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MRx CLINICAL ALERT

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HOT TOPIC: FDA APPROVES CAR-T THERAPY FOR LYMPHOMA

On October 18, 2017, the Food and Drug Administration (FDA) granted Priority approval to Kite's axicabtagene ciloleucel (Yescarta™) to treat adults with relapsed or refractory large B cell lymphoma after ≥ 2 lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL), primary mediastinal large B cell lymphoma (PMBCL), high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma. The Breakthrough therapy and Orphan drug is the second chimeric antigen receptor T cell (CAR-T) therapy in the United States (U.S.), approved on the heels of tisagenlecleucel (Kymriah™; Novartis), which is indicated to treat relapsed or refractory acute lymphoblastic leukemia (ALL) in pediatric and young adult patients. CAR-T therapy is a complex treatment in which a patient's immune T cells are harvested, modified with a chimeric antigen receptor (CAR), and then infused back into the same patient to recognize and kill cancerous B cells that express the CD19 antigen.

Axicabtagene ciloleucel is a 1-time treatment. Dosage is determined by the number of viable CAR-positive T cells. Prior to the CAR-T intravenous (IV) infusion, patients receive lymphodepleting chemotherapy. After the CAR-T infusion, patients are monitored for serious and potentially life-threatening adverse reactions, including cytokine release syndrome (CRS) and neurotoxicities. The interleukin (IL)-6 blocker, tocilizumab (Actemra®) was recently FDA approved to manage CAR-T-related CRS. CAR-T therapy is administered only at certified healthcare centers that have immediate access to tocilizumab.

In the ZUMA-1 trial, axicabtagene ciloleucel demonstrated a 72% overall response rate, with 51% of patients achieving a complete response. The median time to response was 0.9 months. Incidence of CRS ≥ grade 3 was 13% and neurotoxicities was 31%.

Over 72,000 cases of non-Hodgkin's lymphoma (NHL) are diagnosed each year in the U.S.; about 85% are B cell type and 30% are DLBCL. Gene therapies, like CAR-T, give rise to a new approach of personalized salvage therapy for patients who have few options.

FDA APPROVES NEW HERPES ZOSTER (SHINGLES) VACCINE

Shingles affects about 32% of people in the U.S., leading to roughly 1 million cases each year. Approximately 20% of these patients will develop post herpetic neuralgia (PHN), which lasts well beyond resolution of the shingles rash. On October 20, 2017, the FDA approved the second herpes zoster vaccine, Shingrix®, by GlaxoSmithKline. It is indicated to prevent herpes zoster infection in adults aged ≥ 50 years; it is not indicated for the prevention of varicella zoster virus (VZV) infection (chickenpox). Shingrix is administered as 2 intramuscular (IM) injections, given 2 to 6 months apart. The new recombinant vaccine combines an antigen, glycoprotein E, with an adjuvant

system, AS01B, to produce a robust and long-lasting immune response. Pooled clinical trial data in over 37,000 individuals showed >90% efficacy across all age groups and durability of response for over 4 years. Studies for the use of Shingrix in immunocompromised patients are ongoing.

Merck's single-dose live attenuated zoster vaccine, Zostavax®, was the first shingles vaccine in the U.S. Data demonstrate that immunity with Zostavax declines over time and decreases with age. Although, Zostavax is FDA approved for use in adults ≥ 50 years, the Centers for Disease Control and Prevention (CDC) Advisory Committee for Immunization Practices (ACIP) recommends its use only in adults ≥ 60 years of age. Furthermore, in October 2017, the ACIP recommended the use of Shingrix over Zostavax; this recommendation is advisory and awaits final CDC approval. Comparison studies of Shingrix and Zostavax are lacking. Shingrix demonstrated a similar immune response and safety profile in patients with and without prior exposure to Zostavax.

GUIDELINE UPDATE FOR USE OF NON-STATIN LIPID LOWERING AGENTS

The American College of Cardiology (ACC) updated its 2016 consensus decision pathway for the use of non-statin low-density lipotropic cholesterol (LDL-C) lowering drugs in patients with clinical atherosclerotic cardiovascular disease (ASCVD). Factors that may help identify ASCVD patients who are at higher risk for recurrent events include: age ≥ 65 years, previous myocardial infarction or nonhemorrhagic stroke, daily cigarette smoking, residual coronary artery disease with ≥ 40% stenosis in ≥ 2 large vessels, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for men and < 50 mg/dL for women, high-sensitivity C-reactive protein (hs-CRP) > 2 mg/L, and metabolic syndrome.

