in patients for whom alternative treatment options (e.g., nonopioid analgesics) are ineffective, not tolerated, or would be otherwise inadequate.

Xartemis XR contains oxycodone, a Schedule II controlled substance. As an opioid, the medication exposes users to the risks of addiction, abuse, and misuse. Abuse or misuse of Xartemis XR by crushing, chewing, snorting, or injecting the dissolved product will result in the uncontrolled delivery of the oxycodone and can result in overdose and death.

Source: Mallinckrodt, March 12, 2014

Quedexy XR for Seizures

The FDA has approved topiramate extended-release capsules (Quedexy XR, Upsher-Smith Laboratories), a once-daily, broad-spectrum anti-epileptic drug.

The medication is indicated as initial monotherapy in patients 10 years of age and older with partial-onset seizures (POS) or primary generalized tonic-clonic seizures. It is also approved as adjunctive therapy in patients 2 years of age and older with POS, with primary generalized tonic-clonic seizures, or with seizures associated with Lennox-Gastaut syndrome.

As many as two out of three people treated for epilepsy have seizures that are refractory to therapy.

Results from the global phase 3 PREVAIL trial of extended-release topiramate demonstrated that the drug is effective and generally well tolerated. All medication strengths—25 mg, 50 mg, 100 mg, 150 mg, and 200 mg—may be swallowed whole or administered by carefully opening the capsule and sprinkling the entire contents on a spoonful of soft food. This makes Qudexy XR the only approved extended-release topiramate product for patients who have trouble swallowing whole capsules or tablets.

PREVAIL was a randomized, double-blind, placebo-controlled, parallel-group study that evaluated the efficacy and safety of extended-release topiramate as adjunctive therapy in 249 adult patients with refractory POS. The drug met its endpoints for efficacy and demonstrated favorable safety and tolerability. Extended-release topiramate was associated with a significantly greater median percent reduction from baseline in the frequency of POS compared with placebo (39.5% vs. 21.7%, respectively; P < 0.001) after 11 weeks of treatment.

Source: Upsher-Smith Laboratories, March 12, 2014

Noxafil for IV Use

The FDA has approved posaconazole (Noxafil, Merck) injection 18 mg/mL for intravenous (IV) use. The antifungal
agent is also marketed as delayed-release tablets (100 mg) and an oral suspension (40 mg/mL).

All three formulations are indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections because they are severely immunocompromised, such as hematopoietic stem cell transplant recipients with graft-versus-host disease or those with hematological malignancies with prolonged neutropenia from chemotherapy. Posaconazole injection is indicated for patients 18 years of age and older, while the delayed-release tablets and oral suspension are approved for patients 13 years of age and older.

Posaconazole should not be administered to persons allergic to otherazole antifungal medications and should not be used with sirolimus, pimozone, quinidine, atorvastatin, lovastatin, simvastatin, and ergot alkaloids. When administered with posaconazole, some drugs, such as cyclosporine and tacrolimus, require dosage adjustments and frequent monitoring of blood levels. Serious nephrotoxicity and leukoencephalopathy, including deaths, have been reported in patients with increased cyclosporine or tacrolimus blood levels.

Posaconazole should be administered with caution to patients who may develop an irregular heart rhythm, as the drug has been shown to prolong the QT interval. Cases of potentially fatal irregular heart rhythm have been reported in patients taking posaconazole.

Posaconazole injection is administered with a loading dose of 300 mg twice a day on the first day of treatment, followed by 300 mg once a day thereafter. Once combined with a mixture of IV solution (150 mL of 5% dextrose in water or sodium chloride 0.9%), posaconazole injection should be administered immediately through a central venous line with an in-line filter by slow infusion over approximately 90 minutes.

In clinical trials, the adverse reactions reported for posaconazole IV injection were generally similar to those reported in trials of posaconazole oral suspension. The most frequently reported adverse reactions with an onset during the IV phase of 300 mg once-daily therapy were diarrhea (32%), hypokalemia (22%), fever (21%), and nausea (19%).

