NEW DRUG APPROVALS

Lorbrena for NSCLC

The FDA has approved lorlatinib (Lorbrena, Pfizer Inc.), a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) that was developed specifically to inhibit tumor mutations that may drive resistance to other ALK TKIs.

Lorlatinib is indicated for patients with ALK-positive, metastatic, non–small-cell lung cancer (NSCLC) whose disease has progressed on crizotinib (Xalkori, Pfizer) and at least one other ALK inhibitor for metastatic disease, or whose disease has progressed on alectinib (Alecensa, Genentech) or ceritinib (Zykadia, Novartis) as the first ALK inhibitor- therapy for metastatic disease. While many ALK-positive metastatic NSCLC patients respond to initial TKI therapy, they typically experience tumor progression.

Lorlatinib is administered orally once a day. Its approval was based on a non-randomized, dose-ranging, activity-estimating phase 1/2 study, B7461001, where it was evaluated in patients with ALK-positive metastatic NSCLC who were previously treated with one or more ALK TKIs. Among 215 patients, the overall response rate was 48%.

Serious adverse reactions occurred in 32% of patients; the most frequent were pneumonia, dyspnea, pyrexia, mental status changes, and respiratory failure. Fatal adverse reactions occurred in 2.7% of patients and included pneumonia, myocardial infarction, acute pulmonary edema, embolism, peripheral artery occlusion, and respiratory distress.

As this indication received accelerated approval based on tumor response rate and duration of response, its continued approval may be contingent upon verification of clinical benefit in a confirmatory trial.

Source: Pfizer Inc., November 2, 2018

Yupelri for COPD

The FDA has approved revefenacin inhalation solution (Yupelri, Theravance Biopharma, Inc./Mylan N.V.) for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

Revefenacin, a long-acting muscarinic antagonist (LAMA), is the first once-daily, nebulized bronchodilator approved in the U.S. for the treatment of COPD. It can be delivered through any standard jet nebulizer.

In two replicated, pivotal phase 3 efficacy studies, revefenacin demonstrated statistically significant and clinically meaningful improvements compared with placebo in trough forced expiratory volume in one second (FEV_1) and in overall treatment effect on trough FEV_1 after 12 weeks of dosing. Revefenacin had comparable rates of adverse events to placebo, low rates of serious adverse events, and no clinically meaningful differences in blood parameters or electrocardiogram data across all treatment groups (active and placebo).

The most commonly reported adverse events, across both trials and all treatment groups, were cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. In addition, the companies completed a 12-month, phase 3, open-label safety study versus tiotropium, in which no new safety issues were identified. Rates of adverse events in the study were low and comparable to those in the tiotropium arm.

Source: Theravance Biopharma, Inc. /Mylan N.V., November 9, 2018

Xofluza for Influenza

Baloxavir marboxil (Xofluza, Shionogi & Co., Ltd.) has secured FDA approval for the treatment of acute uncomplicated influenza in patients aged 12 years and older who have been symptomatic for no more than 48 hours. This is the first new antiviral flu treatment with a novel mechanism of action to be approved by the FDA in almost 20 years.

The safety and efficacy of baloxavir marboxil, taken as a single oral dose, were demonstrated in two randomized, controlled clinical trials of 1,832 patients. Participants were assigned to receive either baloxavir marboxil, a placebo, or another antiviral flu treatment within 48 hours of experiencing flu symptoms. In both trials, patients treated with baloxavir marboxil had a shorter time to alleviation of symptoms compared with patients who took the placebo. In the second trial, there was no difference in the time to alleviation of symptoms between subjects who received baloxavir marboxil and those who received the other flu treatment.

The most common adverse reactions in patients taking baloxavir marboxil included diarrhea and bronchitis.

The FDA cautions that antiviral drugs to treat flu are no substitute for yearly vaccinations.

Xofluza was granted priority review status.

Source: FDA, October 24, 2018

Bijuva to Ease Menopause

Estradiol and progesterone capsules, 1 mg/100 mg (Bijuva, Therapeutics MD, Inc.), have become the first FDA-approved therapy combining the two bioidentical hormones in a single, oral capsule for the treatment of moderate-to-severe vasomotor symptoms (commonly known as hot flashes or flushes) due to menopause in women with a uterus.

Bioidentical estradiol reduces moderate-to-severe hot flashes, while bioidentical progesterone reduces the risks to the endometrium. Bioidentical hormones are molecularly identical to the hormones circulating naturally in a woman's body. Previously available products include FDA-approved synthetic (nonbioidentical) hormones, separate FDA-approved

bioidentical estrogen and progesterone products that are used together but are not approved for combination use, and unapproved compounded bioidentical hormone products.

The pivotal phase 3 Replenish trial evaluated the safety and efficacy of Bijuva in generally healthy, postmenopausal women with a uterus, for the treatment of moderate-to-severe hot flashes. Bijuva demonstrated a statistically significant reduction from baseline in both the frequency and severity of hot flashes compared to placebo at weeks four and 12, while reducing the risks to the endometrium. The most common adverse reactions were breast tenderness, headache, vaginal bleeding, vaginal discharge, and pelvic pain. There were no unexpected safety signals.

The product has a boxed warning related to the risks for cardiovascular disorders, breast cancer, endometrial cancer, and probable dementia.

Source: TherapeuticsMD, Inc., October 29, 2018

Talzenna for Breast Cancer

Talazoparib (Talzenna, Pfizer Inc.) has received FDA approval for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative, locally advanced or metastatic breast cancer. Patients must be selected for therapy based on an FDA-approved companion diagnostic for talazoparib, a poly (ADP-ribose) polymerase (PARP) inhibitor.

Approval was based on EMBRACA (NCT01945775), an open-label trial randomizing 431 patients in this population to receive oral talazoparib (1 mg) or physician's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). Patients could have received up to three prior cytotoxic chemotherapy regimens and were required to have received treatment with an anthracycline and/or a taxane (unless contraindicated). Estimated progression-free survival was 8.6 and 5.6 months in the talazoparib and chemotherapy arms, respectively.

