NEW DRUG APPROVALS

**Harvoni, a Once-Daily, Single-Tablet HCV Regimen**

The FDA has approved ledipasvir/sofosbuvir (Harvoni, Gilead Sciences, Inc.), the first once-daily, single-tablet regimen for the treatment of chronic hepatitis C genotype 1 infection in adults.

Harvoni combines 90 mg of the NSSA inhibitor ledipasvir with 400 mg of the nucleotide analog polymerase inhibitor sofosbuvir (Sovaldi, Gilead). The combination’s efficacy has been established in patients with chronic hepatitis C virus (HCV) genotype 1 infection with treatment durations of eight, 12, or 24 weeks depending on prior treatment history, cirrhosis status, and baseline viral load. Eight weeks of treatment can be considered for treatment-naïve patients without cirrhosis who have a baseline HCV viral load below 6 million IU/mL.

The approval is supported by data from three phase 3 studies, ION-1, ION-2, and ION-3, that evaluated eight, 12, or 24 weeks of treatment with ledipasvir/sofosbuvir, with or without ribavirin, among nearly 2,000 genotype 1 HCV patients with compensated liver disease. These studies included cirrhotic and noncirrhotic patients who were treatment-naïve or had failed prior therapy with interferon-based regimens, including those containing an HCV protease inhibitor. The primary endpoint for each study was sustained virologic response (undetectable HCV) 12 weeks after completing therapy (SVR12).

Patients who achieve SVR12 are considered cured of HCV. In these studies, ribavirin was not shown to increase response rates. Trial participants in the ribavirin-free arms (n = 863) achieved SVR12 rates of 94% to 99%.

Adverse events led to treatment discontinuation among 1% or less of patients. Fewer adverse events were observed in the ribavirin-free arms compared with the ribavirin-containing arms. The most common adverse reactions with ledipasvir/sofosbuvir (5% or more) were fatigue, headache, nausea, diarrhea, and insomnia.

Source: Gilead Sciences, October 10, 2014

**Trulicity for Type-2 Diabetes**

The FDA has approved dulaglutide (Trulicity, Eli Lilly and Company), a once-weekly subcutaneous injection to improve glycemic control along with diet and exercise in adults with type-2 diabetes.

The safety and effectiveness of dulaglutide, a glucagon-like peptide-1 receptor agonist, were evaluated in six clinical trials; 3,342 patients with type-2 diabetes received dulaglutide and showed reductions in hemoglobin A1c. Dulaglutide has been studied as monotherapy and in combination with other type-2 diabetes therapies, including metformin, sulfonylurea, thiazolidinedione, and prandial insulin. It should not be used to treat people with type-1 diabetes, diabetic ketoacidosis, or severe gastrointestinal problems, or as first-line therapy for patients who cannot be managed with diet and exercise.

A boxed warning notes that thyroid C-cell tumors have been seen in rodent studies with dulaglutide, but it is not known whether the drug causes such tumors, including medullary thyroid carcinoma (MTC), in humans. Dulaglutide should not be used in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2 (which predisposes patients to MTC).

The FDA is requiring post-marketing studies to evaluate dulaglutide’s dosing, efficacy, and safety in pediatric patients; assess its potential effects on sexual maturation, reproduction, and central nervous system development and function in immature rats; compare dulaglutide with insulin glargine for glycemic control in patients with type-2 diabetes and moderate or severe renal impairment; and evaluate dulaglutide’s cardiovascular effects on patients with high baseline risk of cardiovascular disease. The FDA is also requiring an MTC case registry for at least 15 years to identify any dulaglutide-related increase in MTC incidence.

The FDA approved Trulicity with a risk evaluation and mitigation strategy. In clinical trials, the most common side effects were nausea, diarrhea, vomiting, abdominal pain, and decreased appetite.

Source: FDA, September 18, 2014

**Akynzeo for CINV**

Netupitant/palonosetron (Akynzeo, Helsinn Group/Eisai Inc.) has received FDA approval for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including highly emetogenic chemotherapy.

The fixed-combination oral agent targets two critical signaling pathways associated with chemotherapy-induced nausea and vomiting (CINV) by combining netupitant, an NK1 receptor antagonist, and palonosetron, a 5-HT3 receptor antagonist, in a single capsule for the prevention of CINV. The approval was based on phase 2 and 3 trial data from patients undergoing treatment with moderately and highly emetogenic chemotherapy regimens for a variety of tumors. The most common adverse events included headache, asthenia, fatigue, dyspepsia, constipation, and erythema.

Studies show that patients often receive antiemetic drug regimens that are inconsistent with CINV treatment guidelines, which call for multiple-pathway targeted antiemetic prophylaxis. The combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone meets guideline recommendations for optimal antiemetic therapy following highly emetogenic chemotherapy.

The efficacy of netupitant/palonosetron was established in a pivotal phase 2, randomized, double-blind, dose-ranging study.
in 694 patients undergoing cisplatin-based chemotherapy for a variety of tumors; 135 chemotherapy-naïve patients received netupitant 300 mg/palonosetron 0.5 mg and 136 received oral palonosetron 0.5 mg.

A complete response (CR) was defined as no emetic episode and no use of rescue medication. For all phases—acute (0 to 24 hours), delayed (25 to 120 hours), and overall (0 to 120 hours)—netupitant/palonosetron showed significantly higher CRs compared with oral palonosetron: 98.5% versus 89.7%, 90.4% versus 80.1%, and 89.6% versus 76.5%, respectively.