Source: Merck, March 16, 2014

**Hemangeol for Proliferating Infantile Hemangioma**

Propranolol hydrochloride (Hemangeol, Pierre Fabre Dermatologie) has been approved by the FDA for proliferating infantile hemangioma (IH) requiring systemic therapy. An oral solution specially developed for safe and effective use in children, Hemangeol will be available in June 2014.

The efficacy of propranolol in treating IH was discovered in 2007 by a dermatologist at Bordeaux University Hospital in France. Subsequently, off-label use of the medication, long employed in cardiology, became the first-line treatment for IH.

The propranolol hydrochloride formulation was specifically developed for the pediatric population. It was studied in infants 5 weeks to 5 months old (at therapy initiation) with proliferative IH requiring systemic treatment in a randomized, double-blind, placebo-controlled, multidose, multicenter adaptive phase 2/3 trial, which compared four propranolol treatment protocols (1 or 3 mg/kg/day for three or six months) versus placebo.

The treatment protocol of 3 mg/kg/day for six months had a 60.4% success rate versus 3.6% in the placebo group ($P < 0.0001$); 11.4% of patients needed to be retreated after stopping treatment.

Propranolol hydrochloride can cause serious side effects, including hypoglycemia, bradycardia, hypotension, bronchospasm, worsened congestive heart failure, and increased stroke risk in children with PHACE syndrome. The most frequently reported adverse reactions in infants treated with propranolol hydrochloride were sleep disorders, aggravated respiratory tract infections such as bronchitis and bronchiolitis associated with cough and fever, diarrhea, and vomiting.

Source: Pierre Fabre Dermatologie, March 17, 2014

**NEW INDICATIONS**

**Xolair for Chronic Hives**

The FDA has approved omalizumab (Xolair, Genentech/Novartis) for the treatment of chronic idiopathic urticaria (CIU), a form of chronic hives, in patients 12 years of age and older who remain symptomatic despite treatment with H1 antihistamine therapy. Omalizumab is not used to treat other forms of urticaria and is not for use in children younger than 12 years old.

CIU is characterized by hives that spontaneously occur without an identifiable cause and re-occur for six weeks or more. The red, swollen, itchy, and sometimes painful hives on the skin can last for months or even years.

Omalizumab was evaluated for CIU treatment in two pivotal trials, ASTERIA I and ASTERIA II, involving 641 patients. The studies used the Itch Severity Score (ISS) and weekly hive count score (both of which range from 0 to 21) to determine omalizumab’s efficacy.

In ASTERIA I, subcutaneous injections of omalizumab 150 mg every four weeks reduced the ISS from the starting measurement by 6.7 (47%) at week 12, and omalizumab 300 mg reduced the ISS from the starting point by 9.4 (66%), compared with a reduction of 3.6 (25%) for placebo. A larger proportion of patients (36%) treated with omalizumab 300 mg reported no itching and no hives at week 12 compared with patients treated with omalizumab 150 mg (15%) and placebo (9%).
Similar results were observed in ASTE-RIA II. The most common side effects in patients treated with omalizumab were nausea; headaches; swelling of the inside of the nose, throat, or sinuses; cough; joint pain; and upper respiratory tract infection.

Omalizumab is a recombinant DNA-derived humanized immunoglobulin G1-kappa (IgG1-kappa) monoclonal antibody that selectively binds to human IgE.

Sources: Novartis, March 21, 2014, and Xolair Prescribing Information

**Eliquis to Lower Blood-Clot Risk After Hip or Knee Replacement**

The FDA has approved a supplemental new drug application for apixaban (Eliquis, Bristol-Myers Squibb/Pfizer) for the prophylaxis of deep-vein thrombosis (DVT) that may lead to pulmonary embolism (PE) in patients who have undergone hip- or knee-replacement surgery.

As an oral, selective inhibitor of factor Xa, a key blood-clotting protein, apixaban decreases thrombin generation and blood-clot formation.

The prescribing information for apixaban includes boxed warnings for the increased risk of stroke in patients with nonvalvular atrial fibrillation who discontinue the drug without adequate continuance of anticoagulant therapy for five to 10 days, and for the risk of recurrent DVT and PE in previously treated patients.