The prescribing information includes warnings and precautions for myelodysplastic syndrome/acute myeloid leukemia, myelosuppression, and embryo-fetal toxicity. The most common adverse reactions of any grade were fatigue, anemia, nausea, neutropenia, headache, thrombocytopenia, vomiting, alopecia, diarrhea, and decreased appetite.

The FDA also approved the BRACAnalysis CDx test (Myriad Genetic Laboratories, Inc.) to identify patients eligible for talazoparib. The effectiveness of the test was based on the EMBRACA trial population for whom deleterious or suspected deleterious gBRCAm status was confirmed with either prospective or retrospective testing with BRACAnalysis CDx.

The FDA granted this application priority review status.

Source: FDA, October 16, 2018

Yutiq for Chronic Uveitis

The FDA has approved fluocinolone acetonide intravitreal implant (Yutiq, EyePoint Pharmaceuticals, Inc.) for the treatment of chronic noninfectious uveitis affecting the posterior segment of the eye.

The implant, which uses EyePoint's Durasert drug-delivery technology, is a nonbioerodible intravitreal microinsert in a drug-delivery system containing 0.18 mg of fluocinolone acetonide, designed to release consistently over 36 months. Yutiq is supplied in a sterile, single-dose preloaded applicator that can be administered in the physician's office.

The FDA approved the implant based on clinical data from two randomized, sham–injection-controlled, double-masked phase 3 clinical trials, with patient follow-up continuing for three years. For Yutiq versus sham, recurrence of uveitis flares in the first trial was 18.4% versus 78.6% at six months and 27.6% versus 85.7% at 12 months; in the second trial, it was 21.8% versus 53.8% at six months and 32.7% versus 59.6% at 12 months.

The most common adverse reactions were cataract development and increased intraocular pressure.

Source: EyePoint Pharmaceuticals, October 15, 2018

Udenyca, a Neulasta Biosimilar

The FDA has approved pegfilgrastim-cbqv (Udenyca, Coherus BioSciences) for cancer patients who are receiving myelosuppressive chemotherapy. Pegfilgrastim-cbqv is a leukocyte growth factor designed to reduce infections as indicated by febrile neutropenia.

The drug is contraindicated for patients with a history of serious allergic reaction to human granulocyte colony-stimulating factors, and is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem-cell transplantation. The most common adverse reactions associated with pegfilgrastim-cbqv are bone pain and pain in the extremities.

Pegfilgrastim-cbqv is the second biosimilar to pegfilgrastim (Neulasta, Amgen), which Coherus said represents a $4 billion annual cost burden in the U.S. The FDA approved pegfilgrastim-jmdb (Fulphila, Mylan), the first biosimilar to Neulasta, in June 2018.

Sources: Coherus and Healio.com, November 5, 2018; FDA, June 4, 2018

Hyrimoz, a Humira Biosimilar

The FDA has approved adalimumab-adaz (Hyrimoz, Sandoz)—the third biosimilar to Humira (AbbVie)—but a legal settlement between the two companies means Hyrimoz won't be available in the U.S. until 2023.

Adalimumab-adaz is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis in patients

fours years of age and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis.

The approval of adalimumab-adaz was based on analytical, preclinical, and clinical research demonstrating that the drug matches Humira in terms of safety, efficacy, and quality. A randomized, double-blind, three-arm, parallel biosimilarity study confirmed the pharmacokinetics, immunogenicity, and safety of adalimumab-adaz. The study demonstrated bioequivalence for all primary pharmacokinetic parameters. A confirmatory efficacy and safety biosimilarity study (ADACCESS) demonstrated therapeutic equivalence in the sensitive indication of patients with moderate-to-severe, chronic, plaque-type psoriasis, with a similar safety and immunogenicity profile to Humira.

Adalimumab inhibits tumor necrosis factor, a protein that is overproduced in certain autoimmune conditions.

On October 11, 2018, Sandoz announced a global resolution of all intellectual property-related litigation with AbbVie concerning Sandoz's biosimilar adalimumab. The settlement will enable U.S. patient access to Hyrimoz on September 30, 2023.

The FDA has also approved adalimumab-atto (Amjevita, Amgen Inc.) and adalimumab-adbm (Cyltezo, Boehringer Ingelheim). Amgen settled litigation with AbbVie by agreeing not to launch its biosimilar in the U.S. until January 31, 2023. Boehringer Ingelheim remains engaged in patent litigation with AbbVie in the U.S.

Sources: Novartis, October 31, 2018; Amgen, September 28, 2017; Boehringer Ingelheim, September 15, 2017

Generic Approvals

Cefixime Capsules

Alkem Laboratories has received FDA permission to manufacture 400-mg cefixime capsules, the first generic form of 400-mg Suprax capsules marketed by Lupin Ltd. Cefixime is an antibiotic used to treat adults and children six months of age and older with urinary tract infections, pharyngitis, tonsillitis, acute exacerbations of chronic bronchitis, and uncomplicated cervical/urethral gonorrhea.

Source: FDA, October 9, 2018

Nitric Oxide Gas for Inhalation

After winning a patent battle, Praxair Distribution has received FDA approval to market Noxivent (nitric oxide) gas for inhalation (100 ppm and 800 ppm), the first generic version of INOmax (Mallinckrodt Pharmaceuticals) 100 ppm and 800 ppm. Noxivent is used to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in at-term and near-term (more than 34 weeks gestation) neonates with hypoxic respiratory failure.

Source: FDA, October 2, 2018

Albendazole Tablets

Cipla Ltd. has won permission to market albendazole tablets USP, 200 mg, the first generic version of 200-mg Albenza tablets (Impax Laboratories). Albendazole is used to treat parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium*.

Source: FDA, September 21, 2018

NEW INDICATIONS

Keytruda for Liver Cancer

The FDA has given accelerated approval to pembrolizumab (Keytruda, Merck) for the treatment of patients with hepatocellular carcinoma (HCC) who have previously been treated with sorafenib.

