JUNE 2019

MRx CLINICAL ALERT

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HOT TOPIC: GENE THERAPY APPROVED FOR SPINAL MUSCULAR ATROPHY

The United States (US) Food and Drug Administration (FDA) approved onasemnogene abeparvovec-xioi (Zolgensma®) for the treatment of patients < 2 years of age with spinal muscular atrophy (SMA) who have bi-allelic mutations in the survival motor neuron 1 (SMN1) gene, which instructs production of a protein critical for motor neuron function. SMA is the leading genetic cause of infant mortality. The most common form, SMA type 1, occurs in about 1 in 10,000 newborns, leading to about 500 new cases per year in the US. Patients with SMA type 1 experience progressive motor function decline beginning shortly after birth. If left untreated, permanent ventilation or death often occurs by 2 years of age. Zolgensma is the only gene replacement therapy approved for SMA. It is administered as a 1-time intravenous (IV) infusion over 1 hour and is used as part of a multidisciplinary approach to treat SMA type 1. In December 2016, the SMN2-directed antisense oligonucleotide nusinersen (Spinraza®) became the first disease-modifying therapy to treat SMA (all types) in pediatrics and adults; maintenance therapy is given intrathecally every 4 months.

Zolgensma was granted Breakthrough Therapy and Orphan Drug designations as well as Priority Review. FDA-approval of Zolgensma is supported by the ongoing STR1VE trial (n=21) and the completed 2-year START trial (n=12, therapeutic cohort). Both studies enrolled patients with SMA type 1. Treatment with Zolgensma led to significant improvement in reaching developmental motor milestones, such as head control, sitting without support, and/or standing/walking without assistance compared to the natural history of the disease. A durable effect of nearly 4 years was reported in the START long-term follow-up. Zolgensma carries a Boxed warning for acute serious liver injury.

Avexis/Novartis set a wholesale acquisition cost (WAC) of $2.125 million for the 1-time Zolgensma dose, making it the world's most expensive drug. The Institute for Clinical and Economic Review (ICER) published a value-based price benchmark for Zolgensma of $1.2 million to $2.1 million to reach a cost-effectiveness threshold of $100,000 to $150,000 per life year gained (LYG). This amount assumes durable effectiveness and considers the positive results of the SPR1NT trial in presymptomatic patients (< 6 months of age). Safety and efficacy of repeat administration have not been studied, nor has use in patients with advanced SMA (complete limb paralysis or permanent ventilator dependence). While Spinraza use after Zolgensma therapy has been reported, clinical benefits and risks have not been established. Zolgensma is available as patient-specific kits through a specialty pharmacy distributor. The company is working closely with payers to create 5-year outcome-based agreements and novel pay-over-time options.

BIOSIMILAR CORNER

FDA GUIDANCE ON INTERCHANGEABLE BIOLOGICS

To date, 19 biosimilar products have been approved in the US, 7 of which are commercially available. Currently, no biosimilar is considered to be interchangeable with its reference product; therefore, pharmacists cannot substitute a biosimilar for the reference product without involvement of the prescriber. As part of their Biosimilars Action Plan, the FDA recently provided standards for approval of interchangeable biologic agents in their final guidance titled, "Considerations in Demonstrating Interchangeability with a Reference Product Guidance for Industry."

The FDA advises that in addition to showing biosimilarity, the sponsor must demonstrate that the proposed interchangeable biologic product is *expected to yield the same clinical result compared to the reference product* for all of the reference product's FDA-approved indications. Data necessary to meet the interchangeability standards may include critical quality attributes (e.g., safety, purity, potency), target/receptor interactions, pharmacokinetics, and immunogenicity. Any difference between the proposed interchangeable product and the reference product should be justified and proven that it will not prohibit the same clinical results as the reference product *in any given patient.* In addition, if the product is administered more than once to a patient, alternating use between the proposed interchangeable biologic and the reference product should not lead to increased safety risks or reduced efficacy. Considerations regarding interchangeability of container closure systems and delivery device components are also addressed. Furthermore, insulins, historically regulated by the FDA as small molecules, will be deemed biological products as of March 23, 2020. This transition will allow approval of insulins that are interchangeable with their brand competitors.