The approval is based on results from four phase 3 studies. RE-COVER and RE-COVER II, which included patients with DVT and PE who were treated with parenteral anticoagulant therapy for five to 10 days, showed dabigatran was noninferior to warfarin in reducing DVT and PE after a median of 174 days of treatment. RE-MEDY, which included patients who had been previously treated for an acute DVT and PE with anticoagulant therapy for three to 12 months, showed dabigatran was noninferior to warfarin in reducing DVT and PE after a median of 534 days of treatment. In these trials, dabigatran was associated with lower rates of overall bleeding and a higher rate of GI bleeding.

RE-SONATE, which included patients who had been previously treated for an acute DVT and PE with anticoagulant therapy for six to 18 months, showed dabigatran reduced the risk of DVT and PE recurrence by 92 percent compared with placebo after a median of 182 days of treatment. Dabigatran was associated with higher rates of bleeding compared with placebo (10.5% vs. 6.1% percent).

Dabigatran is also approved to reduce the risk of stroke in patients with nonvalvular atrial fibrillation.

Source: Boehringer Ingelheim Pharmaceuticals, April 7, 2014

**DRUG NEWS**

**Studies Show Efficacy of Interferon-Free HCV Regimens**

Hepatitis C patients who took a once-daily combination of Gilead Sciences’ sofosbuvir (Solvadi) and ledipasvir for eight weeks had a sustained virological response 12 weeks after treatment (SVR12) of 94%, according to a study published online in the *New England Journal of Medicine*.

In this study of 647 previously untreated, cirrhosis-free patients with hepatitis C virus genotype 1 (HCV-1), SVR12 rates were 93% when ribavirin was added to ledipasvir and sofosbuvir for eight weeks and 95% when the ledipasvir-sofosbuvir regimen lasted 12 weeks. The researchers found “no additional benefit” to adding ribavirin or lengthening treatment.

The journal published articles on six phase 3 trials of interferon-free HCV-1 treatments with various drug combinations to coincide with a meeting of the European Association for the Study of the Liver. In the other studies:

- **Among 440 HCV-1 patients who did not have a sustained virological response after treatment with peginterferon and ribavirin (with or without a protease inhibitor), SVR12 rates were 94% with ledipasvir-sofosbuvir in a once-daily tablet for 12 weeks, 96% with ledipasvir-sofosbuvir plus ribavirin for 12 weeks, 99% with ledipasvir-sofosbuvir for 24 weeks, and 99% with ledipasvir-sofosbuvir plus ribavirin for 24 weeks.**

- **Among 865 previously untreated HCV-1 patients, SVR12 rates were 99% with ledipasvir and sofosbuvir in a once-daily combination tablet for 12 weeks, 97% with ledipasvir-sofosbuvir plus ribavirin for 12 weeks, 98% with ledipasvir-sofosbuvir for 24 weeks, and 99% with ledipasvir-sofosbuvir plus ribavirin for 24 weeks.**

- **In a study of 394 HCV-1 patients pre-
viously treated with peginterferon and ribavirin, SVR12 rates were 96.3% following a 12-week combination of four AbbVie drugs—the protease inhibitor ABT-450 with ritonavir, the NSSA inhibitor ombitasvir, and the nonnucleoside polymerase inhibitor dasabuvir—plus ribavirin.

• Among 380 HCV-1 patients with compensated cirrhosis (previously treated and untreated), a combination of ABT-450 with ritonavir, ombitasvir, dasabuvir, and ribavirin led to SVR12 of 91.8% and 95.9% after treatment for 12 weeks and 24 weeks, respectively.

• Treatment for 12 weeks combining ABT-450 with ritonavir, ombitasvir, dasabuvir, and ribavirin in previously untreated patients with HCV-1 infection and no cirrhosis led to SVR12 of 96.2% (95.3% in HCV genotype 1a and 98.0% in HCV genotype 1b).

Virological failure during treatment, relapse after treatment, and discontinuation due to adverse events were low in each study. Common adverse events were fatigue, headache, insomnia, nausea, pruritus, and diarrhea.

For an in-depth look at sofosbuvir, see the Drug Forecast on page 345.

