JANUARY 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

EDITORIAL STAFF

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HOT TOPIC: FIRST GENE THERAPY APPROVED FOR INHERITED RETINAL DISEASE (IRD)

On December 19, 2017, the Food and Drug Administration (FDA) granted Priority approval for Spark Therapeutics' breakthrough gene therapy, voretigene neparvovec-rzyl (Luxturna™), for the treatment of confirmed biallelic *RPE65* mutation-associated retinal dystrophy in patients with viable retinal cells. The Orphan drug delivers a functional copy of the *RPE65* gene directly to the eye, allowing regeneration of visual pigment essential for vision. Voretigene neparvovec-rzyl is administered via subretinal injection under sterile conditions by a surgeon skilled in performing intraocular procedures. A 1-time dose of 1.5 x 10^{11} vector genomes is administered in each eye on separate days.

In a phase 3 study (n=31), voretigene neparvovec-rzyl resulted in significant improvements in the patient's ability to complete an obstacle course at low light levels when compared to placebo 1 year after the dose (mean bilateral multi-luminance mobility testing [MLMT] difference of 1.6). Improved vision was detected within about 30 days. However, voretigene neparvovec-rzyl did not meet statistical significance in improvement in visual acuity or quality of life measures. Durability of response has been demonstrated for up to 4 years in phase 1 studies. Common adverse reactions included transient ocular inflammation, transient elevated intraocular pressure (IOP), cataracts, and intraoperative retinal tears.

It is estimated that 1,000 to 2,000 people in the United States (U.S.) have *RPE65*-mediated IRD. Leber congenital amaurosis is the most severe type in which blindness may be present at birth or early childhood. The wholesale acquisition price of voretigene neparvovec-rzyl is $425,000 per eye. The launch of voretigene neparvovec-rzyl is expected in late first quarter of 2018.

STANDARDS OF MEDICAL CARE IN DIABETES 2018

The American Diabetes Association (ADA) has updated their Standards of Medical Care in Diabetes. This key clinical practice guidance will be revised *online* more often than once yearly to keep up to date with the rapidly changing field of diabetes. Select revisions are highlighted here.

Due to potential limitations that can affect hemoglobin A1c (HbA1c) testing, recommendations to clarify the appropriate use of HbA1c testing were added. Recommendations were updated for screening for prediabetes and type 2 diabetes mellitus (T2DM) in obese or overweight patients < 18 years old who have at least 1 additional risk factor. The recommendation for continuous glucose monitoring in adults with type 1 diabetes mellitus (T1DM) has been expanded to all patients ≥ 18 years of age who are not meeting glycemic targets. Recent cardiovascular (CV) outcomes trial data were incorporated, including guidance for preferential use

of agents proven to reduce major CV events and mortality (currently empagliflozin [Jardiance®] or liraglutide [Victoza®]) in adults with T2DM and atherosclerotic CV disease. A table summarizing drug- and patient-specific factors that could impact selection of pharmacologic agent was redesigned to show comparative drug information.

FDA FINAL GUIDANCE FOR INDUSTRY ON ABUSE-DETERRENT GENERICS

The FDA issued their final guidance for evaluating the abuse deterrent potential of generic solid oral opioid drug products to aid the drug industry when constructing an abbreviated new drug application (ANDA) listing an opioid abuse-deterrent formulation (ADF) as the reference listed drug (RLD). In addition to the usual ANDA approval process, applicants must show that the generic is no less abuse deterrent than the RLD with respect to all the potential routes of abuse (e.g., ingestion, injection, insufflation, and inhalation). The guidance document outlines studies, including comparative *in vitro* and pharmacokinetic evaluations, which should be submitted with the ANDA in order to meet this requirement. General principles recommended by the FDA for the comparative evaluation of ADFs include the following: a tier-based approach with a limited number of tests that allows for hierarchical testing; a performance-based evaluation of abuse deterrence (e.g., the design of abuse deterrence does not need to be identical); and testing of the most effective means for physical manipulation of the drug product.

MANAGING BLEEDING IN PATIENTS ON ORAL ANTICOAGULANTS

It is estimated that over 6 million patients in the U.S. are treated with anticoagulants, placing them at increased risk of bleeding and increased morbidity and mortality. The American College of Cardiology (ACC) recently released its Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants to address the clinical problem of acute bleeding management for patients treated with either direct acting oral anticoagulants (OAC) or vitamin K antagonists. The consensus document defines a bleed as major if it is at a critical site (e.g., intracranial), causes a hemoglobin drop ≥ 2 g/dL, is associated with hemodynamic compromise, or requires transfusion of ≥ 2 units of red blood cells. All other bleeds are considered non-major. Regardless of the severity of the bleed, the pathway recommends that measures be initiated to control bleeding. For major bleeds, the pathway recommends interruption of OAC and oral antiplatelet therapy. Reversal of OAC effect is recommended for the majority of patients with major bleeding, if a reversal agent is available. For patients with a non-major bleed, the pathway does not routinely recommend reversal of the OAC; rather, the decision to hold the OAC should be based on patient-specific factors, including the nature of the bleed, intensity of anticoagulation, need for invasive procedures, and bleeding risk of the patient. Once the patient has stabilized after a bleeding event on an OAC, the patient's indication for the OAC should be reassessed to determine if the risks versus benefits warrant continued anticoagulation based on established clinical practice guidelines.