CVD PRIMARY PREVENTION GUIDELINES

The American College of Cardiology (ACC) and American Heart Association (AHA) released a new guideline on the primary prevention of cardiovascular disease (CVD). The guideline emphasizes the importance of a healthy lifestyle in patients with diabetes, hypercholesterolemia, or hypertension. The ACC/AHA recommends a multidisciplinary, team-based approach and shared decision-making between the patient and physician.

According to the guideline, cardiovascular (CV) risk factors should be assessed every 4 to 6 years in patients aged 20 to 39 years to determine the need for treatment. The race- and sex-specific Pooled Cohort Equation (PCE) is recommended to estimate 10-year atherosclerotic CVD (ASCVD) risk for asymptomatic adults aged 40 to 79 years. While use of PCE is best supported in non-Hispanic populations, other risk assessment tools, such as the Framingham CVD risk score, Reynolds risk score, Systematic COronary Risk Evaluation (SCORE), and QRISK/JBS3, can be considered in Hispanics or populations with enhanced risk (e.g., HIV infection, chronic inflammatory disease, low socioeconomic status). Use of the coronary artery calcium (CAC) score is reasonable to estimate ASCVD risk when uncertainty still exists. In addition, serum lipids should be assessed starting in childhood. Statins remain first-line therapy for hypercholesterolemia.

Due to their proven CV benefits in patients with type 2 diabetes mellitus (T2DM), sodium-glucose cotransporter 2 (SGLT 2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1RA) are recommended in patients with T2DM and additional CVD risk factors. While low-dose aspirin is established for secondary prevention of ASCVD, because of a lack of net benefit, it should only be considered for primary prevention in select patients aged 40 to 70 years who are not at increased bleeding risk.

BEHAVIORAL HEALTH CORNER

INSOMNIA TREATMENT SAFETY ALERT

The FDA released a Drug Safety Communication regarding rare but serious injuries associated with prescription sedative-hypnotic agents used to treat insomnia. Over a 26-year period, a total of 66 cases of complex sleep behaviors have been reported in patients taking eszopiclone (Lunesta®), zaleplon (Sonata®), and zolpidem (Ambien®, Ambien CR®, Edluar®, Intermezzo®, Zolpimist®). These included sleepwalking, sleep driving, and other activities while not fully awake. Some cases resulted in death, even in patients taking the lowest recommended dose. As a result, the FDA is strengthening the warnings for the products listed to include a Boxed warning regarding sleep behaviors. Furthermore, a contraindication will be added advising prescribers to avoid use in patients who have previously experienced complex sleep behavior while taking any of these agents. Patients should stop taking their prescribed insomnia agent and contact their physician if they experience complex sleep behavior.

