MAY 2019

# MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS



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## FDA ALERT ON VENCLEXTA® AND MULTIPLE MYELOMA

The United States (US) Food and Drug Administration (FDA) alerted the public of risks associated with the investigational (off-label) use of venetoclax (Venclexta) in patients with multiple myeloma (MM). This is based on findings from the BELLINI clinical trial that showed, after a median follow-up of 17.9 months, there was an increased risk of death with venetoclax (21.1%) compared to placebo (11.3%) when used in combination with bortezomib (Velcade®) and dexamethasone in patients with relapsed/refractory MM (hazard ratio [HR], 2.03). Conversely, there was also a significant improvement in progression-free survival associated with venetoclax compared to placebo (22.4 versus 11.5 months, repectively; HR, 0.63). Trial enrollment of new patients in BELLINI was halted; however, patients who were receiving clinical benefit could continue treatment following reconsent. Also, enrollment in other MM trials with venetoclax was suspended. Notably, this alert does not apply to FDA-approved indications for venetoclax; therefore, patients taking venetoclax for treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma or acute myeloid leukemia should continue their prescribed therapy.

## ADA LIVING STANDARDS FOR DIABETES

The American Diabetes Association (ADA) has established their Standards of Medical Care in Diabetes as a "living" document where new pertinent information is incorporated as appropriate. Recently, data from the REDUCE-IT trial demonstrated a reduction in cardiovascular (CV) events with the lipid-regulating agent icosapent ethyl (Vascepa®). This data led to a recommendation to consider the lipid-regulating agent for select patients with diabetes and atherosclerotic CV disease (ASCVD) or other cardiac risk factors if the patient's low density lipoprotein cholesterol (LDL-C) is controlled with statin therapy but elevated triglycerides levels (135 to 499 mg/dL) persist. Furthermore, the DECLARE-TIMI 58 trial revealed that treatment with dapagliflozin (Farxiga®) resulted in reductions in hospitalization for heart failure (HF) and progression of chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM). As a result, the ADA added dapagliflozin as an antidiabetic option in patients with HF or risk of CKD. Based on dapagliflozin labeling revisions for patients with diabetes and CKD, the approved use per estimated glomerular filtration rate (eGFR) has been revised from ≥ 60 mL/min/1.73 $m^2$ to ≥ 45 mL/min/1.73 $m^2$.

## IDSA GUIDANCE FOR ASYMPTOMATIC BACTERIURIA

The Infectious Diseases Society of America (IDSA) updated their 2005 guidelines on the management of asymptomatic bacteriuria (ASB). Antimicrobial treatment of ASB is recognized as an important contributor to inappropriate antimicrobial use, which promotes emergence of antimicrobial

resistance. The updated guidelines attempt to improve antibiotic stewardship. Furthermore, new recommendations are included for populations not previously addressed.

Screening and treatment for ASB continue to be recommended in pregnant women and patients undergoing certain urologic procedures. Conversely, the IDSA advises against routine screening and treatment in infants and children, people undergoing non-urologic surgery, solid organ transplant recipients, and diabetic men and women. In patients with spinal cord injuries, prescribers should consider atypical presentation of urinary tract infections in treatment decision making. To avoid adverse antimicrobial therapy outcomes in older patients with functional and/or cognitive impairment, the IDSA recommends careful monitoring and assessment of potential non-ASB causes in patients with ASB who experience acute mental status change or a fall, rather than antimicrobial treatment for ASB. Due to insufficient data, no recommendations are provided for or against screening and treatment of ASB in high-risk neutropenic patients.

## OSTEOPOROSIS GUIDELINE UPDATE

The Endocrine Society (ES) released guidelines on osteoporosis treatment in postmenopausal women who are at high risk of fractures, and they included an algorithm to guide therapy decisions. The ES prefers bisphosphonates to reduce fracture risk, while denosumab is an alternative initial therapy. A 2-year regimen of teriparatide (Forteo®) or abaloparatide (Tymlos®) is recommended in patients with very high risk of fracture, and after 2 years, the patient can be switched to a bisphosphate to maintain bone mineral density (BMD). When bisphosphonate and denosumab are not appropriate, a selective estrogen receptor modulator (SERM) (raloxifene [Evista®]) or bazedoxifene (a component in Duavee®) is recommended in patients with a low risk for deep vein thrombosis (DVT) or a high risk of breast cancer. Menopausal hormone therapy (estrogen-only or tibolone) is suggested in select women aged < 60 years or < 10 years past menopause who are at low risk of DVT and without breast cancer or other contraindications. Calcitonin nasal spray is suggested in high-risk women who cannot tolerate the other therapies. Calcium and vitamin D should always be used as adjunctive therapy.