For adults who are taking statins for secondary prevention and have an LDL-C level of 70 to 189 mg/dL, the threshold for a net risk-reduction benefit remains to be an LDL-C reduction ≥ 50%, but targets of LDL-C < 70 mg/dL or a non-HDL-C < 100 mg/dL may be considered for all patients, regardless of comorbidity. For patients who are in this LDL-C range with comorbidities, addition of ezetimibe or a PCSK9 inhibitor (alirocumab or evolocumab) may be considered. Per the ACC, while ezetimibe may be favored in patients who require < 25% additional LDL-C reduction, a PCSK9 inhibitor may be preferred in patients who require > 25% LDL-C reduction. Moreover, ACC down-graded their recommendations on the use of bile acid sequestrants, to use only as a secondary alternative in patients intolerant to ezetimibe. ACC also included clinical diagnostic criteria for heterozygous and homozygous familial hypercholesterolemia.

BEHAVIORAL HEALTH CORNER

FDA ADVISES AGAINST WITHHOLDING OPIOID ADDICTION MEDICATIONS IN PATIENTS ON BENZODIAZEPINES

The medication-assistant treatment (MAT) drugs, buprenorphine and methadone, are prescribed to help patients combat addiction to opioids, including prescription pain medications and heroin. MAT is often used in combination with counseling and behavioral therapies, and may be required indefinitely. Patients on MAT may also be prescribed benzodiazepines or other central nervous system (CNS) depressants. Their concomitant use may pose serious health risks; however, these risks may be outweighed by the harm due to untreated opioid addition.

In August 2016, the FDA released a Drug Safety Communication urging healthcare professionals (HCP) to limit the concomitant prescribing of opioid-containing pain or cough mediations with other CNS depressants, including benzodiazepines, which may result in respiratory depression and death. Based on additional review, the FDA is advising that the use of MAT should not be withheld from patients taking CNS depressants, including benzodiazepines, and that careful medication management can reduce the risk of untoward effects of concurrent use. The FDA further states that withholding benzodiazepines or CNS depressants may lead to their use outside the treatment setting, which can lead to more serious outcomes.

If concurrent use of MAT drugs and CNS depressants are necessary, the FDA recommends the following: instruct patients of the serious risks of combined use, including overdose and death; taper benzodiazepine or CNS depressant to discontinuation, if feasible; confirm the diagnosis in patients prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and consider alternative treatments for these conditions; continue MAT as long as patients derive benefit, possibly indefinitely; coordinate care with other prescribers to ensure all are aware of the use of MAT agents; and monitor for illicit drug use. Lastly, the FDA is requiring this information be added to buprenorphine and methadone drug labels.

DRUG INFORMATION **HIGHLIGHTS**

- Influenza update: For the 2017–2018 influenza season, the CDC reports that influenza activity is low overall across the U.S. In a recent statement, the American College of Obstetricians and Gynecologists (ACOG) advise that all women, including those who are pregnant, receive the influenza vaccination. The flu shot is an essential component of prenatal care. Pregnant women are at an increased risk of serious illness and mortality due to influenza. Vaccination during pregnancy is the most effective way to protect newborns, since the vaccine is not approved for use in infants < 6 months of age.
- Two of Gilead's antiretroviral therapy (ART) agents, emtricitabine/tenofovir alafenamide (Descovy®) and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (Genvoya®), received approval for expanded use in pediatrics with HIV-1 infection. Both agents are now indicated in patients weighing ≥ 25 kg to < 35 kg in combination with other ART agents. Descovy should not be given with protease inhibitors in patients weighing < 35 kg. Complete dosing instructions are available in the product labels.
- CSL Behring's IV immune globulin 10% liquid, Privigen®, was granted a new indication for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment. Privigen is also approved for the treatment of primary humoral immunodeficiency and for chronic immune thrombocytopenic purpura in patients ≥ 15 years of age.
- The FDA granted accelerated approval to the programmed death receptor-1 (PD-1) inhibitor, nivolumab (Opdivo®), for a new indication to treat hepatocellular carcinoma (HCC) in patients previously treated with sorafenib. Dosage for HCC is 240 mg IV every 2 weeks.
- The PD-1 inhibitor, pembrolizumab (Keytruda®), received accelerated approval for a new indication to treat recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in patients whose tumors express PD-L1, as determined by an FDA-approved test, and with disease progression on or after ≥ 2 prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu targeted therapy. The dosage for this new indication is 200 mg IV every 3 weeks.
- Peramivir (Rapivab™), an influenza virus neuraminidase inhibitor, was given an expanded indication to include treatment of acute uncomplicated influenza in patients ≥ 2 years of age who have been symptomatic for up to 2 days. It was previously only indicated for use in adults.
- The agency approved golimumab for IV use (Simponi Aria®) for adults with active ankylosing spondylitis (AS) or active psoriatic arthritis (PsA). Dosage is 2 mg/kg via IV infusion at weeks 0 and 4, then every 8 weeks thereafter. Simponi Aria is also indicated in adults with rheumatoid arthritis (RA). The golimumab subcutaneous (SC) formulation (Simponi®) has an additional indication of ulcerative colitis.