DRUG INFORMATION **HIGHLIGHTS**

- Update on consumer level recalls of generic antihypertension medications due to potential human carcinogenic impurities: Vivimed Life Sciences issued a recall of 19 lots of losartan potassium 25 mg, 50 mg, and 100 mg tablets due to the detection of N-nitroso-N-methyl-4-amino butyric acid (NMBA) above the FDA's acceptable exposure limit. Moreover, the FDA published 2 new tests, HRMS and RapidFire-MS/MS, as options for regulators and industry to detect nitrosamine impurities.
- As part of the continued effort to tackle the opioid crisis, the FDA unveiled a new "Remove the Risk" campaign that provides a stepwise approach for patients to properly dispose of unused prescription opioids. Medicine take-back programs are the preferred method to discard unneeded medicines, including opioids. Authorized locations include law enforcement facilities and pharmacies in retail, hospital, or clinic settings. Mail-back programs or "drop-boxes" are also available in some locations.
- Novartis announced a consumer level voluntary recall of 3 lots of eltrombopag (Promacta®) 12.5 mg for oral suspension due to a risk of potential peanut flour contamination. Exposure to contaminated product can lead to hypersensitivity reactions, including anaphylaxis, in patients with a sensitivity to peanut antigens. No adverse events have been reported. Eltrombopag is indicated to treat chronic immune thrombocytopenia and is distributed through specialty pharmacies.
- The American Urological Association (AUA) released consensus guidelines on the evaluation, testing, treatment, and follow-up of recurrent urinary tract infections (UTI) in women. Initial treatment should be based on the local antibiogram. A short course (generally ≤ 7 days) of antibiotics is considered reasonable to treat acute cystitis; however, antibiotic-resistant cases may require parenteral antibiotics (≤ 7 days). To decrease risk of future UTIs, antibiotic prophylaxis and/or cranberry consumption may be considered. Additionally, in peri- and post-menopausal women, risk of recurrent UTIs may be decreased with vaginal estrogen therapy if no contraindications exist.
- ICER revised its value-based benchmark ranges for the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab (Praluent®). The new ranges are $2,300 to $3,500 per year in all eligible patients and $2,700 to $4,000 per year for higher-risk patients with low-density lipoprotein cholesterol (LDL-C) ≥ 100 mg/dL despite statin therapy. The changes are based on further analysis of the ODYSSEY Outcomes trial, which reported a similar benefit with alirocumab in all patient groups, including those with LDL-C ≤ 100 mg/dL. The value-based benchmark indicates a net price range that is consistent with the treatment's added benefit to patients and the healthcare system.

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

- **June 2019:** bevacizumab, biosimilar to Genentech's Avastin®; IV vascular endothelial growth factor (VEGF) inhibitor; non-small cell lung cancer, colorectal cancer, ovarian cancer, renal cancer; Pfizer.
- **June 2019:** onabotulinumtoxinA (Botox®); intradermal neurotoxin; pediatric upper limb spasticity; Allergan.
- **June 2019:** rituximab, biosimilar to Genentech's Rituxan®; IV anti-CD20 antibody; non-Hodgkin's lymphoma, rheumatoid arthritis; Pfizer.
- **June 2019:** trastuzumab, biosimilar to Genentech's Herceptin®; IV human epidermal growth factor receptor 2 (HER2)/neu receptor antagonist; breast cancer, gastric cancer; Allergan/Amgen.
- **June 10, 2019:** glucagon pen; SC recombinant glucagon; severe diabetes-related hypoglycemia; Xeris.
- **June 17, 2019:** pembrolizumab (Keytruda®); IV programmed death receptor-1 (PD-1) inhibitor; small cell lung cancer; Merck.
- **June 20, 2019:** mannitol; inhaled mucolytic; cystic fibrosis (CF); Chiesi.
- **June 21, 2019:** bremelanotide; SC melanocortin agonist; female sexual arousal disorder; AMAG.
- **June 21, 2019:** olopatadine/mometasone furoate; nasal antihistamine/corticosteroid; seasonal allergic rhinitis; Glenmark.
- **June 25, 2019:** celiprolol; oral beta-adrenergic antagonist; Ehlers-Danlos syndrome; Acer.
- **June 26, 2019:** dupilumab (Dupixent®); SC interleukin (IL)-4 inhibitor; nasal polyposis; Regeneron.
- **June 28, 2019:** avatrombopag (Doptelet®); oral thrombopoietin receptor agonist; immune thrombocytopenic purpura; Dova.
- **June 28, 2019:** eculizumab (Soliris®); IV complement inhibitor; neuromyelitis optica; Alexion.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs
etanercept-ykro (Eticovo™) Samsung Bioepis	• BLA approval 04/25/2019; biosimilar to Amgen's etanercept (Enbrel®) • Indicated for the treatment of adults with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS), pediatric patients ages ≥ 2 years with polyarticular juvenile idiopathic arthritis (JIA), and pediatric patients ages ≥ 4 years with plaque psoriasis (PSO) • Tumor necrosis factor (TNF) inhibitor • Injection: 25 mg/0.5 mL, 50 mg/mL single-dose prefilled syringes • Recommended weight-based dosing in patients ≥ 63 kg is 50 mg SC once weekly, with the exception of adult PSO which is 50 mg SC twice weekly for 3 months, then once weekly thereafter » No dosage form exists for Eticovo that allows weight-based dosing for pediatric patients < 63 kg; use an alternative reconstituted lyophilized powder etanercept product for patients < 63 kg • Boxed warnings for serious infections and malignancies • Product availability may be delayed due to litigation
halobetasol propionate/ tazarotene (Duobrii™) Bausch Health	• NDA approval 04/25/2019 • Indicated for the topical treatment of PSO in adults • Combination topical steroid and retinoid • Topical lotion: halobetasol 0.01%/tazarotene 0.045% in 45 g, 60 g, and 100 g tubes • Recommended dosage is a thin layer applied topically once daily to affected areas • Product availability is anticipated in June 2019
dengue tetravalent vaccine, live (Dengvaxia®) Sanofi Pasteur	• BLA approval 05/01/2019; Priority Review • Indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in adolescents aged 9 to 16 years with laboratory-confirmed previous dengue infection and living in endemic areas • Viral vaccine antigen • Injection: lyophilized powder for suspension with supplied diluent • Recommended regimen is three 0.5 mL doses administered SC 6 months apart (months 0, 6, and 12)
dapagliflozin/ saxagliptin/ metformin extended-release (ER) (Qternmet® XR) AstraZeneca	• NDA approval 05/02/2019 • Indicated for improved glycemic control in adults with T2DM as an adjunct to diet and exercise » Not indicated for type 1 diabetes mellitus » Intended for patients currently taking metformin • Combination SGLT2 inhibitor, dipeptidyl peptidase-4 (DPP-4) inhibitor, and biguanide • Tablets (dapagliflozin/saxagliptin/metformin ER): 2.5 mg/2.5 mg/1,000 mg, 5 mg/2.5 mg/1,000 mg, 5 mg/5 mg/1,000 mg, and 10 mg/5 mg/1,000 mg • Recommended dosage is 1 tablet once daily in the morning with food • Boxed warning for lactic acidosis