BEHAVIORAL HEALTH CORNER

FIRST ONCE-MONTHLY INJECTION TO TREAT OPIOID USE DISORDER

On November 30, 2017, the FDA approved the partial opioid agonist Sublocade™ as the first subcutaneous (SC), once-monthly injectable depot buprenorphine. Granted Priority review, Sublocade is indicated for the treatment of moderate-to-severe opioid use disorder (OUD) in adults on a stable dose of a transmucosal buprenorphine-containing product for ≥ 7 days. Sublocade, a Schedule III controlled substance, should only be administered by a healthcare professional (HCP) in conjunction with a complete treatment program that includes counseling and psychosocial support. Starting dosage is 300 mg SC monthly for 2 doses, followed by 100 mg monthly thereafter. Maintenance doses up to 300 mg monthly may be considered in select patients.

The safety and efficacy of Sublocade were established in clinical studies including 848 adults with a diagnosis of moderate-to-severe OUD. After stabilization on buprenorphine/naloxone sublingual film, patients were switched to monthly doses of Sublocade or placebo. Urine drug screening and self-reported illicit opioid use during the 6-month treatment period measured response. Sublocade-treated patients had more weeks without positive urine tests or self-reported opioid use; a higher proportion also had no evidence of illicit opioid use. Common adverse effects with Sublocade included constipation, nausea, vomiting, and abnormal liver enzymes. A boxed warning informs of the risks of intravenous (IV) self-administration; thus, it must be prescribed and dispensed as part of a Risk Evaluation and Mitigation Strategy (REMS) program to ensure that it is not distributed directly to patients. Sublocade is available as 100 mg/0.5 mL and 300 mg/1.5 mL prefilled syringes.

DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2017-2018): During December 2017, influenza activity increased sharply in the U.S. The number of states reporting widespread activity tripled to 36. The Centers for Disease Control and Prevention (CDC) issued a Health Advisory informing the public of a predominance of influenza A(H3N2) activity, which historically has been associated with more hospitalizations and deaths in people ≥ 65 years of age and young children, and lower influenza vaccine effectiveness (VE). In the 2016-2017 flu season, VE against influenza A(H3N2) in the U.S was 32% and similar VE is expected this season. CDC advises that all hospitalized patients and high-risk patients with suspected influenza should be treated as soon as possible with oseltamivir, zanamivir, or peramivir. The CDC expects the supply of all 3 agents will meet seasonal demand.
- The FDA approved Mylan's trastuzumab-dkst (Ogivri™), the first biosimilar to trastuzumab (Genentech's Herceptin®). Trastuzumab-dkst is approved for the treatment of patients with HER2-overexpressing breast or metastatic gastric or gastroesophageal junction cancers.
- The third biosimilar to Janssen's infliximab (Remicade®), infliximab-qbtx (Ixifi™) by Pfizer, was approved. Other biosimilars to infliximab available in the U.S. are infliximab-dyyb (Inflectra®; Celltrion/Pfizer) and infliximab-abda (Renflexis™; Merck). All 3 biosimilars are granted the same indications as the reference product, except for the treatment of pediatric ulcerative colitis, which is not an eligible indication until September 2018 due to Orphan drug exclusivity. Pfizer does not appear to have current plans to launch Ixifi in the U.S.
- In December 2017, Teva and Greenstone launched the first generics for sildenafil (Viagra®) indicated for male erectile dysfunction. Approved tablet strengths are 25 mg, 50 mg, and 100 mg.
- Sanofi-Aventis' insulin lispro U-100 (Admelog®) is the first short-acting insulin follow-on product approved in the U.S.; its reference product is Eli Lilly's Humalog®. Admelog is indicated to improve glycemic control in patients aged ≥ 3 years with T1DM and adults with T2DM. Unlike Humalog, safety and efficacy of Admelog have not been established in patients < 3 years of age with T1DM, or < 18 years with T2DM. Admelog is expected to be available in early 2018 as a 100 units/mL multi-dose vial and SoloStar® prefilled pen.
- The FDA approved a new indication for the proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor, evolocumab (Repatha®), to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established CV disease. The agency also revised the primary hyperlipidemia indication in adults to read as adjunct to diet, alone or in combination with other lipid-lowering therapies, to reduce low-density lipoprotein cholesterol. Dosage for both indications is 140 mg SC every 2 weeks or 420 mg SC once monthly.
- The anti-CD20 antibody obinutuzumab (Gazyva®) was granted a new indication in combination with chemotherapy for the treatment of adults with previously untreated stage II bulky, III or IV follicular lymphoma. Dosing is 1,000 mg IV on days 1, 8, and 15 of cycle 1, then 1,000 mg on day 1 of cycles 2 to 6 or 2 to 8. In patients achieving at least a partial remission, it is continued as monotherapy as 1,000 mg every 2 months for up to 2 years.
- An expanded indication was approved for the estrogen receptor antagonist, fulvestrant (Faslodex®), for HR(+), HER2(-) advanced or metastatic breast cancer in combination with abemaciclib in women with disease progression after endocrine therapy. Recommended dose is 500 mg intramuscularly (IM) into the gluteal area on days 1, 15, 29, and once monthly thereafter.