Source: New England Journal of Medicine, April 12, 2014

ASHP Recommends Ways To Cope With IV Shortages

New recommendations drafted by the American Society of Health-System Pharmacists (ASHP) with the University of Utah Drug Information Service aim to help health care providers deal with an acute national shortage of large-volume intravenous (IV) solutions.

Many health care sites have been affected by the shortage of large-volume (i.e., 1,000 mL) IV solutions, including 0.9% and 0.45% sodium chloride injection, lactated Ringer’s injection, and 5% dextrose injection. The shortages, which result from an unusual spike in demand, may last until June.

Intravenous Solution Conservation Strategies, available at www.ashp.org, focuses on organizational, patient care, product conservation, and inventory control approaches, including:

• Using oral hydration whenever possible
• Discontinuing infusions as soon as appropriate
• Evaluating patient fluid requirements for surgeries to ensure efficient use
• Using small-volume bags for infusions administered at low rates
• Ensuring that purchasing agents have active backorders in place and are obtaining allocations as available
• Evaluating IV fluid supplies on a systemwide basis to redeploy solutions to areas of greatest need
• Implementing an organizational conservation plan developed in collaboration with clinicians and other organizational stakeholders

Source: ASHP, April 17, 2014

GSK Walks Away From Lung Cancer Vaccine

GlaxoSmithKline (GSK) is stopping the MAGRIT trial, a phase 3 study of its MAGE-A3 cancer immunotherapeutic agent in patients with non–small-cell lung cancer (NSCLC), after establishing that it will not be possible to identify a subpopulation of gene-signature positive NSCLC patients who may benefit from the treatment.

MAGRIT was a double-blind, randomized, placebo-controlled trial designed to assess the efficacy of a recMAGE-A3 + AS15 antigen-specific cancer immunotherapeutic as adjuvant therapy in patients with stage IB, II, and IIIA completely resected NSCLC whose tumors expressed the MAGE-A3 gene. Patients were given up to 13 intramuscular injections of either the MAGE-A3 immunotherapeutic or placebo over 27 months.

Data from the study showed that it did not significantly extend disease-free survival (DFS) when compared with placebo in either the overall MAGE-A3–positive population (the study’s first co-primary endpoint) or in MAGE-A3–positive patients who did not receive chemotherapy (the second co-primary endpoint).

GSK continued MAGRIT to investigate a third co-primary endpoint, DFS in a gene signature-positive subpopulation. This analysis was designed to identify a subset of MAGE-A3–positive patients who may benefit from the treatment. However, the preplanned independent third-party analysis of a portion of the data (to identify a gene signature classifier) has concluded that assessment of the third co-primary endpoint is not feasible because of an insufficient treatment effect.

MAGE-A3 is a tumor-specific antigen expressed in several cancers but not in normal cells. The MAGE-A3 cancer immunotherapeutic consists of recombinant MAGE-A3 protein and the immunostimulant AS15 (a combination of the QS-21 Stimulon adjuvant, monophosphoryl lipid A, and CpG7909, a TLR-9 agonist, in a liposomal formulation).

Source: GlaxoSmithKline, April 2, 2014

FDA Halts Testing of Cancer Drug Imetelstat

The FDA has placed an investigational new drug application for imetelstat on full clinical hold, directing Geron Corporation to suspend company-sponsored phase 2 trials evaluating imetelstat’s use for essential thrombocythemia or polycythemia vera.

The FDA also placed a partial clinical hold on an investigator-sponsored trial of imetelstat for myelofibrosis. No new patients may be enrolled in that Mayo Clinic study, and patients currently enrolled must demonstrate that they are...
deriving clinical benefit in order to continue taking imetelstat.

The FDA told the company and the Mayo Clinic investigator, Ayalew Tefferi, MD, that signs of hepatotoxicity had been identified in clinical studies of imetelstat, and that it is not known whether this hepatotoxicity is reversible.

Most cancers have a high level of telomerase activity and relatively short telomeres compared with normal cells. Imetelstat is a lipid-conjugated 13-mer oligonucleotide sequence that is complementary to and binds with high affinity to the RNA template of telomerase, thereby directly inhibiting telomerase activity.

Imetelstat is the first telomerase inhibitor to advance to clinical development. In phase 1 trials, adverse events were generally manageable and reversible. The dose-limiting toxicities were thrombocytopenia and neutropenia.

