JULY 2019

MRx CLINICAL ALERT

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CANAGLIFLOZIN AND RENAL OUTCOMES

The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial was designed to assess the effects of the sodium-glucose cotransporter-2 (SGLT2) inhibitor canagliflozin on renal outcomes in patients with type 2 diabetes mellitus (T2DM) and albuminuric chronic kidney disease (CKD). CKD was defined as an estimated glomerular filtration rate (eGFR), 30 to < 90 mL/min/1.73 m^2 with albumin (mg) to creatinine (g) ratio > 300 to 5,000. All patients were on stable doses of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB). The double-blind study randomized 4,401 patients 1:1 to canagliflozin 100 mg once daily or placebo. The mean age was 63 years, mean HbA1c was 8.3%, and mean eGFR was 56.2 mL/min/1.73 m^2. After a 2.62 year median follow-up, the primary outcome, a composite of end-stage renal disease (ESRD), doubling of serum creatinine level from baseline over at least 30 days, or death from renal or cardiovascular (CV) disease was 30% lower with canagliflozin compared to placebo (43.2 versus 61.2 per 1,000 patient-years, respectively; 95% confidence interval [CI], 0.59 to 0.82; p=0.00001). The results were consistent across all renal endpoint components. Secondary CV composite outcomes were also significantly lower with canagliflozin and consistent with the prior Canagliflozin Cardiovascular Assessment Study (CANVAS) program. Unlike CANVAS, CREDENCE reported similar rates of amputation and fracture with canagliflozin and placebo. The CREDENCE trial was stopped due to clear evidence of early renal benefit according to prespecified criteria.

The American Diabetes Association (ADA) updated their "living" Standards of Medical Care in Diabetes to include findings from the CREDENCE trial. The ADA recommends the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin in patients with T2DM and established CKD based on the drugs' proven renal benefit.

DIABETES GUIDELINES FOR ELDERLY PATIENTS

In their clinical practice guidelines for treatment of diabetes in older adults, the Endocrinology Society (ES) provides recommendations regarding diabetic screening, assessment, and treatment as well as management of diabetic complications (e.g., retinopathy, neuropathy, renal disease) and comorbid conditions (e.g., hyperlipidemia, hypertension, CVD) in patients ≥ 65 years of age. For ambulatory patients, lifestyle modification is the initial approach to hyperglycemia management. Overall, outpatient pharmacologic treatment regimens should be designed to minimize hypoglycemia; therefore, avoid use of sulfonylureas and glinides and prescribe insulin with caution. For patients who are prescribed insulin, frequent and/or continuous glucose monitoring is recommended.

Other key recommendations include periodic assessment of cognitive

function. If cognitive impairment is detected, a simplified medication regimen and glycemic target tailored to improve compliance and prevent complications are recommended. For management of comorbid conditions, an ACEI or ARB is recommended as initial treatment to maintain target blood pressure of 140/90 mm Hg. In elderly diabetic patients with congestive heart failure, glinides, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors should be used with caution to prevent worsening of heart failure.

PCSK9 INHIBITOR VALUE

The National Lipid Association (NLA) published a statement on the enhanced value of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab (Praluent®) and evolocumab (Repatha®), based on CV outcomes data as well as reductions in list prices (by about 60% to $5,850/year). Since risk reduction is directly proportional to absolute low-density lipoprotein cholesterol (LDL-C), patients with higher starting atherosclerotic CV disease (ASCVD) risk and higher LDL-C levels generally achieved greater reduction in major vascular events when treated with anti-hyperlipidemic pharmacotherapy. Based, at least in part, on ASCVD risk phenotype and LDL-C thresholds, the NLA determined that PSCK9 inhibitors will provide reasonable value (< $100,000 per quality adjusted life year [QALY]) in the following 3 groups of patients on maximally tolerated statin therapy: extremely high-risk (≥ 40% 10-year ASCVD risk) patients with LDL-C ≥ 70 mg/dL, including patients with extensive or active ASCVD burden and those with less extensive ASCVD plus extremely high-risk cardiometabolic risk factors; very high-risk (≥ 30% to 39% 10-year ASCVD risk) patients with LDL-C ≥ 100 mg/dL; and high-risk (< 30% 10-year ASCVD risk) patients with LDL-C ≥ 130 mg/dL, including patients with heterozygous familial hypercholesterolemia (HeFH) or severe hypercholesterolemia ≥ 220 mg/dL. It is generally advised to add ezetimibe to statin therapy before adding a PCSK9 inhibitor; however, the NLA states that adding a PCSK9 inhibitor directly to a statin may be more efficacious for select patients at very high and extremely high ASCVD risk, particularly if their LDL-C is at a lower level.

