DECEMBER 2017

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

NEW ADULT HEPATITIS B VACCINE

A new recombinant hepatitis B virus (HBV) vaccine, Heplisav-B™, by Dynavax, has received approval by the Food and Drug Administration (FDA). This new vaccine is approved for use in adults ≥ 18 years of age as 2 intramuscular (IM) injections given 1 month apart. Heplisav-B vaccine contains a hepatitis B surface antigen plus a proprietary toll-like receptor 9 agonist that is designed to intensify the immune response.

An estimated 850,000 people are living with HBV infection in the United States (U.S.), with almost 22,000 new cases diagnosed each year. In adults, HBV is transmitted through sexual contact or sharing of drug-injection equipment with infected individuals. Acute infections may resolve on their own; however, approximately 5% of adults will develop chronic disease, which has no cure and can lead to cirrhosis, hepatocellular carcinoma, and premature death. Several antiviral agents are available to treat chronic infection and mitigate liver damage.

There are currently 2 single-antigen recombinant HBV vaccinations available in the U.S., Engerix-B® and Recombivax HB®. Both agents are indicated for all ages, from birth through adulthood. The combination vaccine, Twinrix®, provides immunization to HBV and hepatitis A virus in adults. The 3 agents are typically given as 3 IM injections at months 0, 1, and 6; although Recombivax HB has an alternate 2-dose regimen for select age groups.

In a pivotal, phase 3, non-inferiority trial in adults, Heplisav-B (2 doses) demonstrated a statistically significantly higher seroprotection rate compared to Engerix-B (3 doses) 8 weeks after the last dose (90% versus 70.5%, respectively). Seroprotection also has shown to peak earlier with Heplisav-B (at month 6) compared to Engerix-B (at month 7). While the safety profiles for both vaccines were similar and included injection site pain, fatigue, headache, and malaise, the relative risk of autoimmune events was higher with Engerix-B than with Heplisav-B (0.35% versus 0.27%, respectively).

The Centers for Disease Control and Prevention (CDC) recommends HBV vaccination for adults who are at high risk for infection due to their occupation, lifestyle, living situation, and travel to certain areas, as well as for patients with diabetes, end-stage renal disease, chronic liver disease, or human immunodeficiency virus (HIV) infection. Heplisav-B will provide another option for HBV immunization with fewer injections. It also has the potential to provide greater and earlier seroprotection as compared to the currently available Engerix-B. Heplisav-B is expected to be available in early 2018. Due to earlier safety concerns, the FDA is requiring Dynavax to conduct postmarketing studies to determine the risk of myocardial infarction (MI), new onset immune-mediated disease, herpes zoster, and anaphylaxis with Heplisav-B; study completions are projected for 2020, with interim MI data in 2019.

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Magellan Rx MANAGEMENT

ACC/AHA UPDATES HYPERTENSION GUIDELINES

The American College of Cardiology (ACC) and the American Heart Association (AHA), along with several other key medical organizations, updated guidelines for the detection, prevention, management, and treatment of hypertension. This document succeeds the prior Joint National Committee (JNC) reports, JNC-7 (2003) and JNC-8 (2014).

In these guidelines, the ACC/AHA lowered the definition of hypertension from a blood pressure (BP) of 140/90 to 130/80 mm Hg. While normal BP remains as < 120/80 mm Hg, the term "prehypertension" was eliminated. The new BP categories are: Elevated BP = systolic BP (SBP) of 120 to 129 mm Hg *and* diastolic BP (DBP) < 80 mm Hg; Stage 1 hypertension = SBP of 130 to 139 mm Hg *or* DBP of 80 to 89 mm Hg; and Stage 2 hypertension = SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg. Hypertensive crisis is defined as SBP > 180 mm Hg *or* DBP > 120 mm Hg that requires prompt medication changes or immediate hospitalization. The ACC/AHA recommends antihypertensive drug therapy for patients with Stage 1 who have a history of or are at high risk of a cardiovascular (CV) event, or have diabetes mellitus, chronic kidney disease (CKD), or calculated atherosclerotic CV disease (ASCVD) risk. Nonpharmacological therapy is preferred in adults with elevated BP and as first-line treatment in adults with Stage 1 hypertension who have an estimated 10-year ASCVD risk < 10%. The combination of nonpharmacologic and pharmacologic therapy is recommended as first-line treatment in patients with Stage 1 hypertension with an estimated 10-year ASCVD risk ≥ 10%.