The approval was based on data from KEYNOTE-224, a single-arm, open-label trial evaluating pembrolizumab in 104 patients with HCC who had disease progression on or after sorafenib or who were intolerant to sorafenib. The objective response rate (ORR) was 17% (complete response rate, 1%; partial response rate, 16%). Among the 18 responding patients, 89% experienced a duration of response (DOR) of six months or longer and 56% experienced a DOR of 12 months or longer.

Pembrolizumab is an anti-programmed death-1 antibody therapy. Immune-mediated adverse reactions, which may be severe or fatal, can occur with pembrolizumab, which can also cause severe or life-threatening, infusion-related reactions.

As this indication received accelerated approval based on tumor response rate and durability of response, continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

Source: Merck, November 9, 2018

Empliciti Combination For Multiple Myeloma

Elotuzumab injection for intravenous use (Empliciti, Bristol-Myers Squibb) has secured FDA approval for use in combination with pomalidomide and dexamethasone (EPd) for the treatment of adults with multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.

The randomized, open-label, phase 2 ELOQUENT-3 trial compared EPd to pomalidomide and dexamethasone (Pd) in patients with relapsed or refractory multiple myeloma. For EPd versus Pd, the median progression-free survival was 10.25 months versus 4.67 months, overall response rate was 53.3% versus 26.3%, and very good partial responses or better were seen in 20% of patients versus 8.8% of patients.

Serious adverse reactions were reported in 22% of patients treated with EPd and in 15% of patients treated with

Pd. The most frequent serious adverse reactions were pneumonia and respiratory tract infection. Infusion reactions were reported in 3.3% of patients treated with EPd.

Elotuzumab is also indicated in combination with lenalidomide and dexamethasone for the treatment of adults with multiple myeloma who have received one to three prior therapies.

Source: Bristol-Myers Squibb, November 6, 2018

Invokana to Cut CV Risk

Canagliflozin (Invokana, Janssen) has received FDA approval to reduce the risk of major adverse cardiovascular (CV) events, including heart attack, stroke, or death due to a CV cause, in adults with type-2 diabetes (T2D) who have established CV disease. Canagliflozin is the first oral diabetes treatment with this indication.

The CANVAS program evaluated the effect of canagliflozin on CV risk in more than 10,000 adults with T2D who had established CV disease (65%) or two or more risk factors for CV disease (35%). Overall, treatment with canagliflozin compared to placebo, in addition to standard of care, reduced the combined risk of heart attack, stroke, and CV death by 14%. In patients with established CV disease, treatment with canagliflozin reduced the combined risk of heart attack, stroke, and CV death by 18% compared to placebo.

This new indication also applies to fixed-dose combinations of canagliflozin/metformin tablets (Invokamet) and canagliflozin/metformin extended-release tablets (Invokamet XR).

Source: Janssen, October 30, 2018

Dupixent for Asthma

Dupilumab (Dupixent, Regeneron /Sanofi) has received FDA approval as an add-on maintenance therapy in patients with moderate-to-severe asthma who are aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.

The dupilumab asthma pivotal clinical trial program evaluated 2,888 adults and adolescents with moderate-to-severe asthma in three randomized, placebo-controlled, multicenter trials (trial 1, trial 2, and trial 3) for 24 to 52 weeks.

In trial 2, dupilumab reduced exacerbations in patients with eosinophil counts greater than or equal to 150 cells/mcL, and efficacy improved in patients with higher eosinophil counts. For example, in patients with blood eosinophils of 300 cells/mcL or greater, dupilumab reduced severe exacerbations by 67% compared with placebo. In trial 3, which evaluated severe, oral corticosteroid-dependent patients, dupilumab reduced average daily oral corticosteroid use by 70% compared to 42% with placebo.

In the asthma clinical trials, the most common adverse reactions were injection-site reactions, sore throat, and an increase in the number of eosinophils.

Dupilumab inhibits the overactive signaling of interleukin-4 and interleukin-13, proteins that contribute to the type-2 inflammation that may underlie moderate-to-severe asthma.

Dupixent comes in a prefilled syringe for subcutaneous injection by a health care provider or at home. It is also approved in the U.S. for the treatment of adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

Source: Regeneron Pharmaceuticals, Inc., October 22, 2018

Xarelto for CAD, PAD

The FDA has approved rivaroxaban (Xarelto, Janssen) in combination with low-dose aspirin to reduce the risk of major cardiovascular (CV) events in people with chronic coronary artery disease (CAD) or peripheral artery disease (PAD). The drug is the first factor Xa inhibitor approved for patients with these conditions.

The phase 3 COMPASS trial found a 24% reduction in the risk of major CV events (heart attack, stroke, and CV death) in patients with chronic CAD and/or PAD who took rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily compared with those who took aspirin alone. The trial showed a 42% reduction in stroke, 22% reduction in CV death, and 14% reduction in heart attack. The risk of major bleeding was significantly higher in patients taking the rivaroxaban/aspirin regimen compared to those taking aspirin alone, with no significant increase in fatal or intracranial bleeds. COMPASS included more than 27,000 patients.

Atherosclerosis is the most common underlying cause of chronic CAD and PAD, which affect 16.5 million and 10 million Americans, respectively.

Source: Janssen, October 11, 2018

Xyrem for Pediatric Narcolepsy

The FDA has expanded the indication for sodium oxybate oral solution, CIII (Xyrem, Jazz Pharmaceuticals PLC) to include treatment of cataplexy or excessive daytime sleepiness (EDS) in patients with narcolepsy who are seven years of age and older.

The phase 2/3 EXPRESS study enrolled patients aged seven to 17 years who had narcolepsy with cataplexy and who were either using sodium oxybate oral solution already or who were then titrated to a tolerable and effective dose. After all participants underwent a two-week, double-blind, randomized withdrawal period, they were randomly assigned to remain on sodium oxybate at their stable dose or to receive placebo. Participants who were randomized to placebo (withdrawn from sodium oxybate) had a

median increase of 12.7 weekly cataplexy attacks, while those who continued treatment with sodium oxybate had a median increase of 0.3 attacks per week.

The safety profile of sodium oxybate in children and adolescents was similar to that reported in adults.

