SEPTEMBER 2019

MRx CLINICAL ALERT

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HOT TOPIC: ZOLGENSMA® DATA TAMPERING

On May 24, 2019, the United States (US) Food and Drug Administration (FDA) approved the gene therapy onasemnogene abeparvovec-xioi (Zolgensma) for the treatment of spinal muscular atrophy (SMA), a leading cause of infant mortality. Subsequently, the manufacturer of Zolgensma, Avexis/Novartis, notified the FDA of alterations to certain animal testing data that was submitted to the FDA for review for product approval. The affected data was used to support the Zolgensma production process. Although the manufacturer was aware of the data manipulation prior to FDA approval, they did not inform the FDA until after approval. The FDA is carefully examining the matter, including findings from a recent facility inspection; however, the Agency believes that Zolgensma should remain on the market at this time as evidence in humans is compelling and demonstrates a beneficial overall safety and efficacy profile. The FDA could apply civil or criminal penalties against the manufacturer if they deem appropriate.

In April 2019, the Institute for Clinical and Economic Review (ICER) issued an Evidence Report on the treatment of SMA, including use of Zolgensma (updated May 2019). Following the FDA's statement, ICER noted the identified animal data did not influence their assessment; however, they are monitoring the situation and will publish an updated report if necessary.

WHO STRONGLY ENDORSES DOLUTEGRAVIR FOR HIV

The World Health Organization (WHO) updated their guidelines for the treatment of human immunodeficiency virus (HIV)-1 infection. In general, WHO advises that first-line antiretroviral (ARV) therapy for HIV-1-positive adults should consist of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) or an integrase inhibitor (INSTI). Previously, efavirenz (EFV), an NNRTI, was the preferred add-on to NRTIs in all adult HIV-positive patients; however, WHO now recommends the INSTI dolutegravir (DTG) (Tivicay®; Viiv) as part of preferred first- and second-line ARV therapy (ART) for all patients with HIV, including women who are pregnant or of reproductive potential. This new recommendation is based on 2 large clinical trials comparing safety and efficacy of DTG and EFV and on new data from a 5-year surveillance study, which demonstrated a lower risk of neural tube defects (NTD) with maternal ART exposure than suggested in earlier studies. Notably, the surveillance study found that the incidence of NTDs with ART used at conception was 0.3% with DTG-containing ART compared to 0.1% with any non-DTG regimen and 0.04% with an EFV-containing regimen. Also, the rate of NTD was 0.03% when DTG was started during pregnancy. While the reported risk of NTD with DTG used at conception is higher than with other ARVs, it has declined and ongoing studies will further clarify the NTD risk. Moreover, advantages of DTG over EFV include higher viral suppression and lower

risks of HIV drug resistance and drug-drug interaction. This recommendation comes at a time of increasing pretreatment NNRTI resistance, creating demand for access to alternative non-NNRTI ARVs.

Dolutegravir is a component of Viiv's fixed-dose, oral, 2-drug regimens, DTG/lamivudine (Dovato®) and DTG/rilpivirine (Juluca), and its 3-drug regimen abacavir/DTG/lamivudine (Triumeq®).

MIGRAINE PREVENTION IN PEDIATRICS

The American Academy of Neurology (AAN) and American Headache Society (AHS) issued new joint guidelines on pharmacologic treatment for the prevention of migraines in pediatric patients. This marks an update to the AAN 2004 guidelines. Key recommendations (Level B, unless otherwise noted) include counseling for patients and caregivers on the effects of lifestyle and behavioral factors (e.g., sleep habits and tobacco use) on migraine frequency. The role of preventative treatment should be discussed for patients with frequent headache and/or migraine-related disability, including for those with medication overuse. In clinical trials, most agents studied for pediatric migraine prevention failed to demonstrate a reduction by ≥ 50% in headache frequency over placebo; propranolol may possibly achieve this result. Despite the failure to demonstrate superiority over placebo, short-term pharmacotherapy (≥ 2 months) may be considered in patients who could benefit from preventative treatment. Patients and caregivers should be apprised of the risks associated with preventative therapy in adolescents, including suicidality with amitriptyline and teratogenic effects with topiramate and valproate (Level A). Medication effectiveness and side effects should be monitored periodically (Level A), and patients and caregivers should be counseled on the benefits and risks of discontinuing effective therapy. Lastly, the AAN/AHS advise that patients should be screened for mood and anxiety disorders and treated as indicated.