PRE-EXPOSURE HIV PROPHYLAXIS

In 2017, over 38,000 new cases of human immunodeficiency virus (HIV) infection were diagnosed in the United States (US). The US Preventive Services Task Force (USPSTF) issued guidelines recommending that pre-exposure prophylaxis (PrEP) with effective antiretroviral therapy be offered to individuals at high risk of acquiring HIV infection (Grade A recommendation). Persons at risk of HIV infection include men who have sex with men (MSM), persons at risk through heterosexual contact, and persons who inject drugs. Behaviors that increase risk include sexual relationships with a partner living with HIV, inconsistent use of condoms, and shared use of drug injection equipment, as well as diagnosis of select sexually transmitted infections within the previous 6 months. Populations at particular risk include people who engage in transactional or trafficked sex, men who have sex with men and women, and sexually active transgender women and men; these individuals should be assessed for PrEP using the USPSTF-outlined criteria.

Currently, the fixed-dose combination of emtricitabine and tenofovir disoproxil fumarate (Truvada®), given as 1 tablet orally once daily, is the only medication FDA-approved for PrEP.

BEHAVIORAL HEALTH CORNER

ANTIDEPRESSANT ADVERSE EFFECTS IN ELDERLY PATIENTS

In the US, approximately 15% to 20% of people ≥ 65 years of age experience major depressive disorder (MDD). In 2019, the American Geriatrics Society (AGS) updated their Beers Criteria® to advise cautious use or avoidance of selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) in elderly patients.

A recent systematic review and meta-analysis (Sobiera DM, et al.) evaluated the adverse effects of antidepressants in elderly patients and included 19 randomized controlled trials and 2 observational studies. Most trials were conducted during the acute treatment phase (≤ 12 weeks). Antidepressants included SSRIs, SNRIs, TCAs, bupropion, mirtazapine, trazodone, vilazodone, and vortioxetine. Study investigators found that while SNRIs were associated with an increased incidence of adverse events compared to placebo (high strength of evidence [SOE]), SSRIs showed a similar frequency compared to placebo (moderate SOE). Falls were reported more often with duloxetine than placebo (moderate SOE). Limited data prevented differentiation of adverse events for bupropion, mirtazapine, trazadone, or vortioxetine. Since the studies were not designed to evaluate adverse events and there were few head-to-head comparisons among the antidepressants, no conclusions could be drawn comparing agents within a class.

