MARCH 2020

MRx CLINICAL ALERT

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HOT TOPIC: FIRST DRUG APPROVED FOR PEANUT ALLERGY

The United States (US) Food and Drug Administration (FDA) approved Aimmune's biologic oral immunotherapy (OIT), peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia™), as the first product to treat children ages 4 to 17 years with confirmed peanut allergy. Approximately 2.5% of children in the US are affected by peanut allergy which places a significant burden on the children and their caregivers. Avoidance of dietary peanut allergen is the main approach to management. When accidental ingestion does occur, antihistamines can manage mild to moderate reactions, but injectable epinephrine should be readily available in the event of anaphylaxis.

Palforzia consists of 12% defatted peanut flour with a standardized allergen profile. While it is not a cure for peanut allergy, Palforzia may mitigate the allergic effects of accidental peanut exposure. In the PALISADES clinical trial, Palforzia resulted in tolerance to ≥ 600 mg of peanut protein (equivalent to ≥ 2 peanuts) in 67.2% of patients 4 to 17 years of age. Efficacy was not demonstrated in those ages ≥ 18 years. Upon peanut allergen rechallenge even at a much higher dose, significantly fewer Palforzia-treated patients required epinephrine when compared to placebo-treated patients. Palforzia treatment involves 3 phases. The initial dose escalation is given on day 1. This is followed by the up-dosing phase that includes 11 dosage levels, each taken for 2 weeks. Patients are then maintained on a daily dose of 300 mg. The initial dose escalation may be administered to patients aged 4 through 17 years, while the up-dosing and maintenance may be continued in those 4 years and older. Patients must also continue to avoid dietary peanut and carry an epinephrine auto-injector.

Palforzia will be available only through a Risk Evaluation and Mitigation Strategy (REMS) that requires patients, prescribers, pharmacies, and healthcare facilities to be enrolled. The initial dose escalation phase and the first dose of each up-dosing level must be administered in a certified healthcare facility where anaphylaxis can be managed. Palforzia should not be used in patients with uncontrolled asthma, a history of eosinophilic esophagitis, or other eosinophilic gastrointestinal (GI) diseases.

According to the Institute for Clinical and Economic Review (ICER), unregulated OIT for peanut allergy is practiced and has demonstrated varying degrees of desensitization; however, insurers may not cover this experimental practice, and patients, caregivers, and clinicians may be more comfortable using an FDA-approved product. Peanut desensitization therapy is intended to be continued indefinitely, but sustained unresponsiveness to peanut allergens with the long-term use of Palforzia is uncertain. DBV Technologies' transdermal Viaskin peanut is also on the horizon for peanut allergy. The FDA decision on its approval is anticipated by August 5, 2020.

BIOSIMILAR CORNER

DRUG TO BIOLOGIC TRANSITION

Effective March 23, 2020, select biologic medications approved under a New Drug Application (NDA) will be considered biological products under section 351 of the Public Health Service Act (e.g., approved under a Biologics License Application [BLA]). The reclassification will allow certain biological products to be used as a reference product for a proposed biosimilar or interchangeable biosimilar product. Any biosimilar approved for this reference product will then be considered a "biosimilar" rather than a "follow-on" product.

As part of this transition, insulin products will be considered biologics and will have the potential for biosimilar approval. In November 2019, the FDA released the draft guidance for industry, "Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products," that clarified the data required to demonstrate biosimilarity or interchangeability for a proposed insulin.

Notably, in December 2019, the Further Consolidated Appropriations Act amended the definition of a biological product to allow chemically synthesized polypeptides (CSPs), such as lixisenatide (Adlyxin®), to be considered biological products approved under a BLA. This update only impacts CSPs that are considered to be proteins and does not include peptides which have ≤ 40 amino acids.

UPDATED GUIDANCE ON HIV TREATMENT

The Department of Health and Human Services (DHHS) released updated guidance on the use of antiretroviral (ARV) agents in adults and adolescents with human immunodeficiency virus (HIV). Data demonstrates that effective ARV treatment (ART) that consistently suppresses plasma HIV RNA levels to < 200 copies/mL may prevent HIV transmission to sexual partners. This preventive approach is called treatment as prevention (TasP). Under the scope of TasP, an additional method for preventing sexual transmission should be used for ≥ 6 months after starting ART and until HIV RNA suppression is confirmed. Patients using TasP should be counseled on the importance of ART adherence and that interruption of therapy could result in HIV transmission.