PIPELINE NEWS: UPCOMING PRESCRIPTION DRUG/BIOSIMILAR USER FEE ACT (PDUFA/BsUFA) DATES

- **November 2017:** eptacog beta; recombinant IV coagulation factor VIIa; hemophilia A or B; LFB Group.
- **November 2017:** Vraylar®; cariprazine; oral atypical antipsychotic; schizophrenia maintenance; Allergan.
- **November 6, 2017:** Auryxia®; ferric citrate; oral phosphate binder; anemia in chronic kidney disease; Keryx.
- **November 8, 2017:** letermovir; oral DNA synthesis inhibitor; cytomegalovirus prophylaxis; Merck.
- **November 9, 2017:** Sprycel®; dasatinib; oral kinase inhibitor; chronic myeloid leukemia (Ph+, pediatrics); Bristol-Myers Squibb.
- **November 10, 2017:** Heplisav-B; IM hepatitis B vaccine; Dynavax.
- **November 16, 2017:** human, recombinant IV beta-glucuronidase; mucopolysaccharidosis VII; Ultragenyx.
- **November 23, 2017:** Abilify® sensor tablet; aripiprazole; oral atypical antipsychotic; schizophrenia, bipolar I disorder, major depressive disorder; Otsuka/Proteus.
- **November 30, 2017:** Alecensa®; alectinib; oral kinase inhibitor; non-small cell lung cancer (ALK+, 1st-line); Roche.
- **November 30, 2017:** buprenorphine depot; SC partial opioid agonist; opioid dependence; Indivior.
- **December 1, 2017:** Repatha®; evolocumab; SC PCSK9 inhibitor; cardiovascular/cerebrovascular event prevention; Amgen.
- **December 3, 2017:** HERMyl 1401O; trastuzumab biosimilar to Genentech's Herceptin®; IV anti-HER2 antibody; HER2+ breast, gastric, and gastroesophageal junction cancers; Biocon/Mylan.
- **December 5, 2017:** semaglutide; SC glucagon-like peptide-1 agonist; type 2 diabetes (T2DM); Novo Nordisk.
- **Quarter 4, 2017:** benralizumab; SC IL-5R inhibitor; severe uncontrolled asthma, COPD; AstraZeneca.
- **Quarter 4, 2017:** Sensipar®; cinacalcet; oral calcium-sensing receptor agonist; hyperparathyroidism in pediatrics; Amgen.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
abemaciclib	Verzenio™	The kinase inhibitor, abemaciclib (Verzenio), received Priority approval for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. It is indicated in combination with fulvestrant in women with disease progression following endocrine therapy and as monotherapy in adults with disease progression following endocrine therapy and prior to chemotherapy in the metastatic setting. The Breakthrough therapy was approved as 50 mg, 100 mg, 150 mg, and 200 mg oral tablets. The recommended dose is 150 mg twice daily when given in combination with fulvestrant, and 200 mg twice daily as monotherapy.	Eli Lilly	NDA Priority approval 09/18/2017
fluticasone propionate	Xhance™	The FDA approved fluticasone propionate nasal spray (Xhance) to treat nasal polyps in adults. The medication is delivered into the nose by actuating the pump spray into 1 nostril while simultaneously blowing into the mouthpiece of the device. Xhance delivers 93 mcg fluticasone propionate per spray. The recommended dose is 1 spray per nostril twice daily. Two sprays per nostril twice daily may also be effective in some patients. Availability is expected in the second quarter of 2018.	Optinose	NDA approval 09/18/2017
alpha-1-proteinase inhibitor	Prolastin®-C Liquid	A new alanine-stabilized alpha-1 proteinase inhibitor (Prolastin-C Liquid) has been approved for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary alpha-1-antitrypsin deficiency. Prolastin-C Liquid is an alternative dosage form to the lyophilized formulation, Prolastin®-C. The new solution, approved as a 1,000 mg/20 mL single-use vial, is given as 60 mg/kg IV once per week at a rate of 0.08 mL/kg/min (over approximately 15 minutes).	Grifols	BLA approval 09/21/2017
insulin aspart	Fiasp®	Rapid-acting insulin aspart (Fiasp) has been approved to improve glycemic control in adults with type 1 or type 2 diabetes mellitus. Fiasp is similar to Novolog®, with the addition of niacinamide to speed the absorption into the blood (approximately 2.5 minutes). Fiasp may be self-administered as a SC injection in the thigh, upper arm, or abdomen at the start of a meal or within 20 minutes after starting a meal. It may also be administered as an IV infusion under medical supervision after diluting to a 0.5 to 1 unit/mL concentration. Fiasp 100 units/mL was approved as a 3 mL FlexTouch® pen and a 10 mL multidose vial.	Novo Nordisk	NDA approval 09/29/2017