DRUG INFORMATION **HIGHLIGHTS**

- Update on consumer-level recalls of generic antihypertension medications due to potential human carcinogenic impurities: Teva expanded its voluntary recall to include an additional 6 lots of bulk losartan potassium USP tablets (50 mg and 100 mg). In addition, Macleods Pharmaceuticals initiated a voluntary recall of 32 lots of losartan potassium USP tablets 50 mg strength and losartan potassium/hydrochlorothiazide tablets (various strengths). Both recalls are based on detection of N-nitroso-N-methyl-4-amino butyric acid (NMBA) derived from active pharmaceutical ingredient (API) from Hetero Labs.
- Approved in March 2019, Sage Therapeutics' brexanolone (Zulresso™) was recently assigned Schedule IV classification of the Controlled Substance Act by the Drug Enforcement Administration (DEA). The gamma-aminobutyric acid (GABA) A receptor positive modulator is indicated for the treatment of postpartum depression. The medication is only available via a restricted Risk Evaluation and Mitigation Strategies (REMS) program and is administered in medically supervised settings as a continuous 60-hour intravenous (IV) infusion.
- Based on a routine FDA inspection, Pharm D Solutions issued a voluntary consumer-level recall of all sterile compounded drug products within expiry. The FDA found a potential risk of contamination of products intended to be sterile.
- Heritage Pharmaceuticals initiated a consumer-level voluntary recall of 1 lot each of amikacin sulfate injection, USP, 1 g/4 mL (250 mg/mL) and prochlorperazine edisylate injection, USP, 10 mg/2 mL due to potential for microbial growth. There were no reports of adverse events.
- Jazz Pharmaceuticals' oral dual-acting dopamine and norepinephrine reuptake inhibitor solriamfetol (Sunosi™) was also designated Schedule IV Controlled Substance classification. The agent was FDA approved in March 2019 for excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea. Product launch is planned in early July 2019.
- The FDA approved a new 100 mg/mL formation for mepolizumab (Nucala®), indicated for eosinophilic asthma and eosinophilic granulomatosis with polyangiitis, to allow for subcutaneous (SC) administration by the patient or caregiver via a single-dose prefilled auto-injector or syringe. Previously, Nucala was only approved as 100 mg of lyophilized powder in a single-dose vial (SDV) for reconstitution to be given by a healthcare professional (HCP).
- The FDA launched a pilot program called Project Facilitate, designed to assist HCPs requesting access to unapproved cancer treatments outside of clinical trials. As a single point of contact, the FDA will guide HCPs through the Expanded Access program when patients with an immediately life-threatening or serious condition have no alternative options for treatment. The FDA also created a new call center to facilitate the request process. The pilot program will help the FDA evaluate access to investigational treatment and its benefit to patients. Additionally, the Reagan-Udall Foundation, created by Congress, updated its Expanded Access Navigator internet resource that educates patients and HCPs on the request process. Moreover, the FDA recently posted guidance urging drug manufacturers to expand their clinical trial eligibility criteria to allow more patients with cancer to participate.