In a randomized, double-blind, parallel-group, phase 3 study, 1,455 chemotherapy-naïve patients were randomly assigned to receive a single oral dose of either netupitant/palonosetron plus dexamethasone or palonosetron plus dexamethasone prior to receiving anthracycline and cyclophosphamide-based chemotherapy. Among patients taking netupitant/palonosetron compared with palonosetron, a CR was seen in 88.4% versus 85.0% in the acute phase, 76.9% versus 69.5% in the delayed phase, and 74.3% versus 66.6% in the overall phase, respectively.

Source: Helsinn Group/Eisai Inc., October 13, 2014

Movantik for Constipation Related to Opioid Use

Naloxegol (Movantik, AstraZeneca) has received FDA approval as an oral treatment for opioid-induced constipation in adults with chronic noncancer pain. Opioids often reduce the gastrointestinal tract’s motility, hampering bowel movements. Naloxegol, a peripherally acting opioid receptor antagonist, reduces this effect.

Naloxegol’s safety and effectiveness were established in two clinical trials involving 1,352 participants who had been treated with opioids for at least four weeks for noncancer-related pain and who had opioid-induced constipation. Participants were randomly assigned to receive 12.5 mg or 25 mg of naloxegol or placebo once daily for 12 weeks. Results from the first trial showed an increase in bowel movements per week among 44% of the participants receiving naloxegol 25 mg, 41% of those receiving naloxegol 12.5 mg, and 29% of those given placebo. The second trial reported similar results.

Common side effects of naloxegol include abdominal pain, diarrhea, headache, and flatulence. The FDA is requiring a post-marketing study to evaluate the potential risk of cardiovascular adverse events in patients treated with naloxegol.

Source: FDA, September 16, 2014

Stribild Components for HIV-1

Two of the four components of Stribild, Gilead Sciences’ once-daily treatment for human immunodeficiency virus type 1 (HIV-1), have received FDA approval as separate medications.

Elvitegravir (Vitekta, Gilead Sciences) is an HIV-1 integrase strand transfer inhibitor indicated in combination with an HIV protease inhibitor (atazanavir, lopinavir, darunavir, fosamprenavir, or tipranavir) co-administered with ritonavir and another antiretroviral drug for the treatment of HIV-1 infection in antiretroviral treatment-experienced adults. It is available in 85-mg and 150-mg tablets. Cobicistat (Tybost, Gilead Sciences) is a CYP3A inhibitor indicated to increase systemic exposure of atazanavir or darunavir (in a once-daily dosing regimen) in combination with other antiretroviral agents in the treatment of HIV-1 infection in treatment-naïve or treatment-experienced patients. It is available as 150-mg tablets. Stribild also contains emtricitabine and tenofovir disoproxil fumarate.

Source: FDA, September 25, 2014

Generic Approvals

Amlodipine/Valsartan Tablets

Par Pharmaceutical Companies, Inc., has received FDA approval for all four strengths of amlodipine/valsartan tablets—the first generic versions of Novartis’ hypertension medication Exforge.

Amlodipine/valsartan tablets contain amlodipine besylate equivalent to 5 mg or 10 mg of amlodipine free-base with valsartan 160 mg or 320 mg. The following combinations are available: 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg, and 10 mg/320 mg. According to IMS Health data, annual U.S. sales of Exforge are approximately $422 million.

The product has a boxed warning regarding fetal toxicity.

Source: Par Pharmaceutical Companies, Inc., September 30, 2014
**Daptomycin for Injection**

Hospira, Inc., has received FDA approval for daptomycin for injection USP, 500 mg, packaged in single-use vials. This is the first generic equivalent of Cubicin for Injection, manufactured by Cubist Pharmaceuticals, Inc. However, Hospira and Cubist are engaged in ongoing patent litigation that will affect availability.

Cubicin is a lipopeptide antibacterial indicated for the treatment of complicated skin and skin structure infections and *Staphylococcus aureus* bloodstream infections, including those with right-sided infective endocarditis.

Sources: FDA, September 12, 2014, and Cubicin prescribing information

**Moxifloxacin Hydrochloride Ophthalmic Solution**

The FDA has approved Lupin Limited’s moxifloxacin hydrochloride ophthalmic solution USP, 0.5% (base)—the first generic version of Alcon’s Vigamox ophthalmic solution, a topical fluoroquinolone anti-infective indicated for the treatment of conjunctivitis caused by certain susceptible bacteria.

Sources: FDA, September 4, 2014, and Vigamox prescribing information

**NEW INDICATIONS**

**Velcade for Untreated MCL**

Bortezomib for injection (Velcade, Millennium/Takeda) has become the first medication to receive FDA approval for use in previously untreated patients with mantle cell lymphoma (MCL). Bortezomib was approved in 2006 for use in relapsed or refractory MCL, a rare, aggressive type of B-cell non-Hodgkin lymphoma that usually occurs in older adults.

The approval is based on a randomized, open-label, prospective, head-to-head phase 3 study of 487 patients with previously untreated MCL who were ineligible or not considered for a bone-marrow transplant. Patients who received the so-called VcR-CAP regimen—Velcade, rituximab, cyclophosphamide, doxorubicin, and prednisone—experienced a 59% relative improvement in progression-free survival (PFS) compared with those who received the R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) regimen (median PFS, 25 versus 14 months) at a median follow-up of 40 months.

The most common adverse reactions occurring in at least 20% of patients receiving VcR-CAP were neutropenia, leukopenia, anemia, thrombocytopenia, lymphopenia, peripheral neuropathy, pyrexia, nausea, and diarrhea.