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*
tafamidis meglumine (Vyndaqel®)/ tafamidis (Vyndamax™) Pfizer	• NDA approvals 05/03/2019; Breakthrough Therapy (Vyndaqel); Orphan Drug (both); Priority Review (Vyndaqel) • Indicated for the treatment of adults with cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis to reduce CV mortality and CV-related hospitalization • Transthyretin stabilizers • Capsules: tafamidis meglumine 20 mg, tafamidis 61 mg • Recommended dosage is tafamidis meglumine 80 mg (as four 20 mg capsules) or tafamidis 61 mg oral once daily • Vyndamax and Vyndaqel are not substitutable on a milligram-per-milligram basis
amifampridine (Ruzurgi®) Jacobus	• NDA approval 05/06/2019; Orphan Drug; Priority Review • Indicated for Lambert-Eaton myasthenic syndrome (LEMS) in patients aged 6 to < 17 years • Potassium channel blocker • Tablets: 10 mg, scored and can be used to prepare a 1 mg/mL suspension • Recommended dosage is weight-based » Patients weighing ≥ 45 kg: initial dose is 15 mg to 30 mg daily in divided doses; may increase to a maximum of 100 mg per day; maximum single dose is 30 mg » Patients weighing < 45 kg: initial dose is 7.5 mg to 15 mg daily in divided doses; may increase to a maximum of 50 mg per day; maximum single dose is 15 mg
midazolam (Nayzilam®) Proximagen	• NDA approval 05/17/2019; Orphan Drug • Indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy aged ≥ 12 years • Benzodiazepine • Nasal spray: 5 mg/0.1 mL • Recommended dosage is 1 spray (5 mg) into 1 nostril for the initial dose; 1 additional spray (5 mg) into the opposite nostril may be administered after 10 minutes if the patient has not responded to the initial dose; do not use > 2 doses to treat a seizure cluster • Boxed warning for risks from concomitant use with opioids • Scheduled IV controlled substance
	Expanded Indications
alirocumab (Praluent®) Sanofi	• sBLA approval 04/26/2019 • New indication to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established CVD • Expanded indication as an adjunct to diet, alone or in combination with other lipid-lowering therapies, for the treatment of adults with primary hyperlipidemia to reduce LDL-C • Recommended dosage is 75 mg SC once every 2 weeks or 300 mg SC once every 4 weeks; dose may be adjusted to a maximum of 150 mg SC every 2 weeks
belimumab (Benlysta®) Human Genome Sciences	• sBLA approval 04/26/2019 • Expanded indication for the treatment of active, autoantibody-positive, systemic lupus erythematosus in patients who are receiving standard therapy to include those aged 5 to 17 years • Recommended dosage is 10 mg/kg administered IV over 1 hour at 2-week intervals for the first 3 doses and at 4-week intervals thereafter; SC administration is only approved for use in adults