STANDARDS OF MEDICAL CARE IN DIABETES FOCUSED UPDATE

The American Diabetes Association (ADA) updated their 2019 Standards of Medical Care in Diabetes, a "living" document that is revised with new pertinent information, as appropriate, in addition to their full annual review and update. One key revision was the addition of liraglutide (Victoza®), a glucagon-like peptide-1 receptor agonist (GLP-1RA), as an option for pediatric patients ≥ 10 years of age with type 2 diabetes mellitus (T2DM); this follows liraglutide's expanded FDA approval for this age group. Findings from the Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND) clinical trial, which demonstrated major cardiovascular (CV) event risk reduction with the GLP-1RA dulaglutide (Trulicity®) in patients with and without established CV disease, were also incorporated.

Revisions regarding continuous glucose monitoring (CGM) were also added. Real-time CGM devices that alert the user of abnormal glucose levels are recommended in adults with uncontrolled type 1 diabetes mellitus (T1DM) on an intensive insulin regimen. These devices may also be considered in patients who experience frequent hypoglycemic events or who are unaware of these events. An intermittently scanned CGM can be considered in adults who need frequent glucose testing; this method does not provide alerts for abnormal blood glucose levels. A table to help standardize CGM clinical care metrics (e.g., average glucose level and proportion of time in hypoglycemia, hyperglycemia, or target range) was also added to the Standards.

CDC GUIDANCE ON TUBERCULOSIS (TB) IN HEALTHCARE PERSONNEL

The Centers for Disease Control and Prevention (CDC) published guidelines on the screening, testing, and treatment of TB in US healthcare personnel (HCP). The CDC working group systematically reviewed evidence and issued key revisions to their 2005 guidance on preventing transmission of *Mycobacterium tuberculosis*. At baseline (preplacement), the CDC continues to recommend screening of all HCP, which includes a symptom evaluation and test (interferon-gamma release assay [IGRA] or tuberculin skin test [TST]) for those without prior TB disease or latent TB, although they added a recommendation for individual TB risk assessment. The CDC also continues to recommend consideration of serial screening in HCP without latent TB on an individualized basis in select groups with known exposure, occupational risk, or ongoing evidence of TB transmission (e.g., pulmonologists, respiratory therapists, emergency department personnel following prior transmission) and education for all HCP; however, the CDC no longer recommends routine serial TB testing following baseline evaluation. After exposure, the CDC continues to recommend symptom evaluation for all HCP, including a TB test (IGRA or TST) once exposure is recognized and again 8 to 10 weeks later if the initial test is negative. Unless contraindicated, the CDC now encourages treatment for all HCP with untreated latent TB, using recommended regimens on the CDC TB website; previously, they had recommended referral to determine appropriateness of treatment. The guidance details additional information on the evaluation and treatment of HCP with positive test results.