Source: Millennium, October 10, 2014

**Otezla for Plaque Psoriasis**

Apremilast (Otezla, Celgene Corp.) has received FDA approval for the treatment of patients with moderate-to-severe plaque psoriasis for whom phototherapy or systemic therapy is appropriate.

Apremilast, an oral, selective inhibitor of phosphodiesterase 4 (PDE4), was approved in March 2014 for use in adults with active psoriatic arthritis. It is the first PDE4 inhibitor indicated for the treatment of plaque psoriasis.

The new indication is based primarily on safety and efficacy results from two randomized, double-blind, placebo-controlled studies (ESTEEM 1 and ESTEEM 2) conducted in approximately 1,250 adults who had moderate-to-severe plaque psoriasis for at least 12 months prior to screening and who were candidates for phototherapy, systemic therapy, or both.

Treatment with apremilast resulted in significant and clinically meaningful improvements in Psoriasis Area and Severity Index scores at week 16. Clinical improvement, as measured by static Physician Global Assessment (sPGA) scores of “clear” to “almost clear,” was also demonstrated in both studies.

Adverse events associated with apremilast in clinical trials included diarrhea, nausea, upper respiratory tract infection, tension headache, and headache.

Apremilast specifically targets cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, which is thought to modulate indirectly the production of inflammatory mediators.

Source: Celgene, September 23, 2014

**Eylea for Macular Edema**

The FDA has approved aflibercept injection (Eylea, Regeneron Pharmaceuticals) for the treatment of macular edema following retinal vein occlusion (RVO), which includes macular edema following branch retinal vein occlusion (BRVO) in addition to the previously approved indication of macular edema following central retinal vein occlusion (CRVO).

The recommended dosage for patients with macular edema following RVO is 2 mg every four weeks.

The expanded indication is based on the previously approved indication for macular edema following CRVO and on positive results from the double-masked, randomized, controlled phase 3 VIBRANT study in 181 patients with macular edema following BRVO. VIBRANT compared aflibercept 2 mg once every four weeks with macular laser photo coagulation. At 24 weeks, significantly more patients treated with aflibercept gained at least 15 letters in vision (three lines on an eye chart) from baseline compared with patients who received laser photo coagulation (53% versus 27%, respectively).

The incidence of nonocular serious adverse events (AEs) was 8.8% in the aflibercept group compared with 9.8% in the laser photo coagulation group. The most common ocular AEs in patients using aflibercept included conjunctival hemorrhage and cataract.

Aflibercept, a vascular endothelial growth factor inhibitor, recently received continued on page 738
FDA breakthrough therapy designation for the treatment of diabetic retinopathy in patients with diabetic macular edema (DME). The designation is based on positive results in two phase 3 trials (VIVID-DME and VISTA-DME).


### Relistor for Constipation Induced by Opioid Use

The FDA has approved methylnaltraxone bromide (Relistor, Salix Pharmaceuticals) subcutaneous injection, 12 mg/0.6 mL, for the treatment of opioid-induced constipation (OIC) in patients receiving opioids for chronic noncancer pain. It is the only peripherally acting mu-opioid receptor antagonist approved for treating OIC at the cause without interfering with the centrally acting analgesic properties of the opioid.

In a randomized, double-blind, placebo-controlled trial, 312 patients with noncancer pain and OIC who had been taking opioids for at least a month received methylnaltraxone bromide 12 mg or placebo once daily for four weeks, followed by an eight-week open-label phase during which patients could take medications as needed. More patients treated with methylnaltraxone bromide reported having three or more spontaneous bowel movements per week during the four-week double-blind period compared with placebo (59% versus 38%, respectively).

Source: Salix Pharmaceuticals, September 29, 2014

### Rixubis for Hemophilia B Among Children

The FDA has approved coagulation factor IX to be approved for routine prophylaxis and control of bleeding episodes in the U.S. for adults with this condition. The new approval was based on the results of a clinical trial investigating the efficacy and safety of Rixubis in 23 previously treated boys younger than 12 years of age with severe or moderately severe hemophilia B. The patients were treated with a twice-weekly Rixubis prophylaxis regimen (mean dose: 56 IU/kg) for a mean period of six months and a mean of 54 exposure days.

The median annualized bleeding rate was 2.0 (0.0 for spontaneous bleeds and joint bleeds). Nine patients (39%) experienced no bleeds, and 23 bleeding episodes (89%) were treated with one or two infusions. There were no reports of inhibitor development, severe allergic reactions, or thrombotic or treatment-related adverse events (AEs). The most common AEs in clinical studies included dysgeusia, pain in an extremity, and a positive test for furin antibody.

Source: Baxter International Inc., September 15, 2014

### Humira for Pediatric Crohn’s Disease …

The FDA has approved an eighth indication for adalimumab (Humira, AbbVie)—for reducing signs and symptoms of Crohn’s disease and achieving and maintaining clinical remission among pediatric patients 6 years of age and older who have had an inadequate response to corticosteroids or to immunomodulators. Adalimumab is the first biologic approved for use in this patient population that can be administered at home.

The FDA’s decision was supported by the phase 3, randomized, double-blind IMAGINE-1 trial, which evaluated multiple dosing strategies for adalimumab to induce and maintain clinical remission in patients 6 to 17 years of age with moderately to severely active Crohn’s disease (CD) for whom certain other treatments had not worked well.

Adalimumab works by inhibiting tumor necrosis factor alpha. It can be self-administered by patients with proper training and appropriate physician monitoring.