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

- **Jul-Aug 2019:** pitolisant; oral central nervous system stimulant (histamine H3-receptor antagonist/inverse agonist); narcolepsy; Harmony.
- **July 05, 2019:** selinexor; oral nuclear export inhibitor; multiple myeloma; Karyopham.
- **July 11, 2019:** ketotifen preservative-free; ophthalmic histamine antagonist/mast cell stabilizer; allergic conjunctivitis; Bausch Health.
- **July 16, 2019:** relebactam/imipenem/cilastatin; IV beta-lactamase inhibitor/dehydropeptidase inhibitor/beta-lactam antibiotic; complicated intra-abdominal and urinary tract infections (UTI); Merck.
- **July 19, 2019: a**premilast (Otezla®); oral phospho-diesterase 4 (PDE4) inhibitor; Behçet syndrome; Celgene.
- **July 19, 2019:** riluzole; sublingual glutamate modulator; amyotrophic lateral sclerosis; Biohaven.
- **July 26, 2019:** ferric maltol; oral iron supplement; anemia; Shield.
- **August 1, 2019:** filgrastim, biosimilar to Neupogen®; IV/SC colony stimulating factor; neutropenia/leukopenia; Tanvex.
- **August 2, 2019:** pexidartinib; oral tyrosine kinase inhibitor; pigmented villonodular synovitis; Daiichi Sankyo.
- **August 14, 2019:** cefiderocol; IV cephalosporin; complicated UTI; Shionogi.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
alpelisib (Piqray®) Novartis	• BLA approval 05/24/2019; Priority Review; Real-Time Oncology Review • Indicated in combination with fulvestrant for men and postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, phosphatidylinositol-3-kinase catalytic α-subunit (PIK3CA)-mutated, advanced or metastatic breast cancer, as detected by an FDA-approved test, following progression on or after an endocrine-based regimen » FDA also approved the Therascreen® PIK3CA companion diagnostic test • Phosphatidylinositol-3-kinase (PI3K) inhibitor • Tablet: 50 mg, 150 mg, and 200 mg • Recommended dosage is 300 mg (2 x 150 mg tablets) orally once daily with food; dose may be modified based on adverse effects; continue treatment until disease progression or unacceptable toxicity
polatuzumab vedotin-piiq (Polivy™) Genentech	• BLA approval 06/10/2019; Accelerated Approval; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated in combination with bendamustine and a rituximab product for the treatment of adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after ≥ 2 prior therapies • CD79b-directed antibody-drug conjugate • Injectable: 140 mg lyophilized powder in a SDV • Recommended initial dose is 1.8 mg/kg IV over 90 minutes every 21 days for 6 cycles; subsequent infusions may be administered over 30 minutes as tolerated • Product is currently available through authorized specialty distributors
bremelanotide (Vyleesi™) AMAG	• NDA approval 6/21/2019 • Indicated for premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to: a co-existing medical or psychiatric condition, problems with the relationship, or the effects of a medication or drug substance » It is not indicated for use in men or postmenopausal women and is not indicated to enhance sexual performance • Melanocortin 4 receptor agonist • Injectable: 1.75 mg/0.3 mL autoinjector • Recommended dosage is 1.75 mg self-administered SC, as needed, at least 45 minutes prior to anticipated sexual activity; maximum 1 dose in 24 hours and 8 doses per month • Product availability is anticipated in September 2019 through select specialty pharmacies
Expanded Indications	
aflibercept (Eylea®) Regeneron	• sBLA approval 05/13/2019 • Expanded indication to treat all stages of diabetic retinopathy (DR); previously limited to patients with diabetic macular edema • Dosage for DR remains at 2 mg (0.05 mL) intravitreally every 4 weeks for 5 injections, then 2 mg every 8 weeks thereafter
avelumab (Bavencio®) EMD Serono	• sBLA approval 05/14/2019; Breakthrough Therapy; Priority Review • New indication for use in combination with axitinib for first-line treatment of advanced renal cell carcinoma (RCC) • Recommended dosage is 800 mg administered IV over 60 minutes every 2 weeks in combination with axitinib 5 mg orally twice daily

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications *continued*
venetoclax (Venclexta®) Abbvie	• sNDA approval 05/15/2019; Breakthrough Therapy; Orphan Drug; Priority Review; Real-Time Oncology Review • Expanded indication for use in combination with obinutuzumab in previously untreated patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) » The indication is no longer restricted to use in patients who received ≥ 1 prior therapy, including use as monotherapy or in combination with rituximab • Following completion of the 5-week ramp-up period (available as a CLL/SLL starting pack), venetoclax is continued as 400 mg orally once daily from cycle 3 day 1 until the last day of cycle 12
dalteparin sodium (Fragmin®) Pfizer	• sNDA approval 05/16/2019; Priority Review • New indication for the SC injection for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients ≥ 1 month of age • Recommended dosage is based on age and weight and is administered SC twice daily; maintenance dose is based on anti-Xa level
pitavastatin (Livalo®) Kowa	• sNDA approval 05/16/2019 • Expanded indication to include pediatric patients as young as 8 years of age as adjunctive therapy to diet in patients with HeFH to reduce elevated total cholesterol (TC), LDL-C, and apolipoprotein B (Apo B), and to increase high-density lipoprotein cholesterol (HDL-C) » Previously approved in adults with primary hyperlipidemia or mixed dyslipidemia • Recommended initial dose in pediatrics is 2 mg orally once daily; maximum daily dose is 4 mg
teduglutide (Gattex®) Shire-NPS	• sNDA approval 05/16/2019; Orphan Drug • Expanded indication for the treatment of short bowel syndrome (SBS) in patients who are dependent on parenteral support to include pediatric patients aged 1 to 18 years • Recommended dosage is 0.05 mg/kg SC once daily for adult and pediatric patients
trastuzumab-pkrb (Herzuma®) Teva	• sBLA approval 05/16/2019 • Expanded indication as a single agent following multi-modality anthracycline-based therapy for adjuvant treatment of HER2 overexpressing breast cancer • New indication for use in combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of HER2 overexpressing metastatic gastric or gastroesophageal junction cancer in patients who have not had prior treatment for metastatic disease • FDA approved a new 150 mg SDV • Recommended initial dosages for the new and expanded indications are 8 mg/kg IV over 90 minutes, then 6 mg/kg IV over 30 to 90 minute every 3 weeks; duration as a single-agent adjuvant therapy for breast cancer is for a total of 52 weeks; duration for gastric and gastroesophageal cancer is until disease progression
pregabalin (Lyrica®) Pfizer	• sNDA approval 05/23/2019 • Expanded indication to include patients 1 month to < 4 years of age as adjunctive therapy for partial-onset seizures • Recommended dosages: » For patients weighing < 30 kg: 3.5 mg/kg/day in 2 or 3 divided doses, depending on age; maximum daily dose is 14 mg/kg » For patients weighing ≥ 30 kg: 2.5 mg/kg/day in 2 or 3 divided doses; maximum daily dose is 10 mg/kg/day, and not to exceed 600 mg/day