Source: Geron Corporation, March 12, 2014, and March 20, 2014

Breakthrough Therapy Designations

**Pfizer’s Meningococcal B Vaccine**

The FDA has designated Pfizer’s bivalent rLP2086 vaccine a breakthrough therapy. The vaccine is under investigation for prevention of invasive meningococcal disease due to Neisseria meningitidis serogroup B in persons 10 to 25 years old.

Pfizer is conducting phase 2 and 3 trials evaluating rLP2086 in more than 20,000 participants and intends to submit a biologics license application to the FDA by mid-2014. Of the five meningococcal serogroups (A, B, C, W-135, and Y) that historically have been responsible for the majority of meningococcal disease, serogroup B is the only one for which no broadly active vaccine is currently approved in the U.S.

Clinical data from a phase 2 study published in *Lancet Infectious Diseases* showed the rLP2086 vaccine induced bactericidal antibodies in healthy adolescents (ages 11–18 years) that were broadly active against meningococcal B bacteria. Safety data have shown the vaccine has an acceptable safety profile.

Source: Pfizer, March 20, 2014

...And Novartis’ Meningitis B Vaccine

Bexsero, a meningococcal group B vaccine being developed by Novartis, has received a breakthrough therapy designation from the FDA. Meningococcal group B vaccine (rDNA, component, adsorbed) is already approved in Europe, Canada, and Australia to help protect against invasive meningococcal disease caused by serogroup B. Novartis plans to file for U.S. licensure as early as the second quarter of 2014 depending on FDA guidance.

In recent months, Novartis has provided nearly 30,000 doses of the vaccine to students and staff at Princeton University and the University of California at Santa Barbara following meningitis B outbreaks on their campuses under an FDA “investigational new drug” designation. The Centers for Disease Control and Prevention has recommended including incoming freshmen at Princeton in the at-risk group to receive Bexsero.

Meningitis B, the leading cause of bacterial meningitis and septicemia in the developed world, can kill or cause life-long disability within 24 hours of onset. Because initial symptoms are often unspecific and flu-like, it can be difficult to diagnose in its early stages. Vaccination is the best defense against the disease, which leaves little time for intervention.

Source: Novartis, April 7, 2014

**Fast Track Designations**

**EPI-743 for Friedreich’s Ataxia**

The FDA has granted fast track designation to EPI-743 (Edison Pharmaceuticals), which is being investigated in phase 3 studies. IGNITE 1 is evaluating the IV formulation of eravacycline for treatment of complicated urinary tract infections, while IGNITE 2 is evaluating eravacycline IV-to-oral step-down therapy for treatment of complicated intra-abdominal infections.

Erapacycline had earlier been designated a qualified infectious disease product. A new drug application filing is expected in late 2015.

Source: Tetraphase Pharmaceuticals, April 2, 2014

**Bivalirudin Reduces Bleeding Regardless of Baseline Risk**

Unfractionated heparin (UFH), the main antithrombotic therapy for patients undergoing percutaneous coronary intervention (PCI), has major bleeding complications that are associated with higher mortality. As a result, the direct thrombin inhibitor bivalirudin has attracted considerable interest.

Yet bivalirudin’s impact on mortality, myocardial infarction (MI), and major
bleeding complications as a function of baseline hemorrhagic risk has not been studied, says a team of researchers from New York, Italy, and the Netherlands. They conducted a meta-analysis of 12 randomized trials involving 33,261 participants to explore patient outcomes in bivalirudin-supported PCI.

Bivalirudin significantly reduced major and minor bleeding, but this analysis also found that bivalirudin is associated with lower bleeding regardless of baseline hemorrhagic risk. The drug’s benefits were not significantly different from those of UFH in terms of 30-day mortality or MI. Nonetheless, the analysis showed that the higher the baseline hemorrhagic risk, the larger the incremental benefit of bivalirudin over UFH.

Source: *Am Heart J* 2014;167:401–412.e6

**Will Heart Guidelines Cause Unnecessary Statin Use?**

Revised guidelines in 2013 from the American College of Cardiology and the American Heart Association for the treatment of cholesterol expanded the indications for statin therapy for prevention of cardiovascular disease.