Source: AbbVie, September 25, 2014

### … And for Younger JIA Patients

The FDA has extended the indication for adalimumab (Humira, AbbVie) for moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) to include reducing signs and symptoms in patients 2 years of age and older. Adalimumab was approved in the U.S. in 2008 for polyarticular JIA in patients 4 years of age and older.

Source: AbbVie, October 6, 2014

### Stendra Acts Quickly For Erectile Dysfunction

Avanafil (Stendra, Vivus, Inc./Auxilium Pharmaceuticals) has become the only FDA-approved erectile dysfunction medication indicated for use just 15 minutes before sexual activity. The FDA approved new labeling for avanafil under a supplemental new drug application (sNDA).

Avanafil is a phosphodiesterase 5 (PDE5) inhibitor approved for the treatment of erectile dysfunction (ED) in men 18 years of age or older.

In a study that assessed the efficacy of two dosage strengths, 440 men treated with avanafil had a significantly higher proportion of attempts that enabled an erection sufficient for successful sexual intercourse as early as approximately 15 minutes following administration compared with placebo. The previously approved prescribing information recommended administration approximately 30 minutes before sexual activity.

Source: Auxilium Pharmaceuticals, September 18, 2014
**NEW FORMULATION**

**Spiriva Respimat for COPD**

Tiotropium bromide inhalation spray (Spiriva Respimat, Boehringer Ingelheim) has received FDA approval for long-term, once-daily maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) and to reduce exacerbations in COPD patients.

Spiriva Respimat provides a premeasured amount of medicine in a slow-moving mist that helps patients inhale the medicine. It was developed to deliver medication in a way that does not rely on how fast air is breathed in from the inhaler.

Spiriva Respimat has the same active ingredient as Spiriva HandiHaler (tiotropium bromide inhalation powder), which will remain available. Its approval was based on data from seven clinical trials in which 8,700 patients were treated with Spiriva Respimat. The most common side effects included sore throat, cough, dry mouth, and sinus infection.

Source: Boehringer Ingelheim, September 25, 2014

**DRUG NEWS**

**Breakthrough Status for AP26113 In Some Lung Cancer Patients**

AP26113 (Ariad Pharmaceuticals) has received an FDA breakthrough therapy designation for patients with anaplastic lymphoma kinase positive (ALK+) metastatic non–small-cell lung cancer (NSCLC) who are resistant to crizotinib (Xalkori, Pfizer).

This designation was based on results from an ongoing phase 1/2 trial that showed sustained antitumor activity of AP26113 in patients with ALK+ NSCLC, including patients with active brain metastases. Of the 72 ALK+ NSCLC patients evaluable for response, 52 (72%) demonstrated an objective response. The median duration of response was 49 weeks, and the median progression-free survival was 56 weeks. Responses were seen in patients who were either tyrosine kinase inhibitor naïve or resistant to crizotinib.

The most common adverse events were nausea, diarrhea, and fatigue. AP26113 was designed to overcome mutation-based resistance that has been observed in patients who initially responded to crizotinib and then relapsed.

Source: Ariad Pharmaceuticals, October 2, 2014

**Priority Review Status**

**Palbociclib for Breast Cancer**

Palbociclib (Pfizer) has received the FDA’s priority review designation as a first-line treatment, in combination with letrozole, for postmenopausal women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer who have not received previous systemic treatment for the disease.

Pfizer’s submission of a new drug application was based on results from the randomized, phase 2 PALOMA-1 trial, which compared palbociclib plus letrozole with letrozole alone in postmenopausal women with ER+, HER– advanced breast cancer who have not received previous systemic treatment for the disease.

Faster’s submission of a new drug application was based on results from the randomized, phase 2 PALOMA-1 trial, which compared palbociclib plus letrozole with letrozole alone in postmenopausal women with ER+, HER– advanced breast cancer. The Prescription Drug User Fee Act goal for an FDA decision is April 13, 2015.

Palbociclib is an investigational oral, targeted agent that selectively inhibits cyclin-dependent kinases 4 and 6 to regain cell-cycle control and to block tumor cell proliferation. It received a breakthrough therapy designation from the FDA in April 2013 for the first-line systemic treatment of women with advanced or metastatic ER+, HER2– breast cancer.

Source: Pfizer, October 13, 2014

**Vylamne for Eating Disorders**

The FDA has given a priority review designation to a supplemental new drug application for lisdexamfetamine dimesylate (Vyvanse, Shire PLC) as a treatment for adults with binge eating disorder (BED).

A decision is expected in February 2015.

Lisdexamfetamine, approved for the treatment of attention-deficit/hyperactivity disorder in the U.S., is a Schedule II controlled substance. Regulatory approval is being sought for lisdexamfetamine as a BED treatment option based on the results of two randomized, placebo-controlled phase 3 studies that evaluated the efficacy and safety of lisdexamfetamine compared with placebo.

In both studies, lisdexamfetamine was found to be statistically superior to placebo on the primary efficacy analysis of the change from baseline at weeks 11 to 12 in the number of binge days per week.

Source: Shire PLC, September 15, 2014, and November 5, 2013

**Orphan Drug Designations**

**Neuroblastoma Vaccine**

A neuroblastoma vaccine being developed by MabVax Therapeutics Holdings, Inc., has received FDA orphan drug designation. MabVax expects to start a phase 2 clinical trial in 2015 for the bivalent vaccine, which elicits an antibody response targeting the two most common antigens on neuroblastoma cells in an effort to kill residual cancer cells that can cause recurrence.

About 650 to 800 cases of the rare extracranial solid tumor cancer are diagnosed annually in North America; approximately 90% of patients are younger than 5 years of age.