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications *continued*
rituximab-abbs (Truxima®) Teva	• sBLA approval 05/23/2019 • Expanded indication for the treatment of adults with previously untreated DLBCL, CD20-positive non-Hodgkin's lymphoma (NHL) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens • New indication for the treatment of adults with previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC) • Recommended dosages: » For NHL is 375 mg/m^2 administered via IV infusion on day 1 of each chemotherapy cycle for up to 8 infusions » For CLL is 375 mg/m^2 for the administered IV infusion the day before the first FC cycle, then 500 mg/m^2 on day 1 of cycles 2 through 6 (28-day cycles)
cariprazine (Vraylar®) Allergan	• sNDA approval 05/24/2019 • Expanded indication for the treatment of depressive episodes associated with bipolar I disorder in adults • Recommended initial dosage is 1.5 mg daily; may increase to 3 mg daily
ruxolitinib (Jakafi®) Incyte	• sNDA approval 05/24/2019; Priority Review • New indication for steroid-refractory acute graft-versus-host disease (GVHD) in adult and pediatric patients ≥ 12 years of age • Recommended initial dose is 5 mg given orally twice daily; may increase to 10 mg twice daily depending on neutrophil and platelet responses
lenalidomide (Revlimid®) Celgene	• sNDA 05/28/2019; Orphan Drug; Priority Review • New indications for use in combination with a rituximab product for previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL) • Recommended dosage for both indications is 20 mg once daily orally on days 1 through 21 of a 28-day cycle for up to 12 cycles
ceftolozane/ tazobactam (Zerbaxa®) Merck	• sNDA approval 06/03/2019; Qualified Infectious Disease Product; Priority Review • New indications for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in adults • Recommended dosage for both indications is 3 g administered via IV infusion every 8 hours for 8 to 14 days
galcanezumab-gnlm (Emgality®) Eli Lilly	• sBLA approval 06/04/2019; Breakthrough Therapy; Priority Review • New indication for the treatment of episodic cluster headaches • New formulation approved as a 100 mg/mL solution in a single-dose prefilled syringe • Recommended dosage is 300 mg SC (administered as 3 consecutive 100 mg injections) at the onset of the cluster period and then monthly until the end of the cluster period
deflazacort (Emflaza®) Marathon	• sNDA approval 06/07/2019; Orphan Drug • Expanded indication for the treatment of Duchenne muscular dystrophy to include patients 2 to < 5 years of age; previously approved in patients ≥ 5 years • Recommended dosage is 0.9 mg/kg orally once daily for all approved ages
liraglutide (Victoza®) Novo Nordisk	• sNDA approval 06/17/2019 • Expanded indication to include pediatric patients ages ≥ 10 years with T2DM • Recommended initial pediatric dose is 0.6 mg daily; after ≥ 1 week intervals, may increase dose to 1.2 mg daily and then to 1.8 mg daily, if needed, for glycemic control

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