ANDA=AbbreviatedNewDrugApplication;BLA=BiologicsLicenseApplication;NDA=NewDrugApplication;sBLA=SupplementalBiologicsLicenseApplication; sNDA = Supplemental New Drug Application

RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
ascorbic acid	Ascor®	Injectable ascorbic acid (Ascor) has received approval for the short-term (up to 1 week) treatment of scurvy in adults and pediatrics ≥ 5 months of age for whom oral administration is not possible, insufficient, or contraindicated. It is not indicated to treat vitamin C deficiency that is not associated with signs and symptoms of scurvy. Ascor is approved as a 50 mL (500 mg/mL) pharmacy bulk package and must be diluted prior to use. It is intended for dispensing of single doses to multiple patients in a pharmacy admixture program. It is administered as a slow IV infusion once daily in recommended daily dosages of 50 mg (5 to < 12 months of age), 100 mg (1 to < 11 years of age), and 200 mg (≥ 11 years of age).	McGuff	NDA approval 10/02/2017
triamcinolone acetate sustained-release	Zilretta™	The corticosteroid injection, triamcinolone acetate sustained-release (Zilretta), was approved for the management of osteoarthritis pain of the knee. It is administered by an HCP as a single intra-articular 32 mg injection in the knee to provide pain relief over 12 weeks; it is not intended for repeat administration. Ziltretta is not interchangeable for other triamcinolone injectable formulations. The approved single-dose kit contains 1 vial each of triamcinolone acetate microsphere powder and diluent, and 1 sterile vial adapter.	Flexion	NDA approval 10/06/2017
pregabalin extended-release	Lyrica® CR	The FDA approved a new extended-release (ER) formulation of pregabalin (Lyrica CR) for the management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) and PHN. The recommended dosage is 165 mg administered once daily after an evening meal. Maximum daily dose is 330 mg for DPN and 660 mg for PHN. Lyrica CR is approved as 82.5 mg, 165 mg, and 330 mg ER oral tablets. Unlike the immediate-release formulation (Lyrica®), Lyrica CR is not indicated for fibromyalgia, as adjunct therapy for adults with partial onset seizures, or for neuropathic pain related to spinal cord injury.	Pfizer	NDA approval 10/11/2017
exenatide extended-release	Bydureon® BCise™	The continuous-release microsphere exenatide delivery system (Bydureon BCise) has been approved for the treatment of adults with T2DM whose blood glucose remains uncontrolled on 1 or more oral antidiabetic medications. The new formulation is designed to provide a consistent level of exenatide, a glucagon-like peptide 1 (GLP-1) agonist. Approved as a 2 mg single-dose autoinjector, Bydureon BCise is administered SC once weekly. It will be available in the first quarter of 2018.	AstraZeneca	NDA approval 10/20/2017

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References:

acc.org acog.org cdc.gov fda.gov