A phase 1 trial at Memorial Sloan-Kettering Cancer Center reported encouraging results in a small cohort of difficult-to-treat patients who had repeatedly relapsed prior to use of the vaccine. The vaccine is intended for patients with relapsed or recurrent high-risk neuroblastoma in remission or with limited residual disease after best available treatment.

Source: MabVax Therapeutics Holdings, Inc., September 25, 2014
**New Drugs**

**PEGPH20 for Pancreatic Cancer**

Halozyne Therapeutics, Inc., has received an FDA orphan drug designation for PEGylated recombinant human hyaluronidase (PEGPH20) for the treatment of pancreatic cancer. Halozyne is investigating PEGPH20 in a phase 2 study in combination with gemcitabine and nab-paclitaxel in metastatic pancreatic cancer.

Source: Halozyne Therapeutics, Inc., October 3, 2014

**DNX-2401 for Malignant Glioma**

The FDA has granted orphan drug designation for DNX-2401 (DNAtrix, Inc.), a conditionally replicative oncolytic adenovirus for malignant glioma. Glioma is the most common form of primary brain cancer. The DNX-2401 program has already been granted fast-track status, and DNX-2401 is being evaluated in clinical studies in the U.S. and Europe.

Source: DNAtrix, Inc., October 7, 2014

**SYN-005 for Pertussis**

The FDA has awarded orphan drug designation to SYN-005 (Synthetic Bio logics, Inc.), a monoclonal antibody combination for the treatment of pertussis. Synthetic Biologics is developing SYN-005 in collaboration with Intrexon Corporation and researchers at the University of Texas at Austin.

Source: Synthetic Biologics, Inc., September 12, 2014

**Fast-Track Status NurOwn for ALS**

BrainStorm Cell Therapeutics Inc. has received the FDA’s fast-track designation for NurOwn for the treatment of amyotrophic lateral sclerosis (ALS). NurOwn consists of autologous mesenchymal stem cells that have been induced to secrete neurotrophic factors. NurOwn has been administered to more than 30 patients with ALS in clinical trials in Israel and is being studied in a randomized, double-blind, placebo-controlled trial in the United States.

Source: BrainStorm Cell Therapeutics Inc., October 7, 2014

**NKTT120 for Sickle Cell Disease**

The FDA has granted fast-track designation to NKTT120 (NKT Therapeutics), a humanized monoclonal antibody being developed to treat sickle cell disease.

NKTT120 specifically depletes iNKT cells, a regulatory T cell shown to be a key mediator of organ damage in preclinical models of sickle cell disease. Treatment with NKTT120 (which has also received an FDA orphan drug designation) reduces iNKT cell-mediated inflammation. NKT Therapeutics has completed dosing in a phase 1b trial of NKTT120 in patients with sickle cell disease.

Source: NKT Therapeutics, October 2, 2014

**New Xolair Labeling Cites Heart and Brain Risks**

An FDA review of safety studies suggests a slightly increased risk of problems involving the heart and blood vessels supplying the brain in patients being treated with omalizumab (Xolair, Genentech/Novartis) than in patients who were not treated with this asthma drug. The agency has added information about these potential risks to the “adverse reactions” section of the Xolair label.

The FDA’s review of a five-year safety study found a slightly higher rate of heart- and brain-related problems in patients who were treated with omalizumab compared with those not treated with omalizumab. However, limitations in this study prevented the agency from ruling out a potential risk of cancer with omalizumab, so it has added that information to the “warnings and precautions” section of the drug label.

Source: FDA, September 26, 2014

**USPSTF Recommends Aspirin To Prevent Preeclampsia**

The U.S. Preventive Services Task Force is supporting the use of low-dose aspirin (81 mg/day) after 12 weeks of pregnancy to prevent preeclampsia and its related health problems in women who are at high risk for the condition, do not show signs or symptoms of it, and can safely take aspirin.

Preeclampsia—characterized by a rise in blood pressure and by excess protein in the urine after 20 weeks of pregnancy—is a leading cause of health complications for expectant mothers and their babies.

For women at high risk, low-dose aspirin has been found to reduce the risk for preeclampsia by 24%, the risk for premature birth by 14%, and the risk for intrauterine growth restriction by 20%. Before taking aspirin, pregnant women should talk with their health care providers to determine their risk level and discuss whether taking aspirin is right for them.

The task force recommendation was...
published online in the *Annals of Internal Medicine* and on the group’s website.

Source: USPSTF, September 9, 2014

**USPSTF Guidelines for STIs**

The U.S. Preventive Services Task Force (USPSTF) has published three final recommendations on the prevention and detection of sexually transmitted infections (STIs).

The USPSTF recommended intensive behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs. Successful counseling approaches include providing basic information about the infections and their transmission, assessing individual risk, providing education regarding condom use, and providing strategies for communicating with partners about safe sex.

Screening for chlamydia and gonorrhea (the most commonly reported STIs) is recommended for sexually active women ages 24 years and younger and for older women who are at increased risk for infection. Women ages 24 years and younger have the highest rates of chlamydia and gonorrhea infection.

For men, the task force concluded, there is not enough evidence to determine the effectiveness of screening for chlamydia and gonorrhea. Unlike women, men with these infections are more likely to experience symptoms for which they would seek medical attention. This can lead to earlier detection and treatment that makes men with these STIs less likely than women to develop long-term complications.

The recommendations appear online in the *Annals of Internal Medicine* and on the group’s website.