The recommendations represented a major change in assessing a person’s risk for heart disease. Instead of aiming to lower a patient’s low-density lipoprotein-cholesterol (LDL-C) to specific numeric targets, the guidelines ask doctors to use a new online calculator that factors in various characteristics, such as smoking and obesity, to predict an individual’s risk of heart disease.

Now, a study published online by the *New England Journal of Medicine* estimates that the revised ACC/AHA recommendations could mean that 56 million people, or nearly half of the U.S. population between the ages of 40 and 75 years, would be eligible to take a cholesterol-lowering statin to prevent heart disease.

The authors used data from the National Health and Nutrition Examination Surveys of 2005 to 2010 to estimate the number and summarize the risk-factor profile of persons for whom statin therapy would be recommended under the new guidelines compared with the guidelines of the Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program. The authors extrapolated the results to a population of 115.4 million U.S. adults between ages 40 and 75.

The authors found that, compared with the ATP III guidelines, the new recommendations would increase the number of U.S. adults receiving or eligible for statin therapy from 43.2 million (38%) to 56.0 million (49%). Most of this increase (10.4 million of 12.8 million) would occur among adults without cardiovascular (CV) disease.

Among adults 60 to 75 years old without CV disease who are not receiving statin therapy, the percentage who would be eligible for such treatment would increase from 30% to 87% among men and from 21% to 54% among women. This effect would be driven largely by an increased number of adults who would be classified solely on the basis of their 10-year risk of a CV event.

Individuals newly eligible for statin therapy would include persons with a higher blood pressure but a markedly lower level of LDL-C. The authors conclude that, compared with the ATP III guidelines, the new guidelines would recommend statin therapy for more adults who would be expected to have future CV events, but would include many older adults without CV disease.

Sources: *New England Journal of Medicine* and Reuters, March 19, 2014

**Product-Tampering Investigation Focuses on Alli**

GlaxoSmithKline (GSK) Consumer Healthcare recalled all Alli weight loss products from U.S. and Puerto Rico retailers after reports that some packages had been tampered with.

GSK heard from consumers in seven states about bottles of Alli purchased in retail stores that contained tablets and capsules that were not Alli. Tablets and capsules of various shapes and colors were reportedly found inside bottles. Inside the box, some bottles were missing labels and had tamper-evident seals that were not authentic.

GSK asked retailers and pharmacies to remove all Alli from their shelves. Alli, a turquoise blue capsule with a dark blue band imprinted with the text “60 Orlistat,” is packaged in a labeled bottle that has an inner foil seal imprinted with the words: “Sealed for Your Protection.”

Consumers with concerns about products should not use them: They should call GSK at 1-800-671-2554 for instructions.

Source: GlaxoSmithKline, March 27, 2014

**DEVICE NEWS Approvals**

**Auto-Injector to Treat Opioid Overdose**

The FDA has approved a prescription treatment that family members or caregivers can use to help a person known or suspected to have had an opioid overdose.

The naloxone hydrochloride injection device (Evzio, Kaléo, Inc.) delivers a single dose of naloxone via a hand-held auto-injector that can be carried in a pocket or stored in a medicine cabinet. It is intended for the emergency treatment of known or suspected opioid overdose, characterized by decreased breathing or heart rates or loss of consciousness.

Drug overdose deaths, driven largely by fatal prescription drug overdoses, are the leading cause of injury death in the U.S., surpassing motor vehicle crashes.

Naloxone rapidly reverses the effects of opioid overdose, but existing naloxone drugs require administration via syringe and are most commonly used by trained...
medical personnel in emergency departments and ambulances.

Evzio is injected either intramuscularly or subcutaneously. When the device is turned on, it provides verbal instruction to the user on how to deliver the medication, similar to an automated defibrillator.

Because naloxone may not work as long as opioids, repeat doses may be needed. Evzio is not a substitute for immediate medical care, and the person administering Evzio should seek immediate medical attention for the patient.

In a pharmacokinetic study involving 30 patients, a single Evzio injection provided naloxone equivalent to a single dose injected with a standard syringe. The use of Evzio in opioid-dependent patients may result in severe opioid withdrawal. Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, and cardiac arrest.