Xyrem may only be dispensed to patients enrolled in the Xyrem risk evaluation and mitigation strategy (REMS) program.

Source: Jazz Pharmaceuticals PLC, October 29, 2018

Liletta Contraception Extended

The FDA has approved a five-year duration of use for the levonorgestrel-releasing intrauterine system, 52 mg (Liletta, Medicines360/Allergan PLC), for the prevention of pregnancy.

The approval was based on a review of additional efficacy and safety data from the ongoing phase 3 ACCESS IUS clinical trial, in which 1,751 U.S. women have received Liletta. The system proved to be more than 99% effective in preventing pregnancy for up to five years in a broad range of women regardless of age, race, body mass index, or previous childbirth.

Liletta is placed in a woman's uterus to prevent pregnancy and can now be used for up to five years. It should be replaced after five years if continued use is desired. Liletta received initial approval in February 2015.

Source: Medicines360/Allergan PLC, October 16, 2018

Afluria Quadrivalent Influenza Vaccine

The FDA has approved Afluria Quadrivalent Influenza Vaccine (Seqirus) for people six months of age and older. The approval also applies to the trivalent formulation of Afluria Influenza Vaccine. Afluria Quadrivalent was first approved in the U.S. in August 2016, for adults aged 18 and older, and it helps protect against two A strain viruses and two B strain viruses.

Source: Seqirus, October 23, 2018

NEW FORMULATIONS

Dsuvia for Acute Pain

The FDA has approved sufentanil sublingual tablets (Dsuvia, AcelRx Pharmaceuticals, Inc.) for the management of acute pain in adults that is severe enough to require an opioid analgesic in certified, medically supervised health care settings, such as hospitals, surgical centers, and emergency departments.

Sufentanil citrate injection has been in commercial use for more than three decades, but Dsuvia is a 30-mcg sufentanil tablet in a single-dose, prefilled applicator for sublingual administration only by a health care professional. Dsuvia was designed to provide rapid analgesia via a noninvasive route, eliminate dosing errors associated with intravenous administration, and mitigate the possibility of misuse and diversion.

In a randomized, double-blind, placebo-controlled clinical study, Dsuvia demonstrated a statistically greater summed pain intensity difference from baseline over the first 12 hours of the study compared with placebo. The pain intensity difference from baseline was superior to that of the placebo group within 15 minutes, and median meaningful pain relief occurred following a single dose.

Dsuvia will be distributed only to health care settings certified in the Dsuvia REMS program. Dsuvia has a boxed warning related to life-threatening respiratory depression; addiction, abuse, and misuse; cytochrome P450 3A4 interaction; and risks from concomitant use with benzodiazepines or other central nervous system depressants. Sufentanil is a Schedule II controlled substance.

Source: AcelRx Pharmaceuticals, Inc., November 2, 2018

OTC Primatene for Asthma

The FDA has approved an epinephrine inhalation aerosol bronchodilator suspension (Primatene Mist, Amphastar Pharmaceuticals, Inc.) that is delivered by a metered dose inhaler with a non-chlorofluorocarbon (CFC) propellant. The product—the only FDA-approved asthma inhaler available without prescription in the U.S.—is indicated for the temporary relief of mild symptoms of intermittent asthma in people aged 12 years and older.

The new formulation is made with the same active ingredient, epinephrine, that was used in the original Primatene Mist before it was removed from the market in 2011 pursuant to the Montreal Protocol, an international environmental treaty that phased out products containing CFCs. The new inhalation delivery system no longer includes CFC as the propellant and has other new features, including a built-in spray indicator and a metal canister, which replaces the glass container used in the original product.

Source: Amphastar Pharmaceuticals, Inc., November 7, 2018

Sympazan for Seizures

The FDA has approved clobazam oral film (Sympazan, Aquestive Therapeutics, Inc.) for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS), in patients two years of age or older. Sympazan is the first FDA-approved oral film to treat seizures associated with LGS.

Previously, clobazam was marketed as Onfi (Lundbeck) in tablet or oral suspension formulations. LGS patients often have difficulty swallowing pills and large-volume suspensions due to physical, behavioral, or cognitive impacts.

Multiple pharmacokinetic studies were conducted to compare Sympazan with Onfi, and Sympazan was demonstrated to be bioequivalent to clobazam tablets, with

a comparable safety profile. Sympazan oral film is offered in 5-mg, 10-mg, and 20-mg dosages.

The product carries a boxed warning noting that concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death.

Source: Aquestive Therapeutics, Inc., November 2, 2018

Khapzory, a Folate Analog

The FDA has approved the folate analog levoleucovorin for injection (Khapzory, Spectrum Pharmaceuticals, Inc.).

The product has three indications: rescue after high-dose methotrexate therapy in patients with osteosarcoma; diminishing the toxicity associated with overdosage of folic acid antagonists or impaired methotrexate elimination; and the treatment of patients with metastatic colorectal cancer in combination with fluorouracil. Levoleucovorin is not indicated for the treatment of pernicious anemia and megaloblastic anemia secondary to lack of vitamin B_{12} because of the risk of progression of neurological manifestations despite hematologic remission.

Khapzory is the first levoleucovorin product approved by the FDA that contains sodium.

The most common adverse reactions in patients receiving high-dose methotrexate therapy with levoleucovorin rescue were stomatitis and vomiting. The most common adverse reactions in patients receiving levoleucovorin in combination with fluorouracil for metastatic colorectal cancer were stomatitis, diarrhea, and nausea.

Source: Spectrum Pharmaceuticals, Inc., October 23, 2018

FDA REVIEW ACTIVITIES

Breakthrough Therapy Status

Rubraca for Prostate Cancer

The FDA has granted breakthrough therapy designation for rucaparib (Rubraca, Clovis Oncology) as monotherapy for men with *BRCA 1/2*-mutated metastatic castration-resistant prostate cancer (mCRPC) who have received at least one prior androgen receptor-directed therapy and taxane-based chemotherapy.