The guidance regarding neural tube defects (NTD) in infants born to women receiving dolutegravir (DTG) during conception was updated. Although the prevalence of NTD in these infants is lower than previously reported (0.3% versus 0.9%), it is still higher than for infants who were exposed to ART that did not contain DTG. DHHS now considers DTG an alternative ARV drug for females of childbearing potential who are trying to conceive, as well as for patients who are sexually active and not using contraception. DTG is also a recommended option for patients who are using effective contraception.

To enhance the effect of ART, DHHS recommends starting ART immediately or as soon as possible following HIV diagnosis. The 2-drug regimen of DTG/lamivudine (Dovato®) was added as a recommended initial regimen for most people with HIV. Bictegravir/tenofovir alafenamide/emtricitabine (Biktarvy®) was also added as an option for patients with acute/recent HIV infection when ART will be started prior to genotypic resistance testing.

BEHAVIORAL HEALTH CORNER

FDA ALERT: CLOZAPINE

The FDA issued a drug safety communication strengthening the warning regarding bowel concerns in patients taking clozapine. Clozapine is a medication used to treat schizophrenia and is available generically and under the following brand names: Clozaril®, Fazaclo ODT®, and Versacloz®. Constipation is a common adverse effect from clozapine; however, in rare instances the constipation may lead to serious bowel complications, such as bowel obstruction, that may require hospitalization and be life-threatening. This risk appears to be higher with clozapine than other similar schizophrenia medications. As a result, the FDA is requiring additions to the clozapine labeling, including a new warning and updated safety information on these risks.

From 2006 to 2016, the FDA identified 10 cases of constipation progressing to serious bowel complications, including necrotizing colitis, intestinal ischemia and/or necrosis, and abdominal distension resulting in bowel obstruction. In these cases, the complications led to hospitalization, surgery, or death. The FDA is advising that healthcare providers (HCPs) evaluate patient's bowel function prior to starting clozapine, avoid concurrent prescribing of clozapine with anticholinergic agents, counsel patients on this risk, assess bowel habits and monitor for symptoms of complications during treatment, and consider prophylactic laxative treatment in patients with a history of constipation or bowel obstruction.

DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2019–2020): The Centers for Disease Control and Prevention (CDC) reported occurrences of influenza-like illnesses (ILI) remain high but decreased slightly during the week ending February 22, 2020; however, indicators of severity are not high (e.g., hospitalizations, death). Puerto Rico, New York City, and 43 states reported high ILI activity; 5 states reported moderate ILI activity; and the remaining areas reported low or minimal ILI activity. Influenza A(H1N1)pdm09 viruses predominate nationwide, but influenza B/Victoria viruses continue to circulate. The CDC estimates a 45% effectiveness of the influenza vaccine for preventing medically attended, laboratory-confirmed influenza virus infection.
- The American Academy of Dermatology and National Psoriasis Foundation published guidelines for management and treatment of psoriasis (PSO) in pediatric patients. Recommended topical treatments include corticosteroids (off-label), tacrolimus 0.1% ointment (off-label) for PSO of face and genital regions, calcipotriene/calcipotriol, calcipotriol/betamethasone dipropionate (ages ≥ 12 years), tazarotene (off-label) + corticosteroids, anthralin, coal tar, and phototherapy/photochemotherapy. Systemic treatments include methotrexate, cyclosporine, oral retinoids, and biologics (e.g., etanercept, infliximab, adalimumab, and ustekinumab). Ongoing assessment for comorbidities, including diabetes, other autoimmune diseases, and mental health conditions, is recommended.
- The FDA released an update regarding the potentially carcinogenic impurity N-Nitrosodimethylamine (NDMA) in the US metformin drug supply. At this time, no metformin products have been recalled as none of the tested samples detected NDMA levels above the agency's previously defined acceptable intake level of 96 ng/day.
- The CDC continues to monitor the novel coronavirus (COVID-19) outbreak, which began in China and has spread to the US. As a result, the FDA authorized emergency use of the CDC's 2019-nCoV Real-Time Rt-Polymerase Chain Reaction Diagnostic Panel in any CDC-qualified lab in the US to test patients for coronavirus who meet CDC's criteria. Positive results of the test, which uses a nasal or oral mucosa swab, signify high likelihood of COVID-19 infection; however, a diagnosis based on a negative result should also consider the patient's clinical presentation, history, and epidemiological findings.
- The first generic version of brand-name Zohydro® ER (hydrocodone) extended-release (ER) capsules has received approval. The generic product is manufactured by Alvogen. In addition, Persion-Macoven launched an authorized generic of Zohydro ER. Hydrocodone ER is a Schedule II controlled substance indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
- The FDA issued a safety communication for the prescription weight-loss medication lorcaserin (Belviq®, Belviq XR®) requesting the product be voluntarily withdrawn from the US market. This is based on a 5-year study in 12,000 individuals that identified a diagnosis of cancer, including pancreatic, colorectal, and lung cancers, occurred more often in patients taking lorcaserin (7.7%) compared to patients receiving placebo (7.1%). The manufacturer has also submitted a request for voluntary withdrawal of the medication. No special cancer screenings are required for patients who have taken lorcaserin, but patients are advised to discontinue use and discuss alternative weight loss medications with their HCP.