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications *continued*
ivacaftor (Kalydeco®) Vertex	• sNDA approval 04/29/2019 • Expanded indication for the treatment of CF in patients with 1 mutation in the CF transmembrane conductance regulator (CFTR) gene to include patients aged 6 months to < 12 months • Recommended weight-based dosage in this age group: » Patients weighing 5 kg to < 7 kg: one 25 mg granule packet every 12 hours » Patients weighing 7 kg to < 14 kg: one 50 mg granule packet every 12 hours » Patients weighing ≥ 14 kg: one 75 mg granule packet every 12 hours • Mix contents of packet with 5 mL of soft food or liquid and administer orally with fat-containing food
glecaprevir/ pibrentasvir (Mavyret™) Abbvie	• sNDA approval 04/30/2019 • Expanded indications to include patients as young as 12 years or weighing ≥ 45 kg for the treatment of chronic hepatitis C virus (HCV) genotype (GT) 1, 2, 3, 4, 5, or 6 infection in patients without cirrhosis or with compensated cirrhosis and the treatment of HCV GT1 infection in patients previously treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both • Recommended dosing is 3 tablets orally once daily with food
ivosidenib (Tibsovo®) Agios	• sNDA approval 05/02/2019; Orphan Drug; Priority Review • Expanded indication for the treatment of adults with newly diagnosed acute myeloid leukemia (AML) who are ≥ 75 years of age or who have comorbidities that preclude use of intensive induction chemotherapy • Recommended dosage is 500 mg orally once daily with or without food until disease progression or unacceptable toxicity, avoiding high-fat meals
ado-trastuzumab emtansine (Kadcyla®) Genentech	• sBLA approval 05/03/2019; Breakthrough Therapy; Priority Review • Expanded indication for adjuvant treatment of patients with HER2-positive early breast cancer who have residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment • Recommended dosage is 3.6 mg/kg given IV every 3 weeks for a total of 14 cycles unless there is disease recurrence or unacceptable toxicity
calcipotriene (Sorilux™) Mayne	• sNDA approval 05/06/2019 • Expanded indication to treat PSO of the scalp and body in patients as young as 12 years • Recommended dosage is a thin layer applied topically to affected areas twice daily
incobotulinumtoxinA (Xeomin®) Merz	• sBLA approval 05/10/2019 • Expanded indication for the treatment of blepharospasm in adult patients; no longer limited to use in patients previously treated with onabotulinumtoxinA (Botox) • Recommended initial total dose is 50 Units (25 Units per eye) administered intramuscularly
ramucirumab (Cyramza®) Eli Lilly	• sBLA approval 05/10/2019 • Expanded indication as a single agent for the treatment of hepatocellular carcinoma in patients with an alpha fetoprotein (AFP) ≥ 400 ng/mL and have been previously treated with sorafenib • Recommended dosage is 8 mg/kg administered IV every 2 weeks

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