The FDA previously designated rucaparib as a breakthrough therapy as monotherapy for some advanced ovarian cancer patients and for treatment of some women with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who have been treated with two or more chemotherapies. Rucaparib has also been approved for the maintenance treatment of adults with recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer who respond partially or completely to platinum-based chemotherapy.

CRPC has a high likelihood of metastasizing and is usually associated with a poor prognosis. Approximately 12% of mCRPC patients have a deleterious mutation in *BRCA1* or *BRCA2*. These markers may be used to select patients for treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor. Rubraca is an oral, small-molecule inhibitor of PARP1, PARP2, and PARP3.

The new breakthrough designation is based on initial efficacy and safety results from TRITON2, a phase 2 study in men with advanced prostate cancer with *BRCA 1/2* mutations (germline or somatic) and deleterious mutations of other homologous recombination repair genes in the mCRPC setting.

Source: Clovis Oncology, October 2, 2018

Fast-Track Designations

Rezafungin for Fungal Infections

The FDA has granted qualified infectious disease product (QIDP) and fast-track designations to the prophylaxis development program for rezafungin (Cidara Therapeutics). The QIDP designation is for the development of rezafungin to prevent invasive fungal infections in adults undergoing allogeneic bone marrow transplantation.

Approximately 97,000 Americans die each year from hospital-related invasive fungal infections, 90% of which are caused by *Candida* and *Aspergillus*.

Rezafungin, a novel antifungal echinocandin, is a once-weekly, high-exposure therapy for the treatment and prevention of serious invasive fungal infections. It is being studied in the treatment of candidemia and invasive candidiasis as well as prophylaxis of invasive fungal infections due to *Candida*, *Aspergillus,* and *Pneumocystis*. No single agent is approved today to prevent infections caused by these pathogens, and current prophylaxis regimens often require multiple antifungal drugs with safety and tolerability issues.

Source: Cidara Therapeutics, September 25, 2018

HTD1801 for Primary Sclerosing Cholangitis

HighTide Therapeutics has received fast-track designation for its investigational new drug HTD1801, which is being developed to treat patients with primary sclerosing cholangitis (PSC).

A chronic, progressive liver disease, PSC is characterized by inflammation and fibrosis of the bile ducts, leading to the formation of multifocal bile-duct strictures. PSC progresses to fibrosis, cirrhosis, and liver failure, with an increased risk of malignancy. There are no approved therapies.

HTD1801 is being developed for the treatment of PSC and other chronic dis-

orders. HighTide completed a first-in-humans study in healthy volunteers and is enrolling adults in a phase 2 trial.

Source: HighTide Therapeutics, September 27, 2018

Hepcidin Mimetic PTG-300 For Chronic Anemia

The FDA granted fast-track designation to PTG-300 (Protagonist Therapeutics), an injectable hepcidin mimetic for the treatment of chronic anemia due to ineffective erythropoiesis in patients with beta-thalassemia, a rare disease characterized by chronic anemia and iron overload.

Hepcidin is a natural peptide hormone that governs the body's iron absorption, recycling, and utilization. Abnormally low hepcidin levels, caused by genetic mutations or secondary pathology, can be supplemented by a hepcidin mimetic to restore iron homeostasis.

A phase 2 clinical trial is planned for the fourth quarter of 2018.

Source: Protagonist Therapeutics, September 27, 2018

ProCase for Blood Clots

The FDA has given fast-track designation to ProCase (E-WE thrombin, AB002, Aronora Inc.), an enzyme that reverses blood-clot formation without increasing the risk of bleeding.

More than one million people die from blood clots every year in the U.S. The FDA approved the last clot-busting drug, tissue-plasminogen activator (tPA), in 1987. However, tPA can significantly increase the risk of bleeding, and is used only in a very small percentage of patients. ProCase is a bioengineered enzyme that targets blood clots and safely augments the body's own natural antithrombotic, thrombolytic, and cytoprotective mechanisms.

Source: Aronora Inc., September 26, 2018

Priority Review Status

Imbruvica with Obinutuzumab for Chronic Lymphocytic Leukemia

The FDA has accepted AbbVie's supplemental new drug application with priority review for ibrutinib (Imbruvica, AbbVie) in combination with obinutuzumab (Gazyva, Genentech) for adults with untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

CLL is one of the two most common forms of leukemia in adults. SLL is a slow-growing lymphoma biologically similar to CLL, in which too many immature white blood cells cause lymph nodes to become larger than normal. The median age at diagnosis of CLL/SLL in adults is between 65 and 70 years of age.

Ibrutinib is an oral, once-daily inhibitor of Bruton's tyrosine kinase, a key molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells. The application is based on positive results from the phase 3 iLLUMINATE (PCYC-1130) trial, which showed the combination treatment was associated with significantly longer progression-free survival versus chlorambucil plus obinutuzumab, in adults with previously untreated CLL/SLL.

If approved, ibrutinib with obinutuzumab could become the first chemotherapy-free, anti-CD20 combination for the first-line treatment of CLL/SLL.

Source: AbbVie, October 17, 2018

Rare Pediatric Disease Designations

Lonafarnib for Rapid Aging

Eiger BioPharmaceuticals has received a rare pediatric disease designation for lonafarnib in the treatment of Hutchinson-Gilford Progeria Syndrome (HGPS) and progeroid laminopathies.

Progeria, which affects about 400 children worldwide, is a rapidly fatal genetic condition that causes accelerated aging. Children with progeria die of arteriosclerosis at an average age of 14.5 years. There is no approved treatment for progeria or progeroid laminopathies.

Progeria is caused by a point mutation in the *lamin A* gene yielding the farnesylated aberrant protein progerin. Lamin A protein is the structural scaffolding that holds the nucleus together. Researchers believe that defective lamin A protein makes the nucleus unstable, and that cellular instability leads to premature aging.

Progeroid laminopathies are genetic conditions of accelerated aging caused by a constellation of mutations in the *lamin A* and/or *Zmpste24* genes yielding farnesylated proteins that are distinct from progerin. These genetic mutations result in disease manifestations with phenotypes that overlap with, but are distinct from, progeria.