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

- **March 2020:** durvalumab (Imfinzi®); intravenous (IV) programmed death ligand-1 (PD-L1) inhibitor; small cell lung cancer (SCLC); AstraZeneca.
- **Mar-Apr 2020:** bimatoprost sustained-release; implanted intraocular prostaglandin analog; glaucoma, increased intraocular pressure; Allergan.
- **March 9, 2020:** exenatide subdermally implanted mini-pump; continuous subcutaneous (SC) glucagon-like peptide-1 receptor agonist (GLP-1RA); type 2 diabetes mellitus (T2DM); Intarcia/Janssen.
- **March 10, 2020:** nivolumab (Opdivo®) + ipilimumab (Yervoy®); IV programmed death-1 (PD-1) inhibitor + IV cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor; hepatocellular carcinoma (combination use in patients previously treated with sorafenib); Bristol-Myers Squibb.
- **March 25, 2020:** fenfluramine low-dose; oral serotonin reuptake inhibitor and serotonin release stimulator; Dravet syndrome; Zogenix.
- **March 25, 2020:** ozanimod; oral sphingosine 1-phosphate receptor modulator; relapsing multiple sclerosis; Celgene.
- **March 27, 2020:** ferric pyrophosphate (Triferic®); IV iron supplement; anemia due to chronic kidney disease (dialysis-dependent); Rockwell.
- **April 3, 2020:** luspatercept-aamt (Reblozyl®); SC erythroid maturation agent; myelodysplastic syndrome; Celgene.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs
influenza A (H5N1) monovalent vaccine, adjuvanted (Audenz™) Seqirus	• BLA approval 01/31/2020; Accelerated Approval • Indicated for active immunization for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine; approved for use in persons ages ≥ 6 months at increased risk of exposure to the influenza A virus H5N1 subtype contained in the vaccine • Inactivated vaccine • Injection: 0.5 mL prefilled syringe • Recommended dosage is 2 intramuscular (IM) injections (0.5 mL each) given 21 days apart • Will not be commercially available; will be distributed to the US government as part of the national pandemic preparedness initiative
lactitol (Pizensy®) Braintree	• 505(b)(2) NDA approval 02/12/2020 • Indicated for the treatment of chronic idiopathic constipation (CIC) in adults • Osmotic laxative • Powder for oral solution: 280 g and 560 g bottles and 10 g unit-dose packets • Recommended dosage is 20 g orally once daily, preferable with meals; may be reduced to 10 g daily for persistent loose stools
cysteamine bitartrate oral granules (Procysbi®) Horizon	• 505(b)(2) NDA approval 02/14/2020; Orphan Drug • Indicated for the treatment of nephropathic cystinosis in adults and pediatric patients ≥ 1 year of age • Cystine-depleting agent • Delayed-release oral granules: 75 mg and 300 mg in single-use packets; already available as 25 mg and 75 mg delayed-release capsules • Recommended starting dose is one-sixth to one-quarter of the maintenance dose, with patients ages 1 year to < 6 years receiving titrations every 2 weeks and patients ≥ 6 years of age receiving dose titration over 4 to 6 weeks; additional dosage increases may be required to achieve a therapeutic target white blood cell (WBC) cystine concentration; maximum daily dose is 1.95 g/m^2 • Product availability is expected in 1H 2020
levonorgestrel/ ethinyl estradiol (Twirla®) Agile	• 505(b)(2) NDA approval 02/14/2020 • Indicated as a method of contraception for use in women of reproductive potential with a body mass index (BMI) < 30 kg/m^2 for whom a combined hormonal contraceptive is appropriate • Combination hormonal contraceptive • Transdermal system (patch): 120 mcg/day levonorgestrel and 30 mcg/day ethinyl estradiol • Recommended dosage is 1 patch applied to the abdomen, buttock, or upper torso (excluding breasts) every 7 days for 3 consecutive weeks, followed by 1 patch-free week; repeat 28-day cycle • Boxed warning for cigarette smoking and serious cardiovascular (CV) events • Product availability is expected in 4Q 2020