Similar to earlier guidelines, ACC/AHA recommends initial treatment with thiazide diuretics, calcium channel blockers, and angiotensin converting enzyme inhibitors or angiotensin II receptor blockers. If more than 1 agent is required to meet BP goal, agents from different classes should be chosen. ACC/AHA acknowledges that combination drug products may increase medication adherence.

The lower BP threshold will likely lead to hypertension being diagnosed earlier, resulting in a higher reported rate of occurrence. ACC/AHA anticipates 46% of the U.S. population will be diagnosed with hypertension versus 32% as identified using the JNC-7 definition. While more people will be managed with lifestyle modifications, ACC/AHA predicts only a small increase in patients requiring pharmacotherapy.

BEHAVIORAL HEALTH CORNER

FIRST DIGITAL TABLET APPROVED

The first oral tablet with a digital ingestible tracking system has been approved. Aripiprazole tablet with sensor, Abilify MyCite® by Otsuka and Proteus, is FDA-approved for the treatment of adults with schizophrenia, bipolar I disorder, or major depressive disorder. The product contains a 1 mm sized event marker sensor embedded in the oral aripiprazole tablet. The sensor, which is digested by the body, contains magnesium and copper that reacts with gastric fluid to generate an electrical signal. This signal is transmitted to a wearable battery-operated patch, which then transmits the data to a mobile application (MyCite® App) allowing patients to track when the dose was taken on a compatible smartphone. With the patient's permission, caregivers and healthcare providers (HCPs) may also access the information via a web-based portal.

Patients and HCPs must receive proper training on how to use the system. It has not been established if Abilify MyCite can improve patient compliance. Use of the product to track drug ingestion in real-time or during an emergency is not recommended since detection of the dose may be delayed or not occur at all.

Abilify MyCite is approved as 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg tablets with a sensor. It is taken orally once daily, without regard to food, and should be swallowed whole. The patch is placed on the left side of the upper torso and is changed once weekly, or sooner if needed, as prompted by the app.

Dosage and labeled warnings for Abilify MyCite are similar to other aripiprazole oral formulations (tablets, oral disintegrating tablets, oral solution). Aripiprazole is also available as long-acting injectable formulations (Abilify Maintena®, Aristada®) given IM every 1 to 2 months for bipolar 1 disorder and/or schizophrenia. Unlike the other oral formulations, Abilify MyCite is not indicated for use in pediatrics or for irritability associated with autistic disorder, Tourette's disorder, or agitation related to schizophrenia or bipolar mania.

This novel drug-device system may provide valuable information to help decision making for physicians and their patients with serious mental illness. A limited roll-out of Abilify MyCite to select health plans and HCPs is planned to enable the manufacturer to solicit and respond to feedback from stakeholders.

DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2017–2018): The CDC reports that influenza activity increased during the week ending November 18, 2017, with several flu activity indicators higher than usual for this time of year. Two states reported widespread flu activity and 26 states reported regional or local activity.
- The FDA approved a new indication for dasatinib (Sprycel®) to treat pediatric patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. It is also indicated in select adults with Ph+ CML. Dosage in pediatrics is weight-based.
- The CD30-directed antibody-drug conjugate, brentuximab vedotin (Adcetris®), garnered a new indication in adults with primary cutaneous anaplastic large cell lymphoma (ALCL) or CD30-expressing mycosis fungoides after systemic therapy. It is also indicated for classical Hodgkin lymphoma and systemic ALCL, in select patients.
- The FDA granted a new indication for ferric citrate (Auryxia®) tablets, a phosphate binder, as an iron replacement for the treatment of iron deficiency anemia in adults with CKD not on dialysis. Starting dose is 1 gram 3 times daily with meals. Auryxia is also indicated for hyperphosphatemia in patients with CKD on dialysis.
- Rivaroxaban (Xarelto®), an oral anticoagulant, was approved as 10 mg once daily to reduce the risk of venous thromboembolism (VTE) recurrence in patients at continued risk after ≥ 6 months of standard anticoagulation treatment.
- The anticonvulsant lacosamide (Vimpat®) was granted an expanded indication for use in patients ≥ 4 years of age as monotherapy or adjunctive therapy for partial-onset seizures (POS). Previously, it only was approved in those ≥ 17 years of age for POS. Pediatric dosing is weight-based, given orally twice daily as a tablet or solution. The IV formulation has not been studied in pediatrics.
- The FDA awarded full approval to alectinib (Alecensa®), an oral anaplastic lymphoma kinase (ALK) inhibitor, for first- and second-line treatment of ALK+ metastatic non-small cell lung cancer (NSCLC), as detected by an FDA-approved test. Previously, it had received Accelerated approval as second-line therapy in patients who failed or were intolerant to crizotinib.
- The complement inhibitor eculizumab (Soliris®) gained a new indication for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive. The dosage for gMG is 900 mg via IV infusion weekly for 4 weeks, 1,200 mg 1 week later, then 1,200 mg every 2 weeks thereafter. Eculizumab is also approved to treat paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome.
- The FDA expanded the indication for the interleukin (IL)-12 and -23 inhibitor ustekinumab (Stelara®) for the treatment of moderate to severe plaque psoriasis to include patients ages 12 to 17 years who are candidates for photo or systemic therapy. Dosage in pediatrics is weight-based.