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

- **January 19, 2018:** buprenorphine depot; SC partial opioid agonist; substance use disorder; Apple Tree.
- **January 26, 2018:** Linhaliq; ciprofloxacin; inhaled fluoroquinolone; bronchiectasis; Grifols.
- **January 26, 2018:** Lutathera; lutetium lu 177 dotatate; IV somatostatin analog; neuroendocrine tumors; Advanced Accelerator Applications.
- **January 26, 2018:** Trulance®; plecanatide; oral guanylate cyclase stimulant; irritable bowel syndrome with constipation; Synergy.
- **February 2, 2018:** Feraheme®; ferumoxytol; IV iron supplement; iron deficiency anemia (resistant/intolerant to oral iron); AMAG.
- **February 2, 2018:** Xgeva®; denosumab; SC RANK ligand inhibitor; prevention of bone fracture in patients with multiple myeloma; Amgen.
- **Quarter 1, 2018:** Avycaz®; ceftazidime/avibactam; IV cephalosporin/beta-lactam antibiotics; nosocomial pneumonia; Allergan.
- **Quarter 1, 2018:** Lynparza®; olaparib; oral PARP inhibitor; germline BRCA(+), HER2(-) breast cancer; AstraZeneca.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
aliskiren hemifumarate	Tekturna®	An oral 37.5 mg pellet formulation of the renin inhibitor aliskiren (Tekturna) was approved for the treatment of hypertension in patients ≥ 6 years of age. The contents of the capsule are emptied onto a spoon and administered by mouth followed by milk (dairy- or soy-based) or water. Alternatively, the pellets can be mixed with 1 or more teaspoons of water, vanilla pudding, or dairy- or soy-based vanilla ice cream or milk. The pellets should not be chewed or crushed. The starting dose is 75 mg once daily for children weighing 20 kg to < 50 kg (maximum 150 mg/day). The recommended dose for children ≥ 50 kg and adults is 150 mg once daily (maximum 300 mg/day). It is not recommended for use in children < 20 kg.	Noden	NDA Priority approval 11/14/2017
sunitinib maleate	Sutent®	The FDA approved a new indication for the kinase inhibitor, sunitinib maleate (Sutent), for adjuvant treatment of adults at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy. It is administered as nine 6-weeks cycles, each cycle as 50 mg orally once daily for 4 weeks, followed by 2 weeks off-treatment. It is also indicated in select patients with gastrointestinal stromal tumors or neuroendocrine tumors.	Pfizer	sNDA approval 11/16/2017
epinephrine	Auvi-Q®	The first epinephrine 0.1 mg auto-injector, Auvi-Q, was approved and is indicated for patients who weigh 7.5 kg to 15 kg. The new strength uses a shorter needle that is appropriate for infants and small children. The 0.15 mg and 0.3 mg strengths are indicated for patients weighing 15 kg to 30 kg and ≥ 30 kg, respectively. All Auvi-Q strengths are FDA approved for the emergency treatment of allergic reactions (Type I) including anaphylaxis. Availability of the 0.1 mg strength is expected in the first half of 2018.	Kaleo	sNDA approval 11/17/2017
dolutegravir/ rilpivirine	Juluca®	Juluca, a combination tablet containing dolutegravir (50 mg), an integrase strand transfer inhibitor (INSTI), and rilpivirine (25 mg), a non-nucleoside reverse transcriptase inhibitor (NNRTI), was approved as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. It can be used to replace the current antiretroviral (ARV) regimen in patients who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ARV regimen for ≥ 6 months with no history of treatment failure and no known substitutions associated with resistance to its individual components. It is taken once daily with a meal. A dosing adjustment is required when used with rifabutin.	Viiv	NDA Priority approval 11/21/2017