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; H = Half; 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*	
meloxicam (Anjeso™) Baudax Bio	• NDA approval 02/20/2020 • Indicated for use in adults for the management of moderate-to-severe pain, alone or in combination with a non-nonsteroidal anti-inflammatory drug (non-NSAID) analgesic • NSAID • Injection: 30 mg/mL dispersion in a single-dose vial (SDV) • Recommended dosage is 30 mg once daily administered by IV bolus over 15 seconds; use for the shortest duration consistent with the patient treatment goals; not recommended for rapid pain relief due to delayed onset of analgesia • Boxed warning for serious CV and GI events • Product availability is expected in late April or early May 2020
bempedoic acid (Nexletol™) Esperion	• NDA approval 02/21/2020 • Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low density lipoprotein cholesterol (LDL-C) • Adenosine triphosphate-citrate lyase (ACL) inhibitor • Tablet: 180 mg • Recommended dosage is 180 mg orally once daily with or without food • Product availability is expected on March 30, 2020
eptinezumab-jjmr (Vyepti™) Lundbeck	• BLA approval 02/21/2020 • Indicated for the preventive treatment of migraine in adults • Calcitonin gene-related peptide (CGRP) antagonist • Injection: 100 mg/mL solution in a SDV • Recommended dosage is 100 mg via IV infusion over 30 minutes every 3 months; some patients may benefit from 300 mg every 3 months; must be diluted prior to administration • Product availability is expected in April 2020
bempedoic acid/ ezetimibe (Nexlizet™) Esperion	• 505(b)(2) NDA approval 02/26/2020 • Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C • ACL inhibitor and cholesterol absorption inhibitor • Fixed-dose combination tablet: 180 mg/10 mg • Recommended dosage is 1 tablet orally once daily with or without food; administer ≥ 2 hours before or ≥ 4 hours after a bile acid sequestrant • Product availability is expected in July 2020
Expanded Indications	
vigabatrin (Sabril®) Lundbeck	• sNDA approval 01/24/2020 • Expanded indication for the treatment of refractory complex partial seizures as adjunctive therapy in patients ≥ 2 years of age; previously approved in patients ≥ 10 years of age • Recommended pediatric dose is based on body weight and is administered orally twice daily

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications *continued*
canagliflozin/ metformin (Invokamet®, Invokamet® XR) Janssen	• sNDA approval 01/27/2020 • New indication to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria; already indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM • Recommended starting dose is based on patient's current antidiabetic regimen and renal function per the package insert
dulaglutide (Trulicity®) Eli Lilly	• sBLA approval 02/21/2020 • New indication to reduce the risk of major adverse cardiovascular events (MACE) in adults with T2DM who have established CV disease or multiple CV risk factors; already indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM • Recommended initial dosage for MACE is 0.75 mg SC once weekly; may be increased to 1.5 mg once weekly if needed for glycemic control

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References:

aidsinfo.nih.gov cdc.gov fda.gov icer-review.org jaad.org