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

- **December 2017:** Bosulif®; bosutinib; oral tyrosine kinase inhibitor; Ph+ CML (1st-line); Pfizer.
- **December 2017:** ciprofloxacin dry powder for inhalation; fluoroquinolone; noncystic fibrosis bronchiectasis; Bayer.
- **December 2017:** Corlanor®; ivabradine; oral hyperpolarization-activated cyclic nucleotide-gated channel blocker; heart failure in pediatrics; Amgen.
- **December 2017:** ertugliflozin; oral sodium-glucose linked transporter 2 (SGLT2) inhibitor; type 2 diabetes (T2D); Pfizer/Merck.
- **December 2017:** ertugliflozin/sitagliptin; oral SGLT2 inhibitor + dipeptidyl peptidase-4 (DPP-4) inhibitor; T2D; Pfizer/Merck.
- **December 2017:** ertugliflozin/metformin; oral SGLT2 inhibitor + biguanide; T2D; Pfizer/Merck.
- **December 2017:** PF-06438179; infliximab, biosimilar to Janssen's Remicade®; IV tumor necrosis factor-α inhibitor; rheumatoid arthritis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis; Pfizer.
- **December 2017:** Xeljanz®/Xeljanz XR®; tofacitinib; oral Janus kinase inhibitor; psoriatic arthritis; Pfizer.
- **December 2, 2017:** Repatha®; evolocumab; SC proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor; major CV event risk reduction; Amgen.
- **December 5, 2017:** semaglutide; SC glucagon-like peptide-1 (GLP-1) agonist; T2D; Novo Nordisk.
- **December 15, 2017:** glycopyrrolate bromide; inhaled long-acting muscarinic antagonist; chronic obstructive pulmonary disease (COPD); Sumitomo Dainippon.
- **December 22, 2017:** sirolimus; intraocular immunosuppressant; uveitis; Santen.
- **December 29, 2017:** macimorelin; oral ghrelin receptor agonist; adult growth hormone deficiency; Aeterna Zentaris.
- **January 12, 2018:** voretigene neparvovec; intraocular gene therapy; inherited retinal disorder; Spark.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
acalabrutinib	Calquence®	A Bruton tyrosine kinase inhibitor, acalabrutinib (Calquence), was approved under the Accelerated approval pathway for the treatment of mantle cell lymphoma (MCL) in adult patients who have received at least 1 prior therapy; continued approval is contingent upon results of confirmatory trials. Approved as a 100 mg oral capsule, the recommended dose is 100 mg every 12 hours, swallowed whole, with or without food. Acalabrutinib was granted Breakthrough therapy and Orphan drug status.	Acerta	NDA Accelerated Priority approval 10/31/2017
latanoprostene bunod	Vyzulta™	Latanoprostene bunod 0.024% ophthalmic solution (Vyzulta) was approved to reduce intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. It is the first prostaglandin analog that uses nitric oxide (NO) as a metabolite, which is theorized to increase aqueous outflow. It is administered as 1 drop into the affected eye(s) once daily in the evening.	Bausch and Lomb	NDA approval 11/02/2017
vemurafenib	Zelboraf™	Vemurafenib (Zelboraf), a kinase inhibitor, received a new indication as the first drug approved for the treatment of patients with Erdheim-Chester disease (ECD) with BRAF V600 mutation. It is also approved for select patients with melanoma. The recommended dose for all indications is 960 mg orally twice daily taken approximately 12 hours apart, with or without a meal. Vemurafenib received Breakthrough therapy and Orphan drug status for ECD.	Genentech	sNDA Priority approval 11/06/2017
letermovir	Prevymis™	The FDA approved letermovir (Prevymis), a non-nucleoside cytomegalovirus (CMV) inhibitor, for the prophylaxis of CMV infections and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). The Agency granted Orphan drug status to letermovir for this indication. The recommended dosage is 480 mg administered IV or orally once daily, initiated on day 0 to 28 post-transplantation (before or after engraftment), and continued through day 100 post-transplantation. If it is co-administered with cyclosporine, the oral or IV dose should be decreased to 240 mg once daily. It was approved as 240 mg and 480 mg strengths as tablets and injection for IV infusion.	Merck Sharp Dohme	NDA Priority approval 11/08/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
aprepitant	Cinvanti™	Aprepitant (Cinvanti), a polysorbate 80-free IV formulation of the substance P/neurokinin-1 (NK 1) receptor antagonist, is indicated for the treatment of acute and delayed nausea and vomiting associated with initial and repeat courses of highly- (HEC) and moderately- (MEC) emetogenic cancer chemotherapy. Data demonstrated bioequivalence of Cinvanti to Emend® IV (fosaprepitant). When given with HEC, Cinvanti is given as a single dose of 130 mg IV over 30 minutes on day 1, prior to chemotherapy. For MEC, Cinvanti is given as part of a 3-day regimen as 100 mg on day 1 IV over 30 minutes, prior to chemotherapy, plus aprepitant 80 mg capsule (Emend®) given orally on days 2 and 3. Cinvanti is approved as a single-dose vial (SDV) containing 130 mg of aprepitant emulsion for injection.	Heron	NDA approval 11/09/2017
benralizumab	Fasenra™	Benralizumab (Fasenra), an IL-5 receptor alpha-directed cytolytic monoclonal antibody (IgG1, kappa), was approved for add-on maintenance treatment of patients aged ≥ 12 years with severe asthma of eosinophilic phenotype. It is not indicated for the treatment of other eosinophilic conditions or relief of acute bronchospasm or status asthmaticus. Approved as a 30 mg/mL solution in a single-dose prefilled syringe, it is administered as 30 mg SC every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter.	AstraZeneca	BLA approval 11/14/2017
vestronidase alfa-vjbk	Mepsevii™	The FDA granted approval to the recombinant human lysosomal beta-glucuronidase, vestronidase alfa-vjbk (Mepsevii), for the treatment of pediatric and adult patients with the rare genetic lysosomal storage disorder, mucopolysaccharidosis VII (MPS VII), also known as Sly syndrome. This Orphan drug's effect on central nervous system (CNS) manifestations has not been determined. The dosage is 4 mg/kg via IV infusion every 2 weeks. A boxed warning of anaphylaxis advises HCPs to closely monitor patients during and for 60 minutes after the infusion.	Ultragenyx	BLA approval 11/15/2017
emicizumab-kxwh	Hemlibra®	Emicizumab-kxwh (Hemlibra), a bispecific factor IXa- and factor X-directed antibody, was approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with factor VIII inhibitors. Recommended dose is 3 mg/kg SC once weekly for the first 4 weeks, then 1.5 mg weekly thereafter. This first-in-class agent was designated as a Breakthrough therapy and Orphan drug by the FDA. It is approved as SDVs of 30 mg/mL, 60 mg/0.4 mL, 105 mg/0.7 mL, and 150 mg/mL.	Genentech	BLA Priority approval 11/16/2017

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References:

acc.org cdc.gov fda.gov