Lonafarnib is a late-stage, orally active inhibitor of farnesyltransferase, an enzyme involved in the modification of proteins through prenylation. Lonafarnib blocks the farnesylation of progerin.

Source: Eiger BioPharmaceuticals, October 22, 2018

Iduronicrin Genleukocel-T for MPS I

The FDA has granted a rare pediatric disease designation for iduronicrin genleukocel-T (Immusoft), transposon-engineered autologous plasmablasts for the expression and delivery of alpha-L-iduronidase (IDUA) to treat mucopolysaccharidosis type I (MPS I).

MPS I is a childhood genetic disease that affects the body's ability to produce IDUA, an essential enzyme that helps break down long-chain sugars inside cells. When the body cannot break down and dispose of sugar chains, they accumulate in the cells and cause progressive damage.

Immusoft's technology modifies a patient's B cells and instructs the cells

to produce gene-encoded medicines. The B cells that are reprogrammed using the technology become miniature drug factories that are expected to survive in patients for many years.

Source: Immusoft, October 17, 2018

LBS-008 for Stargardt Disease

Lin BioScience has received a rare pediatric disease designation for LBS-008, a first-in-class oral therapy for the treatment of Stargardt disease.

Stargardt disease is an inherited condition caused by a mutation in the *ABCA4* gene. It leads to the accelerated formation and accumulation of toxic vitamin A dimers in the retina that cause progressive retinal-cell death and permanent vision loss. LBS-008 prevents toxin buildup in the eye that causes Stargardt and atrophic age-related macular degeneration.

Source: Lin BioScience, September 17, 2018

Orphan Drug Designations

PAAG15A for Cystic Fibrosis

Synspira has received orphan drug status for poly (acetyl, arginyl) glucosamine (PAAG15A) for the treatment of cystic fibrosis (CF).

Synspira is developing PAAG15A as SNSP113, a glycopolymer-based inhaled treatment. PAAG15A, the active modified polysaccharide in SNSP113, breaks apart structural polymers in protective bacterial biofilms and interacts with native glycoproteins in mucus, normalizing its viscosity. SNSP113 also interacts with invading bacteria's cell walls, increasing their permeability, reducing their inherent viability, and enhancing the efficacy of antibiotics.

Because SNSP113 treats infection, airway congestion, and inflammation, it has the potential to treat a broad population of CF patients regardless of genetic mutation.

Source: Synspira, October 11, 2018

X4P-001-RD for WHIM Syndrome

The FDA has granted orphan drug status to X4P-001-RD (X4 Pharmaceuticals) for the treatment of WHIM syndrome, a primary immunodeficiency disease.

WHIM syndrome is caused by genetic mutations in the CXCR4 receptor gene, resulting in susceptibility to certain types of infections. WHIM is an abbreviation for the characteristic clinical symptoms of the syndrome: warts, hypogammaglobulinemia, infections, and myelokathexis. Between 15,000 and 100,000 U.S. patients are classified with primary immunodeficiency disease of unknown origin (including WHIM). The precise prevalence of the genetic mutation responsible for WHIM syndrome is unknown.

Patients with WHIM syndrome are more susceptible to potentially life-threatening bacterial infections. There is no approved therapy. Current treatments are limited to prophylactic intravenous immunoglobulin or granulocyte colony-stimulating factor, or antibiotics for the acute infections.

X4P-001-RD is being tested in patients in a phase 2/3 clinical trial.

Source: X4 Pharmaceuticals, October 15, 2018

Lynparza for Pancreatic Cancer

The FDA has granted orphan drug designation for olaparib (Lynparza, Astra Zeneca/Merck) for the treatment of germline *BRCA*-mutated (gBRCAm) metastatic pancreatic cancer, in patients whose disease has not progressed following first-line, platinum-based chemotherapy.

Pancreatic cancer accounts for about 3% of all U.S. cancers. Due to the late onset of symptoms, patients are often diagnosed after the cancer has progressed to locally advanced or metastatic stages of the disease. The five-year survival rate is 8.5%.

The ongoing phase 3 POLO trial is investigating olaparib as maintenance monotherapy versus placebo. Results from the trial are expected in the first half of 2019.

Source: AstraZeneca and Merck, October 16, 2018

STRO-001 for Multiple Myeloma

Sutro Biopharma has received an orphan drug designation for STRO-001 for the treatment of multiple myeloma. STRO-001 is a potential first-in-class antibody drug conjugate targeting CD74, a protein highly expressed in B-cell malignancies such as multiple myeloma.

STRO-001 is being studied in a phase 1 clinical trial enrolling separate dose-escalation cohorts for myeloma and B-cell lymphoma.

Source: Sutro Biopharma, October 12, 2018

Advisory Committee Vote

Zulresso for Postpartum Depression

The FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) jointly voted 17–1 that data support the favorable benefit–risk profile of brexanolone injection (Zulresso, Sage Therapeutics) for the treatment of postpartum depression (PPD), when the drug is administered by qualified staff in a facility that has been certified under a REMS program. The committees based their joint recommendation on safety and efficacy data from three placebo-controlled clinical studies.

Brexanolone is the first medicine under FDA review specifically for treating PPD, the most common medical complication of childbirth. PPD affects approximately one in nine women who have given birth in the U.S. and 400,000 women annually.

Source: Sage Therapeutics, November 2, 2018

DRUG SAFETY

Keystone OTC Drug Ban

A federal court has ordered a Tennessee company to stop selling over-the-counter (OTC) drug products until it complies with the Federal Food, Drug, and Cosmetic Act and other requirements.

U.S. District Judge John T. Fowlkes Jr. for the Western District of Tennessee entered a consent decree of permanent injunction against Keystone Laboratories, Inc., of Memphis, Tennessee; the company's owner, Melinda Menke; and its president, Elizabeth Jumet. According to the complaint filed with the consent decree, Keystone manufactured and distributed OTC hair care and skin care products that violated federal law.