The FDA reviewed Evzio under the agency’s priority review and fast track programs.

Source: FDA, April 3, 2014

Implantable Device for Hearing Loss

The FDA has approved the first implantable device for adults 18 years of age and older with severe or profound sensorineural hearing loss of high-frequency sounds in both ears who can still hear low-frequency sounds with or without a hearing aid. The Nucleus Hybrid L24 Cochlear Implant System (Cochlear Ltd.) may help individuals with this kind of hearing loss who do not benefit from conventional hearing aids.

Sensorineural hearing loss occurs because of damage to the inner ear (cochlea). It may be caused by aging, heredity, exposure to loud noise, drugs that are toxic to the inner ear (e.g., antibiotics), and certain other illnesses. People with severe or profound sensorineural hearing loss of high-frequency sounds may have difficulty hearing faint sounds, understanding people with higher-pitched voices, hearing certain speech sounds, and, in some cases, hearing high-pitched emergency vehicle sirens or safety alarms.

The Nucleus Hybrid L24 Cochlear Implant System combines the functions of a cochlear implant and a hearing aid. An external microphone and speech processor pick up sounds from the environment and convert them into electrical impulses. The impulses are transmitted to the cochlea through a bundle of implanted electrodes, creating a sense of sound that users learn to associate with the mid- and high-frequency sounds they remember.

The hearing-aid portion of the device, inserted into the outer ear canal like a conventional hearing aid, can amplify sounds in the low-frequency range. The device is intended for use only on one ear.

The FDA evaluated a clinical study involving 50 individuals with severe to profound high-frequency hearing loss who still had significant levels of low-frequency hearing. Most reported statistically significant improvements in word and sentence recognition at six months after activation of the device compared with their baseline pre-implant performance using a conventional hearing aid.

Of the 50 individuals in the study, 68% experienced one or more anticipated adverse events, such as low-frequency hearing loss, tinnitus, electrode malfunction, and dizziness. Twenty-two subjects (44%) developed profound or total low-frequency hearing loss, tinnitus, electrode malfunction, and dizziness. Twenty-two subjects (44%) developed profoundly or totally low-frequency hearing loss. Some patients learned to associate the mid- and high-frequency sounds they remember.

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The FDA reviewed Evzio under the agency’s priority review and fast track programs.

Source: FDA, March 20, 2014

Recalls

Two Abbott Glucose Monitors

Abbott is recalling the FreeStyle Blood Glucose Meter and FreeStyle Flash Blood Glucose Meter, which, when used with Abbott FreeStyle test strips, may produce mistakenly low blood glucose results.

Other Abbott Diabetes Care meters are not affected by the recall. People with the affected meters, which have not been

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Dräger Ventilator Power Supply

Dräger is recalling the optional PS500 Power Supply Unit used with Evita V500 and Babylog VN500 ventilators. PS500 batteries can be depleted much earlier than expected, but the battery indicator may show a significant charge. As a result, the first indication of diminished battery capacity could occur when the battery is totally depleted.

Should the battery become totally depleted, mechanical ventilation will stop and manual ventilation will be required until the device is connected to main power.

Affected devices were distributed between June 2011 and January 2014. Replacement batteries (and eventually a more permanent solution) will be free. For questions, call Dräger Service Technical Support at 1-800-543-5047 (press 4 at the prompt) from 8 a.m. to 8 p.m. Eastern time Monday through Friday.

Source: Dräger, April 2, 2014

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Macy Catheter
Manufacturer: Hospic Corporation, Newark, California
Approval Date: February 17, 2014
Purpose: The Macy Catheter is a single-use disposable medical device designed to facilitate discreet and comfortable rectal administration of medications.
Description: The Macy Catheter is comprised of a dual-port, dual-lumen balloon-ended tube that is inserted into the rectum just past the rectal sphincter, where the retention balloon is inflated (via the balloon inflation port) to hold the device in place.