The ES recommends obtaining BMD measurements every 1 to 3 years during treatment to assess response to therapy. After 3 to 5 years of bisphosphate therapy, a drug holiday for up to 5 years can be considered if fracture risk is determined to be low to moderate. BMD should be reassessed every 2 to 4 years during a drug holiday. For denosumab therapy monitoring, BMD should be reassessed after 5 to 10 years of treatment.

Notably, the ES recommendations differ from recent guidelines by the American College of Physicians (ACP). The ACP recommends against BMD monitoring during the treatment period as well as the use of raloxifene or menopausal hormones. The ACP also does not differentiate between length of therapy for bisphosphonates and denosumab and does not address the use of teriparatide or abaloparatide.

## BEHAVIORAL HEALTH CORNER

### FDA ACTIONS ON OPIOID PRESCRIBING

The FDA received reports of serious harm after rapid dose decreases or abrupt discontinuation of opioids in patients physically dependent on opioid pain medicines. While labels for opioids currently advise against abrupt discontinuation, the FDA is now requiring the addition of guidance on how to safely taper dosages in patients who are physically dependent on opioid analgesics. A rapid decrease in dose can result in uncontrolled pain or withdrawal symptoms. This can cause patients to seek other sources of opioid pain medicines and may be mistaken for drug-seeking for the purpose of abuse. Moreover, patients may attempt to treat their pain or withdrawal symptoms with illicit opioids. The FDA recommends an individualized approach to tapering off an opioid following consideration of several factors, including the opioid dosage, duration of treatment, type of pain being treated, and the physical and psychological status of the patient.

The FDA is also strengthening the Risk Evaluation and Mitigation Strategy (REMS) program around transmucosal immediate-release fentanyl (TIRF) products. The FDA states that while outpatient use of TIRF products has declined in recent years, data indicates that some prescribing is not consistent with the approved labeling. Specifically, an estimated 35% to 55% of patients prescribed a TIRF were not opioid-tolerant, which is a contraindication for these products, and many patients were being treated off-label for non-cancer-related pain. Now, the FDA is requiring that prescribers document the patient's opioid tolerance with each outpatient TIRF prescription. Opioid tolerance must also be recorded at inpatient and outpatient pharmacies at the time of dispensing. Lastly, a new patient registry will be created to monitor for serious adverse events, including fatal and non-fatal overdose.

# DRUG INFORMATION **HIGHLIGHTS**

- Final approval was granted to Teva's naloxone 4 mg/0.1 mL nasal spray, the first generic of Narcan® nasal spray, indicated for the emergency treatment of known or suspected opioid overdose. This marks the first generic nasal formulation for use without training by individuals in the community. A launch date has not been announced and could potentially be delayed due to litigation.
- Alvogen announced a voluntary consumer-level recall of 2 lots of fentanyl transdermal system 12 mcg/h patches due to mislabeling. In the affected lots, 50 mcg/h patches individually labeled as 50 mcg/h were found in cartons labeled 12 mcg/h. Use of a 50 mcg/h patch instead of a prescribed 12 mcg/h patch could result in serious, life-threatening, or fatal respiratory depression. No cases of adverse events have been reported.
- Update on consumer-level recalls of generic antihypertension medications due to potential human carcinogenic impurities: Torrent expanded their recall of losartan-containing products to include an additional 36 lots of losartan potassium tablets and 68 lots of losartan potassium/hydrochlorothiazide. Legacy added 1 more lot of losartan potassium tablets to their recall. Teva also recalled 35 lots of bulk losartan potassium tablets due to the presence of N-nitroso-N-methyl-4-aminobutyric acid (NMBA). Additionally, to ensure patient access to losartan, the FDA announced that it will temporarily allow certain manufacturers to distribute losartan tablets containing NMBA above 0.96 parts per million (ppm) and below 9.82 ppm. An adequate nitrosamine-free supply of losartan is anticipated in the US in approximately 6 months.
- The agency approved the reintroduction of US WorldMeds' tegaserod (Zelnorm™) for irritable bowel syndrome with constipation (IBS-C) in women < 65 years of age. The product was originally approved in 2002 and was voluntarily withdrawn from the US market in 2007 due to a potential risk of CV ischemic events; it did remain available for compassionate use. Prior to its market removal, tegaserod was indicated in women with IBS-C with no age restriction and in nongeriatric adults with chronic idiopathic constipation. While women with low CV risk (generally, women aged < 65 years) are expected to have the most favorable benefit-to-risk profile, CV adverse events remain a primary concern. Contraindications now include history of myocardial infarction (MI), transient ischemic attack, stroke, angina, or intestinal ischemic conditions. Tegaserod is approved as 6 mg tablets to be dosed twice daily. Treatment should be discontinued if response is not seen after 4 to 6 weeks. Unrestricted distribution is expected.
- 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), Teva's generic version of Epipen (limited supply), and Adamis' Symjepi® 0.3 mg (clinics and institutions only). Symjepi 0.15 mg and Teva's generic for Epipen Jr have not launched in the US.