Keystone's drug products were not manufactured, processed, packed, or held according to current good manufacturing practice (CGMP) requirements. For example, Keystone failed to adequately investigate sources of contamination found in some of its products, and failed to ensure its drug products met their specifications before releasing them to consumers. Some of Keystone's product labels did not include adequate directions for use or other label requirements for OTC drug products.

The consent decree requires Keystone to cease operations until it completes corrective actions.

The FDA issued a warning letter to Keystone in March 2013 for similar violations, and observed repeat violations during inspections in February 2016 and November 2017.

Source: FDA, October 23, 2018

DEVICE APPROVALS

Real-Time Detection Of Parathyroid Tissue

The FDA has permitted marketing of two devices that provide real-time location of parathyroid tissue during surgical procedures such as thyroidectomy and parathyroidectomy. Real-time identification of parathyroid tissue (which can be visually difficult to distinguish) can help surgeons preserve healthy tissue or remove diseased tissue.

The Fluobeam 800 Clinic Imaging Device (Fluoptics) is used to assist in the imaging of parathyroid glands and can help surgeons locate parathyroid tissue visually during surgery. Parathyroid tissue emits a fluorescent glow when exposed to the device's light source, avoiding the need for a contrast agent. The device was previously cleared as an imaging system used to capture and view fluorescent images for the visual assessment of blood flow as an adjunctive method for the evaluation of tissue perfusion. The FDA reviewed five peer-reviewed published studies, including one that compared the rate of postoperative hypocalcemia (PH), which occurs when healthy parathyroid tissue is inadvertently removed. In 93 patients who had surgery using the Fluobeam device, 5% experienced fluctuating PH following surgery compared with 21% of the 153 patients who had surgery without the device.

The Parathyroid Detection PTeye System (AiBiomed) aids in detecting parathyroid tissue during surgery by using a probe that emits fluorescent light. Tissue detection is based on how the parathyroid tissue reacts to the fluorescent light. When parathyroid tissue is detected, the system provides an audio and visual display to indicate its presence. In a single-blinded study of 81 patients who had surgery using the PTeye, it could correctly identify the presence of parathyroid tissue as compared to histology 93% of the time, and correctly identify the absence of parathyroid tissue as compared to intraoperative visualization by an expert 97% of the time, with an overall accuracy of 96%.

The use of either device is intended to assist, not replace, experienced visual assessment in identifying the parathyroid tissue along with a biopsy to confirm thyroid tissue per standard of care. The systems are not intended to be used to confirm the absence of parathyroid tissue or glands and are only to be used to assist the surgeon in locating potential parathyroid tissue or glands.

Both devices were reviewed under the FDA's *de novo* premarket review pathway.

Source: FDA, November 2, 2018

HeartMate 3 LVAD For Permanent Use

The FDA has approved Abbott's HeartMate 3 left ventricular assist device (LVAD) as a destination therapy for people living with advanced heart failure. With this approval, physicians can now offer the HeartMate 3 to patients who are not eligible for a transplant, who will live with their device for the rest of their lives.

More than 5.7 million Americans suffer from heart failure. For patients with advanced heart failure who can no longer rely on earlier-stage treatments, LVADs ease the workload of a weakened heart by pumping blood through the body. Abbott reduced the HeartMate 3's size while reimagining how blood passes through a heart pump, using technology known as Full MagLev (fully magnetically levitated) Flow to reduce trauma to the blood passing through the pump while improving its flow.

The approval was supported by clinical data from the MOMENTUM 3 trial. At two years, patients with the HeartMate 3 LVAD had a survival rate of 82.8%, a suspected pump thrombosis rate of 1.1%, and a stroke rate of 10%. MOMENTUM 3 included more than 1,000 patients with New York Heart Association IIIB or IV heart failure; two-year data on the first 366 patients were published in the *New England Journal of Medicine*.

The HeartMate 3 system includes the LVAD pump as well as other components

that help power and monitor the technology, including an external, wearable controller and battery system. The HeartMate 3 system received FDA approval for short-term support of heart failure patients in August 2017.

Source: Abbott, October 19, 2018

Rapid Ebola Test

The FDA has issued an emergency use authorization (EUA) for the DPP Ebola Antigen System (Chembio Diagnostic Systems, Inc.), a rapid, single-use test for the detection of Ebola virus. The test's portable, battery-operated reader can help provide clear diagnostic results outside of laboratories and in areas where patients are likely to be treated.

The test is used with blood specimens, including capillary "fingerstick" whole blood, from individuals with signs and symptoms of Ebola virus disease (EVD) in addition to other risk factors, such as living in an area with large numbers of EVD cases and/or having contact with other individuals exhibiting signs and symptoms of EVD.

The DPP Ebola Antigen System provides rapid diagnostic results with tests that can be performed in locations where a health care provider does not have access to authorized Ebola virus nucleic acid tests (PCR testing), which are highly sensitive but can only be performed in certain, adequately equipped laboratory settings.

The FDA has now issued EUAs for nine nucleic acid tests and two rapid diagnostic tests for Ebola virus detection in human specimens.

Source: FDA, November 9, 2018

23andMe Genomic Test

The FDA has permitted marketing, with special controls, of the Personal Genome Service Pharmacogenetic Reports (23andMe) as a direct-to-consumer test for providing information about genetic variants that may be associated with a patient's ability to metabolize some medications, to help inform their discussions with health care providers. The FDA is authorizing the test (which analyzes DNA from a self-collected saliva sample) to detect 33 variants for multiple genes.

This test does not determine whether a medication is appropriate for a patient, does not provide medical advice, and does not diagnose any health conditions. Any medical decisions should be made only after discussing results with a health care provider and results have been confirmed using clinical pharmacogenetic testing.

The FDA's review of the test determined that the company provided data to show that the test is accurate and can provide reproducible results. The company submitted data on user comprehension studies demonstrating that the test instructions and reports were understood by consumers. The test report provides information describing what the results might mean, what the test does not do, and how to interpret the results.

The FDA reviewed data for the test through the *de novo* premarket review pathway. Along with this authorization, the FDA is establishing special controls that set forth the agency's expectations in assuring the test's accuracy, clinical performance, and labeling.