DRUG INFORMATION **HIGHLIGHTS**

- The intermittent shortage of epinephrine auto-injectors persists nationwide in the US. Backorders with periodic shipments to distributors continue for Impax's authorized generic (AG) versions of the discontinued Adrenaclick® and Mylan's Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and their respective AGs. Availability continues for Kaleo's Auvi-Q® (3 strengths) and Teva's generic version of Epipen (limited supply). Adamis' Symjepi® has launched in both approved strengths (0.15 mg and 0.3 mg) to retail pharmacies nationwide. Also, Teva's AB-rated generic for Epipen Jr became available in the US in August 2019.
- The FDA approved a prefilled syringe (PFS) for Regeneron's aflibercept (Eylea®), designed to reduce preparation steps of the product that is administered by intravitreal injection to treat macular degeneration, macular edema, and diabetic retinopathy. The PFS containing 2 mg/0.05 mL is expected to be available in 2019; a 2 mg single-dose vial (SDV) is already marketed in the US.
- Pfizer is voluntarily recalling 2 lots of the antimigraine medication Relpax® (eletriptan) 40 mg tablets due to potential microbial contamination, specifically genus *Pseudomonas* and *Burkholderia*. Patients who consume affected product may experience temporary gastrointestinal (GI) distress. Moreover, while the risk is low for the general population, there is a potential for serious or life-threatening infection caused by the spread of bacteria from the GI tract to the blood. To date, no adverse events have been reported.
- Jubilant Cadista issued a consumer-level, voluntary recall of 1 lot of oral contraceptive tablets containing drospirenone 3 mg and ethinyl estradiol 0.02 mg packaged in 28 x 3 blister packs. The recall is due to out-of-specification dissolution results at the 3-month stability time point that could indicate decreased product efficacy. To date, no adverse events related to this recall have been reported.
- Bayer issued a patient-level voluntary recall of 2 lots of Kogenate® FS antihemophilic factor (recombinant) 2,000 IU vials due to mislabeling of the vials. Certain vials in these lots were labeled as Kogenate FS but contained Jivi® antihemophilic factor (recombinant) pegylated-aucl 3,000 IU. Bayer has advised patients to immediately stop using any affected product and contact their physician. No lots of Bayer's Jivi or Kovaltry® were impacted by this recall.
- In March 2010, the FDA alerted the public to a possible increased risk of prostate cancer associated with entacapone, a component of Comtan® and Stalevo®. After reviewing additional data from a required study and data from the Department of Veterans Affairs, the FDA found that the addition of entacapone to anti-Parkinson's therapy did not increase the risk of prostate cancer (hazard ratio [HR], 1.05) or prostate cancer death (HR, 0.93) compared with non-entacapone-containing treatment. Clinicians should follow standard prostate cancer screening recommendations in males using these agents.