Source: USPSTF, September 23, 2014

**Lilly to Drop Lupus Drug**

Eli Lilly and Company will discontinue development of tabalumab for the treatment of systemic lupus erythematosus (SLE) after two pivotal phase 3 trials revealed insufficient efficacy.

In the ILLUMINATE 1 study, tabalumab did not achieve the primary endpoint, at either dose studied, of statistically significant improvement on the SLE Responder Index-5, a measurement of lupus disease activity and response, compared to standard of care therapy. In ILLUMINATE 2, the higher dose of tabalumab met this endpoint. However, the collective data from these studies did not meet expectations for efficacy in the context of existing treatments.

Source: Eli Lilly and Company, October 2, 2014

**Medication Recalls**

**Ketorolac Tromethamine Injection**

Sagent Pharmaceuticals, Inc., has recalled three lots of ketorolac tromethamine injection, USP, 30 mg/mL single-dose vials manufactured by Cadila Healthcare Ltd. and distributed by Sagent because the labels provide an incorrect expiration date. Lots MP5021, MP5024, and MP5025 were distributed from September 17, 2014, through October 1, 2014. Questions about returns should be directed to the customer call center at 1-866-625-1618, Monday through Friday, 8 a.m. to 7 p.m. Central time.

Source: Sagent Pharmaceuticals, Inc., October 3, 2014

**One Lot of Hospira Heparin Sodium**

Hospira, Inc., recalled one lot of heparin sodium, 1,000 USP heparin units/500 mL (2 USP heparin units/mL), in 0.9% sodium chloride injection, 500 mL, because human hair was found sealed between the tube and the film at the round seal of the unused administrative port on the nonprint side of a single container. Lot 41-046-JT (expiring November 1, 2015) was distributed from June 2014 to August 2014. The product is used as an anticoagulant to maintain catheter patency. For assistance, call Stericycle at 1-855-201-4337, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Source: Hospira, September 12, 2014

**One Lot of Hospira Vancomycin HCI**

Hospira, Inc., is recalling one lot of vancomycin hydrochloride for injection, USP, equivalent to 1 g vancomycin (sterile powder), because the product may have experienced temperature variations during shipment. Lot 35-315-DD has an expiration date of November 1, 2015. For assistance, call Stericycle at 1-844-861-6215 between 8 a.m. and 5 p.m. Eastern time, Monday through Friday.

Source: Hospira, Inc., October 7, 2014

**RESEARCH BRIEFS**

**New Vaccine Could Prevent 90% of Cervical Cancer**

Effective vaccination programs with a new nine-valent human papillomavirus (HPV) vaccine could prevent approximately 90% of invasive cervical cancer cases worldwide, according to a study published in *Cancer Epidemiology, Biomarkers, and Prevention*. To achieve that potential, however, the vaccine would have to be used more extensively than those already in production.

The investigational nine-valent HPV vaccine provides high-efficacy protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Approximately 85% or more of precancerous lesions of the cervix are attributed to these HPV types. Researchers based their estimates on data from 12,514 women, ages 15 to 45 years, enrolled in the placebo arms of three clinical trials testing a quadrivalent HPV vaccine. The researchers estimated the number of precancers harboring the HPV types included in the nine-valent vaccine being developed by Merck and currently under review at the FDA.

Source: American Association for Cancer Research, October 1, 2014
Benzodiazepines Linked With Dementia ...

Guidelines advise only short-term benzodiazepine use in elderly patients, but long-term treatment remains common—even though extended treatment for insomnia and anxiety has not been proven effective and may be harmful.

Long-term benzodiazepines impair memory and cognition; however, the effects on dementia are less clear, say researchers from the University of Montreal and the University of Bordeaux. Benzodiazepines are given for symptoms (anxiety, insomnia, depression) that increase before dementia is diagnosed. Could benzodiazepines cause those prodromes?

The study assessed benzodiazepine treatments initiated more than five years before a dementia diagnosis using an administrative claims database. The researchers matched 1,796 patients with 7,184 controls and followed them for at least six years.

The risk of Alzheimer’s disease, the study showed, increased by 43% to 51% among people who had used benzodiazepines in the past: 894 people (49.8%) with Alzheimer’s disease had used benzodiazepines, compared with 2,873 controls (40%). At the time of diagnosis, 64.8% of patients and 60.6% of controls were still taking benzodiazepines. Short-term use did not differ between the two groups, but long-term use was markedly more common among Alzheimer’s patients: 32.9% versus 21.8%.

Risk of Alzheimer’s increased when long-acting benzodiazepines were used. Adjusting for potential prodromes for dementia, such as depression, anxiety, and sleep disorders, did not meaningfully alter the results.

While concerned that the drugs are used for too long, in the wrong patients, the researchers nonetheless call benzodiazepines “indisputably valuable tools for managing anxiety disorders and transient insomnia.” They urge focusing on the duration of benzodiazepine use.

Source: BMJ, September 9, 2014

... And With Higher Mortality Than Propofol in ICUs

Continuous-infusion benzodiazepines are linked to an increased likelihood of death in patients who receive mechanical ventilation compared with the sedative propofol, according to a study in the American Journal of Respiratory Critical Care Medicine.

Sedation is often required for ventilated patients in intensive care units (ICUs) to reduce anxiety, provide comfort, and assist in respiratory support. Benzodiazepines, including lorazepam and midazolam, were once considered the standard of care.

University of Utah researchers analyzed data from 13,692 mechanically ventilated patients at 104 U.S. hospitals from 2003 to 2009. ICU mortality was 19.7% in propofol-treated patients compared with 28.8% in midazolam-treated patients, and 19.3% in propofol-treated patients compared with 25.2% in lorazepam-treated patients. Those treated with benzodiazepines spent more time on ventilation and in the ICU.