Once in place, it can be used for repeat administration of liquid medications in solution or suspension form. The Macy Catheter medication port is specifically designed to be compatible only with oral/enteral connectors, reducing the probability of connection errors. The medication port features a valve to prevent leakage and is designed not to clog. The Macy Catheter is designed to expel with defecation, or it can be removed easily prior to a patient's bowel movement. The balloon is smaller and softer than typical stool in the rectum. The Macy Catheter is intended as a disposable single-use device.

Benefit: The Macy Catheter is a simple and innovative rectal administration device using a successful route of delivery that can be particularly useful during serious or terminal illness or in any situation where the oral route of administration is compromised.

Source: http://hospicorp.com

Name: Reveal LINQ Insertable Cardiac Monitor System
Manufacturer: Medtronic Inc., Minneapolis, Minnesota
Approval Date: February 19, 2014
Purpose: The Reveal LINQ Insertable Cardiac Monitor (ICM) System, a wireless implant, is the smallest implantable cardiac monitoring device to gain FDA approval.
Description: The Reveal LINQ ICM is approximately one-third the size of a AAA battery (about 1 cubic centimeter), making it more than 80 percent smaller than other ICMs. Despite its size, the device is part of a powerful system that allows physicians to continuously and wirelessly monitor a patient’s heart for up to three years, with 20 percent more data memory than its larger predecessor, Reveal XT. Implanted through a tiny incision (less than 1 cm) in the upper left side of the chest, the device is safe for magnetic resonance imaging use.

Benefit: Constant cardiac monitoring helps patients and health care providers find answers to cardiac arrhythmias and other heart-related problems. A tiny wireless device is also an improvement over larger implants, or the more common practice of wearing an outside portable battery-powered monitor connected to wires and electrodes pasted to the chest. The new miniaturized monitoring implant (which works with a remote patient data transfer monitor) results from many years of development work focused on shrinking the size of medical devices while maintaining their power and improving benefits for patients.

In addition to its continuous and wireless monitoring capabilities, the system provides remote monitoring through the Carelink Network; physicians can request notifications of their patients’ cardiac events. The Reveal LINQ ICM is indicated for patients who experience symptoms such as dizziness, palpitation, syncope, and chest pain that may suggest a cardiac arrhythmia, and for patients at increased risk for cardiac arrhythmias.


Name: Cefaly
Manufacturer: STX-Med, Herstal, Liege, Belgium
Approval Date: March 12, 2014
Purpose: Cefaly is the first device approved as a preventive treatment for migraine headaches. It is also the first transcutaneous electrical nerve stimulation (TENS) device specifically authorized for use prior to the onset of pain.

Description: Cefaly is a small, portable, battery-powered prescription device that resembles a plastic headband worn across the forehead and atop the ears. The user positions the device in the center of the forehead, just above the...
eyes, using a self-adhesive electrode. The device applies an electric current to the skin and underlying tissues to stimulate branches of the trigeminal nerve, which has been associated with migraine headaches. The user may feel a tingling or massaging sensation where the electrode is applied. Cefaly is indicated for patients 18 years of age and older and should only be used once a day for 20 minutes.

Cefaly works by introducing safe, painless electrical impulses to act on the trigeminal nerve. This endorphin-producing mechanism carries information about touch, temperature, perception, and pain from the face and scalp to the brain stem.

The Cefaly design covers this bifurcated nerve and acts on its main portion. Through an electrode covering the middle of the forehead, Cefaly sustains a constant link between migraine pain-specific nerves and the electrical impulses they generate. Cefaly transmits extremely specific electrical impulses to safely stimulate the trigeminal nerve.

As the impulses are produced very slowly, they are virtually imperceptible. A feedback mechanism enables adjustment of the electrical impulses to the specific requirements of the individual user for personalized efficacy and comfort.

**Benefit:** Migraine headaches are characterized by intense pulsing or throbbing pain in one area of the head, accompanied by nausea or vomiting and sensitivity to light and sound. Left untreated, a migraine can last from four to 72 hours. According to the National Institutes of Health, these debilitating headaches affect approximately 10 percent of people and are three times more common in women than men.

Cefaly provides an alternative to medication for migraine prevention and may help patients who cannot tolerate current medications for preventing or treating migraines.

Sources: www.fda.gov, www.cefaly.ca