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

- **Sept-Oct 2019:** rituximab (Rituxan®); intravenous (IV) CD20-directed cytolytic antibody; granulomatosis with polyangiitis and microscopic polyangiitis in combination with glucocorticoids, ages ≥ 2 years; Genentech.
- **September 6, 2019:** nintedanib (Ofev®); oral kinase inhibitor; systemic sclerosis-associated interstitial lung disease; Boehringer Ingelheim.
- **September 10, 2019:** glucagon pump; subcutaneous (SC) recombinant glucagon; hyperinsulinemia/hypoglycemia; Xeris.
- **September 13, 2019:** tenapanor; oral sodium-hydrogen exchanger inhibitor; irritable bowel syndrome-constipation predominant (IBS-C); Ardelyx.
- **September 19, 2019:** mepolizumab (Nucala®) lyophilized powder; SC interleukin (IL)-5 inhibitor; eosinophilic asthma; GlaxoSmithKline.
- **September 20, 2019:** canagliflozin (Invokana®); oral sodium-glucose linked transporter 2 (SGLT2) inhibitor; T2DM-related diabetic nephropathy risk reduction; Janssen.
- **September 20, 2019:** doravirine (Pifeltro®); oral ARV; HIV-1 infection treatment (switch from stable ART); Merck.
- **September 20, 2019:** doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo®); fixed-dose oral ARV; HIV-1 infection (switch from stable ART); Merck.
- **September 20, 2019:** semaglutide; oral GLP-1RA; T1DM, T2DM; Novo Nordisk.
- **September 26, 2019:** daratumumab (Darzalex®); IV anti-CD38 antibody; multiple myeloma (newly diagnosed, autologous stem cell transplant-eligible, in combination with bortezomib, thalidomide, and dexamethasone [VTd]); Janssen.
- **September 27, 2019:** filgrastim, biosimilar to Neupogen®; SC colony stimulating factor; neutropenia; Tanvex.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs
ferric maltol (Accrufer®) Shield Therapeutics	• NDA approval 07/25/2019 • Indicated for the treatment of iron deficiency in adults • Iron replacement • Capsule: 30 mg • Recommended dosage is 30 mg orally twice daily taken 1 hour before or 2 hours after a meal; continue until adequate iron stores are achieved (typically for 12 weeks) • Shield is seeking a partner for commercialization in the US
darolutamide (Nubeqa®) Bayer	• NDA approval 07/30/2019; Priority Review • Indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer • Androgen receptor inhibitor • Tablet: 300 mg • Recommended dosage is 600 mg (2 x 300 mg) orally twice daily with food; patients should also receive a concurrent gonadotropin-releasing hormone or have had bilateral orchiectomy
pexidartinib (Turalio™) Daiichi Sankyo	• NDA approval 08/02/2019; Breakthrough Therapy, Orphan Drug, Priority Review • Indicated for the treatment of adults with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery • Kinase inhibitor • Capsule: 200 mg • Recommended dosage is 400 mg (2 x 200 mg) orally twice daily administered at least 1 hour before or 2 hours after a meal or snack • Boxed Warning for hepatotoxicity • Available only through a Risk Evaluation and Mitigation Strategies (REMS) program
pretomanid (no trade name) The Global Alliance for TB Drug Development/ Mylan	• NDA approval 08/14/2019; Limited Population Pathway for Antibacterial and Antifungal Drugs, Orphan Drug, Priority Review, Qualified Infectious Disease Product • Indicated in combination with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant tuberculosis (MDR-TB); indicated for use in a limited and specific population • Antimycobacterial agent • Tablet: 200 mg • Recommended dosage of pretomanid is 200 mg once daily with food for 26 weeks » Taken with bedaquiline 400 mg orally once daily for 2 weeks followed by 200 mg 3 times per week for 24 weeks and linezolid 1,200 mg daily orally for up to 26 weeks • Product availability is anticipated by the end of 2019
pitolisant (Wakix®) Harmony Biosciences	• NDA approval 08/14/2019; Orphan Drug, Priority Review • Indicated for the treatment of excessive daytime sleepiness (EDS) in adults with narcolepsy • Histamine-3 (H_3) receptor antagonist/inverse agonist • Tablets: 4.45 mg and 17.8 mg • Recommended initial dose is 8.9 mg once daily during week 1, increase to 17.8 mg once daily in week 2, and may increase to a maximum of 35.6 mg once daily at week 3; administer in the morning upon awakening • No Controlled Substance scheduling • Product availability is anticipated in Q4, 2019

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; Q = Quarter; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application; 505(b)(2) = FDA approval pathway that allows for submission of data from studies not conducted by or for the applicant.

RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs *continued*	
entrectinib (Rozlytrek™) Genentech	• NDA approval 08/15/2019; Accelerated Approval (solid tumor), Breakthrough Therapy (solid tumor), Orphan Drug, Priority Review • Indicated for the treatment of adults with metastatic non-small cell lung cancer (NSCLC) whose tumors are proto-oncogene tyrosine-protein kinase ROS1 (ROS1)-positive • Indicated for the treatment of adults and pediatrics ≥ 12 years of age with solid tumors that: » have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation; » are metastatic or where surgical resection is likely to result in severe morbidity; AND » have progressed following treatment or have no satisfactory alternative therapy • Kinase inhibitor • Capsules: 100 mg and 200 mg • Recommended dosage: » For ROS1-positive NSCLC, 600 mg orally once daily » For NTRK gene fusion-positive solid tumors, 600 mg once daily in adults and based on body surface area in pediatric patients (ages ≥ 12 years) ranging from 400 mg to 600 mg once daily • No companion diagnostic is currently available
fedratinib (Inrebic®) Celgene	• NDA approval 08/16/2019; Orphan Drug, Priority Review • Indicated for the treatment of adults with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis • Kinase inhibitor • Capsule: 100 mg • Recommended dosage is 400 mg orally once daily with or without food for patients with baseline platelet count ≥ 50 x 10^9/L • Boxed Warning for encephalopathy, including Wernicke's
upadacitinib (Rinvoq™) Abbvie	• NDA approval 08/16/2019; Priority Review • Indicated for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate (MTX) • Janus kinase (JAK) inhibitor • Tablet, extended-release (ER): 15 mg • Recommended dosage is 15 mg orally once daily; may be used as monotherapy or in combination with MTX or other nonbiologic disease-modifying antirheumatic drug (DMARD) » Use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants, such as azathioprine and cyclosporine, is not recommended • Boxed Warnings for serious infections, malignancy, and thrombosis
Expanded Indications	
trametinib (Mekinist®) Novartis	• sNDA approval 07/16/2019 • Indicated as a single agent for the treatment of BRAF-inhibitor treatment-naive patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test » The revised indication clarifies use in treatment-naïve patients • Limitation of use was removed regarding lack of approval in patients with melanoma who have progressed on prior BRAF-inhibitor therapy • Recommended dosage is 2 mg orally once daily