Source: FDA, October 31, 2018

Test of Menopausal Status

The PicoAMH Elisa diagnostic test (Ansh Labs) can be marketed as an aid in determining a woman's menopausal status, the FDA has ruled. The test, when used in conjunction with other clinical assessments and laboratory findings, can help inform discussions about preventive care, such as ways to help prevent loss in bone mineral density or to address cardiovascular disease, both of which increase after menopause.

The PicoAMH Elisa test measures the amount of anti-Müllerian hormone (AMH) in the blood. AMH levels represent one indicator available to clinicians to determine whether a woman is approaching or is likely to have reached her final menstrual period.

The FDA reviewed data submitted by Ansh that included 690 women, aged 42 to 62 years, who participated in the Study of Women's Health Across the Nation. The data showed that the PicoAMH Elisa test performed reasonably well at determining levels of AMH in the blood, and at identifying women who had had their last menstrual period and women who were more than five years away from their last menstrual period.

Clinicians should carefully evaluate PicoAMH Elisa test results in the context of a full clinical work-up.

The FDA reviewed data for the PicoAMH Elisa test through the *de novo* premarket review pathway, and established special controls that set forth the agency's expectations in assuring the accuracy, clinical performance, and labeling of such tests.

Source: FDA, October 24, 2018

SMILE for Astigmatism

The FDA has approved marketing of the VisuMax femtosecond laser (Carl Zeiss Meditec) to correct myopia with astigmatism through the small-incision lenticule extraction (ReLEx SMILE) corneal refractive procedure. The small-entry incision allows the SMILE procedure to be potentially less disruptive to the corneal surface tissue.

ReLEx SMILE utilizes the high-precision laser to create a lenticule inside the cornea and access incision in a single treatment step. Incisions are made through microscopic photo-disruptions of tissue, created by ultrashort pulses.

Source: Carl Zeiss Meditec, October 5, 2018

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BioMimics 3D Vascular Stent

The BioMimics 3D Vascular Stent System (Veryan Medical Ltd.) has received FDA premarket approval for the treatment of symptomatic *de novo* or restenotic lesions in the native superficial femoral artery and/or proximal popliteal artery.

The BioMimics 3D stent has a helical shape designed to impart natural curvature to the diseased femoropopliteal artery, to promote swirling flow, and to elevate wall shear, which has a protective effect on the endothelium.

The MIMICS-2 clinical study enrolled 271 patients with peripheral arterial disease undergoing endovascular intervention in the femoropopliteal artery. Freedom from major adverse events at 30 days was 99.6%, and Kaplan-Meier estimates of freedom from loss of primary patency and clinically driven target lesion revascularization were 83% and 88%, respectively, at 12 months. No stent fractures were detected in a core laboratory imaging review.

Source: Veryan Medical Ltd., October 4, 2018.

Blood Compatibility Test

The FDA has approved ID CORE XT (Progenika Biopharma S.A.), a molecular-based assay used in blood transfusion medicine to help determine blood compatibility. The assay can be used to determine blood donor and patient non-ABO red blood cell (RBC) types. ID CORE XT is the second molecular assay approved for use in transfusion medicine, and the first to report genotypes as final results.

The approval of the ID CORE XT test can streamline blood compatibility testing.

Human blood can be classified into different groups based on the antigens on the surfaces of RBCs. In addition to the ABO blood group antigens, the presence or absence of other specific blood group antigens can be important when matching blood for transfusions because some people develop antibodies to non-ABO antigens. If RBCs with poorly matched non-ABO antigens are transfused, RBC destruction and a transfusion reaction can occur in a transfusion recipient.

Traditionally, RBC antigens have been identified using serological methods that involve the use of antisera, a blood serum that contains antibodies for testing.

A study compared the typing results of the ID CORE XT test with licensed serological reagents, the first FDA-approved molecular assay, and DNA sequencing tests. The results demonstrated comparable performance between the methods.

Source: FDA, October 11, 2018

Voyant for Spine Surgery

The FDA has awarded 510(k) clearance to the Voyant System for Minimally Invasive Spine Surgery (Viseon, Inc.), which features proprietary high-definition (HD) imaging sensor and illumination technology.

The Voyant System includes a sterile, single-use, disposable retractor device with integrated visualization technology and a reusable controller enabling digital intraoperative manipulation of the surgical site image, displayed on existing HD flat-panel display monitors in operating rooms. The sterile device also allows the surgeon to adjust intraoperative depth of focus.

This system offers an alternative to surgical microscope and surgical loupes visualization for many minimally invasive spine surgery procedures.

Source: Viseon, Inc., October 18, 2018

DEVICE SAFETY

Roche INR Test Strips

Certain test strips used with at-home or in-office medical devices to monitor levels of the blood thinner warfarin may provide inaccurate results and should not be relied upon to adjust the drug dosage, the FDA warns. Roche Diagnostics issued a voluntary recall of some test strip lots used with its CoaguChek test meter devices. The Class I recall includes more than 1.1 million packages of CoaguChek XS PT Test Strips that were distributed nationwide from January 12 to October 29, 2018.

Achieving the correct warfarin dosage is crucial, and patients need regular monitoring to test how long it takes their blood to clot. The response is measured by a blood test to check the international normalized ratio (INR). Medical device reports submitted by Roche Diagnostics to the FDA indicate that the test strips may provide results that are higher than the actual INR. As a result, some patients may be prescribed an insufficient warfarin dose or instructed to interrupt warfarin use, which may increase the risk for dangerous blood clots. Approximately 90 medical device reports and two serious patient injuries involving strokes were reported to the FDA.

Roche Diagnostics attributes the problem the test strips being recalibrated to a different international standard, which occurred earlier this year. The test strips are used with the CoaguChek XS Plus, CoaguChek XS Pro, CoaguChek XS professional, CoaguChek XS PST, and CoaguChek Vantus test meter devices.

Until they receive replacement test strips from Roche, providers were advised to rely on INR tests using blood drawn from a vein and tested by a laboratory, or to use an alternative meter.

Source: FDA, November 1, 2018 ■