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
raltegravir	Isentress®	The integrase inhibitor, raltegravir (Isentress) received an expanded indication, in combination with other ARV agents, to treat HIV-1 infection in neonates 0 to < 4 weeks of age weighing ≥ 2 kg. Guidance for weight-based dosing of the oral suspension is provided in the product label.	Merck	sNDA approval 11/22/2017
citric acid/ magnesium oxide/ sodium picosulfate	Clenpiq™	The FDA approved Clenpiq for colon cleansing as a preparation for colonoscopy in adults. It is a combination of anhydrous citric acid (12 g) and magnesium oxide (3.5 g), which forms magnesium citrate, and sodium picosulfate (10 g). The osmotic and stimulant laxative requires no dilution prior to administration. Clenpiq is administered orally as 2 doses of 160 mL each (2 bottles total), either as a split-dose regimen or the day-before method.	Ferring	NDA 505(b)(2) approval 11/28/2017
clobetasol propionate	Impoyz™	Clobetasol 0.025% cream (Impoyz) was approved as a treatment of moderate to severe plaque psoriasis in adults. The topical corticosteroid is applied to affected skin twice daily for up to 2 consecutive weeks. Avoid use on the face, scalp, axilla, groin, or other intertriginous areas. Extended use and larger than recommended dose can lead to systemic effects that may appear as Cushing's syndrome, hyperglycemia, and glucosuria.	Promius	NDA 505(b)(2) approval 11/28/2017
ixekizumab	Taltz®	Ixekizumab (Taltz®), an interleukin-17A antagonist, received a new indication for the treatment of adults with active psoriatic arthritis. The recommended dose is 160 mg SC (two 80 mg injections) for 1 dose, followed by 80 mg every 4 weeks, administered alone or in combination with a conventional disease modifying antirheumatic drug (DMARD). If plaque psoriasis (PSO) is also present, the dosing regimen for PSO should be used (160 mg for 1 dose, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks).	Eli Lilly	sNDA approval 12/01/2017
glycopyrrolate	Lonhala™ Magnair™	The FDA approved glycopyrrolate inhalation solution (Lonhala Magnair), the first nebulized, long-acting muscarinic antagonist, for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The Magnair delivery device uses the eFlow® technology system that allows for normal breathing during administration. It is dosed as 25 mcg (1 vial) via oral inhalation over 2 to 3 minutes twice daily. Launch is planned in early 2018.	Sunovion	NDA 505(b)(2) approval 12/05/2017

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
semaglutide	Ozempic®	The agency approved semaglutide (Ozempic), a glucagon-like peptide 1 (GLP-1) receptor agonist, as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The recommended starting dose is 0.25 mg SC once weekly. After 4 weeks, the weekly dose may be increased to 0.5 mg, and then to 1 mg after another 4 weeks, if needed. Semaglutide is approved as a 2 mg/1.5 mL solution for injection in a single-use pen that delivers 0.25 mg, 0.5 mg, or 1 mg per injection. Availability is expected in the first quarter of 2018.	Novo Nordisk	NDA approval 12/05/2017
mometasone furoate	Sinuva™	Mometasone furoate (Sinuva), a corticosteroid-eluting sinus implant, was granted approval for the treatment of nasal polyps in adult patients who have had ethmoid sinus surgery. It is implanted by a physician trained in otolaryngology into the nasal cavity and delivers drug for 90 days; it may be removed earlier by an HCP, as deemed appropriate. Repeat use of the implant, which contains 1,350 mcg of mometasone furoate, has not been studied. Launch is planned in the second quarter of 2018.	Intersect ENT	NDA 505(b)(2) approval 12/08/2017
ozenoxacin	Xepi™	The topical quinolone antimicrobial, ozenoxacin (Xepi), was approved for the treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in patients ≥ 2 months of age. The 1% cream is applied topically to the affected area twice daily for 5 days. Availability of 10 g, 30 g, and 45 g tubes is expected in the first quarter of 2018.	Medimetriks	NDA approval 12/11/2017
mepolizumab	Nucala®	The FDA approved an additional indication for the interleukin-5 antagonist monoclonal antibody, mepolizumab (Nucala), to treat adults with eosinophilic granulomatosis with polyangiitis (EGPA). It is the first medication approved for EGPA. It is also indicated as an add-on, maintenance treatment of patients ≥ 12 years old with severe asthma of eosinophilic phenotype. The dosage for EGPA is 300 mg as 3 separate 100 mg injections administered SC once every 4 weeks by an HCP.	GlaxoSmithKline	sBLA approval 12/12/2017
netarsudil	Rhopressa®	The agency granted approval for the Rho kinase inhibitor, netarsudil (Rhopressa), for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension. The 0.2 mg/mL ophthalmic solution is administered as 1 drop into the affected eye(s) once daily in the evening. Anticipated launch is in the first quarter of 2018.	Aerie	NDA Priority approval 12/18/2017

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References:

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