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications *continued*
calcipotriene/ betamethasone dipropionate (Enstilar®) Leo	• sNDA approval 07/30/2019 • Expanded indication for the topical treatment of plaque psoriasis to include patients ages ≥ 12 years; previously approved only in adults • Recommended dosage in pediatric patients is consistent with adults; apply to affected areas once daily for up to 4 weeks; do not exceed 60 g every 4 days
pembrolizumab (Keytruda®) Merck	• sBLA approved 07/30/2019; Priority Review • New indication for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express programmed death-ligand 1 (PD-L1) (Combined Positive Score [CPS] ≥ 10) as determined by an FDA-approved test, with disease progression after ≥ 1 prior line of systemic therapy • Recommended dosage is 200 mg every 3 weeks by IV infusion
sodium picosulfate/ magnesium oxide/ anhydrous citric acid (Clenpiq™) Ferring	• 505(b)(2) sNDA approval 08/08/2019 • Expanded indication to include use in pediatric patients ≥ 9 years of age for cleansing of the colon as a preparation for colonoscopy; previously only approved for use in adults • Dosage in pediatric patients is consistent with adults; 2 doses are required for complete colon preparation; consume additional fluids after every dose
bedaquiline (Sirturo®) Janssen	• sNDA approval; 08/09/2019; Accelerated Approval, Orphan Drug • Expanded indication to include use in pediatric patients ages ≥ 12 years to < 18 years and weighing ≥ 30 kg to be used as part of combination therapy for pulmonary multidrug-resistant TB when an effective treatment regimen cannot otherwise be provided; previously only approved for use in adults • Recommended dosage in this age/weight range is consistent with the adult dosage 400 mg orally once daily for 2 weeks followed by 200 mg twice per week for 22 weeks (for a total of 24 weeks)
mometasone furoate (Asmanex® HFA [hydrofluoroalkane]) Merck	• sNDA approval 08/12/2019 • Expanded indication for the maintenance treatment of asthma as prophylactic therapy to include patients 5 to 11 years of age; previously approved in patients ages ≥ 12 years » Asmanex Twisthaler™ (mometasone powder for inhalation) is already approved for asthma prophylactic therapy in patients ≥ 4 years of age • Recommended dosage in the new age group is 2 oral inhalations of 50 mcg mometasone twice daily • To accommodate dosing in the younger patients, the FDA approved a new 50 mcg formulation; availability is anticipated in Q1, 2020
mometasone furoate/formoterol fumarate (Dulera®) Merck	• sNDA approval 08/12/2019 • Expanded indication for the maintenance treatment of asthma to include patients 5 to 11 years of age; previously approved in patients ages ≥ 12 years • Recommended dosage in the new age group is 2 oral inhalations of fixed-dose 50 mcg mometasone and 5 mcg formoterol twice daily • To accommodate dosing in the younger patients, a new 50/5 mcg formulation was approved; availability is anticipated in Q1, 2020

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cdc.gov diabetes.org fda.gov icer-review.org n.neurology.org