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

- **Quarter 2, 2019:** bevacizumab, biosimilar to Genentech's Avastin; intravenous (IV) vascular endothelial growth factor (VEGF) inhibitor; non-small cell lung cancer (NSCLC), colorectal cancer, ovarian cancer, renal cancer; Pfizer
- **Quarter 2, 2019:** cariprazine (Vraylar®); oral atypical antipsychotic; bipolar 1 disorder depression; Allergan
- **Quarter 2, 2019:** rituximab, biosimilar to Genentech's Rituxan®; IV anti-CD20 antibody; non-Hodgkin's lymphoma, rheumatoid arthritis; Pfizer
- **May 2019:** adalimumab, biosimilar to Abbvie's Humira®; subcutaneous (SC) tumor necrosis factor (TNF) inhibitor; several autoimmune conditions; Samsung Bioepis/Merck
- **May 2019:** dapagliflozin (Farxiga®); oral sodium-glucose cotransporter-2 inhibitor; T2DM-related CKD; AstraZeneca
- **May 2019:** exenatide extended-release (Bydureon®); SC glucagon-like peptide-1 receptor agonist; T2DM-related CV events; AstraZeneca
- **May 2019:** onasemnogene abeparvovec; IV gene therapy; spinal muscular atrophy; Novartis
- **May 13, 2019:** aflibercept (Eylea®); intravitreal VEGF inhibitor; non-proliferative diabetic retinopathy; Regeneron
- **May 24, 2019:** ruxolitinib (Jakafi®); oral Janus kinase inhibitor; graft versus host disease; Incyte
- **May 28, 2019:** NKTR-181; oral opioid agonist; chronic low back pain; Nektar
- **June 3, 2019:** ceftolozane/tazobactam (Zerbaxa®); IV cephalosporin/beta-lactam antibiotic; hospital-acquired pneumonia; Merck

## RECENT FDA APPROVALS

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** |
| siponimod (Mayzent®) Novartis | • NDA approval 03/26/2019; Priority Review<br>• Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease in adults<br>• Sphingosine 1-phosphate receptor modulator<br>• Tablets: 0.25 mg and 2 mg<br>• After treatment titration, the recommended maintenance dose is 2 mg orally once daily starting on day 6; dosage adjustments for patients with select CYP2C9 genotypes are provided in the prescribing information |
| testosterone undecanoate (Jatenzo®) Clarus | • 505(b)(2) NDA approval 03/27/2019<br>• Indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone<br>• Androgen<br>• Capsules: 158 mg, 198 mg, and 237 mg<br>• Recommended starting dose is 237 mg orally twice daily (morning and evening) with food; the minimum recommended dose is 158 mg twice daily and the maximum recommended dose is 396 mg (two 198 mg capsules) twice daily based on serum testosterone levels<br>• Boxed warning for increased blood pressure |
| aclidinium bromide/ formoterol fumarate (Duaklir® Pressair®) AstraZeneca | • NDA approval 03/29/2019<br>• Indicated for maintenance treatment of chronic obstructive pulmonary disease (COPD)<br>» It is not indicated for the relief of acute bronchospasm or for the treatment of asthma<br>• Fixed-dose anticholinergic and a long-acting beta2-adrenergic agonist (LABA) combination<br>• Breath-actuated dry powder inhaler: aclidinium bromide 400 mcg and formoterol fumarate 12 mcg per actuation<br>• Recommended dosage is 1 oral inhalation twice daily<br>• Product availability is expected in the second half of 2019 |
| acyclovir (Avaclyr™) Fera | • 505(b)(2) NDA approval 03/29/2019; Orphan Drug<br>• Indicated for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus (HSV-1 and HSV-2)<br>• Synthetic HSV nucleoside analog DNA polymerase inhibitor<br>• Ophthalmic ointment: acyclovir 3%<br>• Recommended dosage is a 1 cm ribbon of ointment applied to the lower cul-de-sac of the affected eye 5 times daily (approximately every 3 hours while awake) until the corneal ulcer heals, then a 1 cm ribbon 3 times daily for 7 days |
| cladribine (Mavenclad®) EMD Serono | • NDA approval 03/29/2019<br>• Indicated for relapsing forms of MS in adults, including relapsing-remitting disease and active secondary progressive disease<br>» Use is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug for MS<br>» Not indicated for patients with CIS<br>• Nucleoside metabolic inhibitor<br>• Tablet: 10 mg<br>• Recommended cumulative dosage is 3.5 mg/kg orally, divided into 2 yearly treatment courses (1.75 mg/kg/treatment course); each treatment course is divided into 2 treatment cycles; details are provided in the prescribing information<br>• Boxed warnings for malignancies and teratogenicity |