Patients with renal failure and liver dysfunction have trouble clearing benzodiazepines and are more likely to be oversedated. Patients who stay on a ventilator longer are at higher risk for developing ventilator-associated pneumonia and other complications that come from being sedated for long periods.

Earlier, smaller studies linking benzodiazepines with adverse outcomes triggered a drop in the use of benzodiazepines during the last 10 years. Nevertheless, benzodiazepines remain the sedatives of choice in some U.S. hospitals—largely because these drugs are generic and cost less than other sedatives.

Source: University of Utah, September 30, 2014

Pricier Drugs, Fewer Patients?

The median price of the top 100 drugs rose seven-fold from $1,260 in 2010 to $9,400 in 2014, according to market analyst Evaluate. Meanwhile, the median patient population size served by a top-100 drug fell by more than three-quarters, from 690,000 in 2010 to 146,000 in 2014.

The number of treatments costing in excess of $100,000 per patient per year rose to seven in 2014 versus four in 2010.

The Evaluate report describes a fundamental shift to high-priced medicines treating smaller patient population sizes, causing friction between payers and companies. Still, the firm expects the costly drugs to get an increasing slice of the U.S. market as payers drop poorly differentiated products. The report was derived from the company’s new EvaluatePharma USA Sales, Volume, and Pricing Analysis.

Source: Evaluate Ltd., September 25, 2014

Probiotics May Reduce Radiation-Caused Diarrhea

Probiotics may help ease a common side effect of pelvic cancer radiation therapy—diarrhea—but the benefits might not show up right away. According to researchers from Hôtel Dieu de Québec, probiotics were most effective in the weeks after radiation treatment.

No prophylactic agents are approved for preventing pelvic radiation enteritis, the researchers note, and evidence is weak for nutritional interventions. But more research is pointing to a role for probiotics in various gastrointestinal uses.

In the study, 229 patients undergoing radiotherapy received placebo or one of two regimens using the probiotic Bifilact: a standard dose twice a day, or a high dose three times a day. Patients recorded their digestive symptoms every day and met with a registered dietician and radiation oncologist each week.

Although the differences were not
statistically significant, probiotics eventually halved the proportion of patients with moderate-to-severe diarrhea. After 60 days, 33% of patients in the standard-dose Bifilact group did not have moderate-to-severe diarrhea, compared with 17% in the placebo group. For patients who underwent surgery before radiation, probiotic intake tended to reduce all levels of diarrhea, especially grade 4.

The researchers say six clinical studies have shown positive results for probiotics on diarrhea toxicity, frequency of bowel movement, and/or stool consistency during radiation treatment. The benefits of probiotics may be delayed because of the time required by bacteria to exert their influence on the inflammatory process, the researchers add.

Source: Clinical Nutrition, October 2014

771 Cancer Therapies in Pipeline

American biopharmaceutical research companies have 771 medicines and vaccines for cancer in clinical trials or awaiting FDA review, according to a report by the Pharmaceutical Research and Manufacturers of America. The list includes 98 for lung cancer, 87 for leukemia, 78 for lymphoma, 73 for breast cancer, 56 for skin cancer, and 48 for ovarian cancer.

Source: Pharmaceutical Research and Manufacturers of America, October 6, 2014

DEVICE NEWS

FDA Seeks Better Cybersecurity

Manufacturers should consider cybersecurity risks as they design and develop medical devices, the FDA says. Companies should submit documentation to the FDA about the risks they identify and the steps they’ve taken to mitigate them.

The recommendations are part of final guidance the FDA has given manufacturers for managing medical-device cybersecurity risks to better protect patient health and information. The guidance also recommends that manufacturers provide the FDA with plans for providing patches and updates to operating systems and medical software.

FDA concerns about cybersecurity vulnerabilities include malware infections on network-connected devices or computers, smartphones, and tablets used to access patient data; unsecured or uncontrolled distribution of passwords; failure to provide timely security software updates and patches to medical devices and networks; and security vulnerabilities in off-the-shelf software designed to prevent unauthorized access to the device or network.

The FDA has no indications that specific devices or systems have been purposely targeted and no reports that patients have been harmed as a result of cybersecurity breaches.

Source: FDA, October 1, 2014

Glucose Monitoring System

The FDA has approved a new indication for the Nova StatStrip Glucose Hospital Meter System (Nova Biomedical), extending its use to critically ill patients—making it the first blood glucose monitoring system (BGMS) specifically indicated for use in all types of hospital patients.

BGMSs, also called blood glucose meters, are handheld devices that analyze the glucose level in a drop of blood on a test strip. The FDA determined that the Nova StatStrip Glucose Hospital Meter System is simple to use and has a low risk of false results.

The FDA gave the device a “clearance waived” test system status under the Clinical Laboratory Improvement Amendments (CLIA). This will allow a variety of health care professionals to perform the test at the point of care, such as a patient’s bedside, instead of requiring that the test be performed in a lab that meets CLIA requirements for high-complexity testing.

Data supporting this clearance included a study of more than 1,650 patients with a range of medical conditions. The results showed agreement in blood glucose results compared with a laboratory glucose analyzer in all patient types tested.

Source: FDA, September 24, 2014

Device Recalls

EnVe and ReVel ventilators

EnVe and ReVel ventilators (CareFusion 203, Inc.) are being recalled because potential damage to power-cord adaptors could cause them to shut down. The ventilators can operate on battery or external power. However, the pins of the external power connector do not always align properly with the input port of the ventilator. Misalignment can damage these pins and possibly short-circuit the ventilator. A short-circuit in the power supply may prevent the ventilator battery from recharging, and the ventilator could lose power unexpectedly. The company has received 256 reports of incidents, with no injuries or deaths.

The units were distributed from December 10, 2010, until August 6, 2014. Call the CareFusion Recall Center with questions about the Class I recall at 1-888-562-6018, Monday through Friday, 7 a.m. to 4 p.m. Pacific time.

Source: FDA, October 9, 2014

Hudson RCI Pediatric Anesthesia Breathing Circuits

Teleflex Medical is recalling its Hudson RCI Pediatric Anesthesia Breathing Circuits (which deliver anesthesia and other gases from a mechanical ventilator to a hospital patient) because the ends of the devices may crack or break, causing serious and potentially fatal health risks.

About 27,000 devices were distributed worldwide from June 2013 to May 2014. A list of product codes and lot numbers is available at http://tinyurl.com/HudsonRCI. Those with questions about this Class 1 recall should contact Customer continued on page 785
continued from page 743

Service at cs@teleflex.com or 1-866-246-6990, Monday through Friday, 8 a.m. to 7 p.m. Eastern time.
Source: FDA, October 7, 2014

**ConMed Stat2 Flow Controller**
ICU Medical, Inc., is recalling ConMed Stat2 Flow Controllers, used in intravenous administration sets, because they were assembled with the wrong internal component. The controller may deliver fluid at a much higher rate than the setting indicates, with potentially serious or fatal consequences.

The Class I recall covers items 011-C9801, 011-C9802, AH7007, B9897, and Z2648. The affected lots, 2768416, 2768417, 2758229, 2785379, 2801951, 34-128-HE, 34-540-Y1, 35-151-SJ, 35-805-JW, 36-137-SL, and 36-469-SL, were distributed from October 2013 to January 2014. Those with questions should contact Customer Service at 1-866-829-9025 (option 8), Monday through Friday, 8:30 a.m. to 4 p.m. Pacific time.
Source: FDA, October 9, 2014

**DEVICE SPOTLIGHT**

**Kunj Gohil, PharmD, RPh**

**Name:** MyLab Gamma
**Manufacturer:** Esaote, Genoa, Italy
**Approval Date:** October 3, 2014

**Purpose:** MyLab Gamma is an ultrasound system that resembles a laptop in its size, lightweight portability, and use of applications. These applications allow the system to be used in a variety of scenarios in clinics and other point-of-care sites.

**Description:** The system has the capability to record both 3D and 4D images, and with the wide range of probes it can be used by physicians in women’s health, general imaging, and nontraditional point-of-care applications. The advanced clinical technologies can also perform cardiac and vascular exams such as transesophageal echo, strain, stress echo, and other qualitative studies. MyLab Gamma maintains wireless connectivity, remote service capabilities, and quick boot times.

**Benefit:** Physicians are increasingly pressured to deliver high-quality services at an affordable cost in a timely manner. This easy-to-use system gives providers a new device they can employ in various environments whenever they need.

**Sources:** www.firstwordmedtech.com, www.esaote.com

**Name:** T2Candida
**Manufacturer:** T2 Biosystems, Lexington, Massachusetts

**Approval Date:** September 23, 2014

**Purpose:** T2Candida is a diagnostic product developed to assist physicians in the timely identification of a *Candida* infection. The test utilizes a patient’s blood and can look for five clinically relevant species of *Candida*.

**Description:** This product uses technologies that break down yeast and release its DNA. Once the DNA is released into the device’s medium, it is rapidly copied and the device will detect the DNA through magnetic resonance technology. If DNA from yeast is found, the T2Candida device will identify the species category and provide an indication for the testing provider. The product uses patient blood to identify a yeast pathogen in only three to five hours.

**Benefit:** *Candida* is the most lethal pathogen involved with bloodstream infections causing sepsis. Whereas traditional tests may take up to six days, T2Candida provides physicians a simple way to quickly identify *Candida* infections within hours. Patient mortality can be dramatically decreased if treatment is initiated within 12 hours upon presentation of symptoms. This test may reduce duration of hospitalization and, in turn, decrease the cost of hospital stays for patients receiving intensive care.

**Sources:** www.t2biosystems.com, www.fda.gov

**Name:** eCareCoordinator and eCareCompanion
**Manufacturer:** Royal Philips, Andover, Massachusetts

**Approval Date:** October 1, 2014

**Purpose:** Both the eCareCompanion and eCareCoordinator are clinical applications that focus on chronic-care management. The applications, parts of the Philips Transition to Ambulatory Care (eTrAC) program, are designed to aid in the reduction of hospital readmissions and health care costs.

**Description:** The eCareCompanion is a patient portal used to share patient-specific characteristics collected by a tablet. Information may be obtained from various devices that can be connected to the tablet, such as a scale, blood pressure meter, blood oximeter, and medication dispenser. The companion may also provide patients with specific alerts, such as medication reminders.

The eCareCoordinator is an application that allows health care professionals to access and monitor patient data every day; data can include weight, blood pressure, and other vital signs collected by the patient. This can also be used to administer health questionnaires to patients and as a communication medium between the various members of a patient care team.

**Benefit:** Digital health care is a rapidly evolving field that will soon play an integral role in patient care. These applications take a dual approach by providing benefits to both the patient and physician and enabling daily monitoring of various patient characteristics. It will be interesting to see the role these applications assume as more physicians embrace digital modes of communication.

**Sources:** www.fiercemedicaldevices.com, www.philips.com