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 |
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| immune globulin IV, human – slra (Asceniv™) ADMA Biologics | • BLA approval 04/01/2019<br>• Indicated for the treatment of primary humoral immunodeficiency in adults and adolescents (12 to 17 years old)<br>• Concentrated human immunoglobulin (IgG) antibodies<br>• Injectable solution: 10% IgG (100 mg/mL) in a 50 mL single-use vial<br>• Recommended dosage is 300 to 800 mg/kg IV every 3 to 4 weeks<br>• Boxed warnings for thrombosis, renal dysfunction, and acute renal failure<br>• Product availability is expected in the second half of 2019 |
| dolutegravir/ lamivudine (Dovato®) ViiV | • NDA approval 04/08/2019<br>• Indicated as a complete regimen for the treatment of human immunodeficiency virus type-1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known substitutions associated with resistance to dolutegravir or lamivudine<br>• Integrase strand transfer inhibitor (INSTI) and nucleoside analogue reverse transcriptase inhibitor (NRTI)<br>• Fixed-dose combination tablet: dolutegravir 50 mg and lamivudine 300 mg<br>• Recommended dosage is 1 tablet orally once daily with or without food<br>• Boxed warning for lamivudine-resistant hepatitis B virus (HBV) infection and HBV exacerbation in HIV/HBV co-infected patients |
| romosozumab-aqqg (Evenity™) Amgen | • BLA approval 04/09/2019<br>• Indicated for the treatment of osteoporosis in postmenopausal women at high risk for fracture, defined as a history of osteoporotic fracture or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy<br>» Limit duration of use to 12 monthly doses; if osteoporosis therapy remains warranted, continued therapy with an anti-resorptive agent should be considered<br>• Sclerostin inhibitor<br>• Injectable solution: 105 mg/1.17 mL in a single-use prefilled syringe (PFS)<br>• Recommended dosage is 210 mg administered as 2 SC injections (2 syringes, one after the other) once every month for 12 doses<br>• Boxed warning for MI, stroke, and CV death |
| erdafitinib (Balversa™) Janssen | • NDA approval 04/12/2019; Accelerated Approval; Breakthrough Therapy; Priority Review<br>• Indicated for the treatment of adults with locally advanced or metastatic urothelial carcinoma that has susceptible fibroblast growth factor receptor (FGFR) 3 or FGFR2 genetic alterations and has progressed during or following at least 1 line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy; select patients for therapy based on an FDA-approved companion diagnostic<br>• FGFR kinase inhibitor<br>• Tablets: 3 mg, 4 mg, and 5 mg<br>• Recommended starting dose is 8 mg (two 4 mg tablets) orally once daily; may increase to 9 mg (three 3 mg tablets) once daily based on serum phosphate levels and tolerability at 14 to 21 days; administered until disease progression or unacceptable toxicity occurs<br>• Product will be available via a single-source specialty pharmacy provider |

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| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| risankizumab-rzaa (Skyrizi™) Abbvie | • BLA approval 04/23/2019<br>• Indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy<br>• Interleukin-23 inhibitor<br>• Injectable solution: 75 mg/0.83 mL in each single-dose PFS<br>• Recommended dose is 150 mg SC (2 injections) at weeks 0 and 4 followed by 150 mg every 12 weeks thereafter; may be self-administered with proper training |
| **Expanded Indications** | |
| atezolizumab (Tecentriq®) Genentech | • sBLA approval 03/18/2019; Orphan Drug; Priority Review<br>• New indication for use in combination with carboplatin and etoposide for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC)<br>• Recommended dosage is 1,200 mg IV infusion every 3 weeks until disease progression or unacceptable toxicity |
| certolizumab pegol (Cimzia®) UCB | • sBLA approval 03/28/2019<br>• New indication for the treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation<br>• Recommended dose is 400 mg SC (2 injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks |
| palbociclib (Ibrance®) Pfizer | • sNDA approval 04/04/2019<br>• Expanded indication for use with an aromatase inhibitor or fulvestrant to include men with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer<br>• Recommended starting dose is 125 mg once daily taken with food for 21 days followed by 7 days off treatment |
| pembrolizumab (Keytruda®) Merck | • sBLA approvals 04/11/2019 and 04/19/2019; Accelerated Approval; Breakthrough Therapy; Priority Review (all designations for renal cell carcinoma [RCC])<br>• New indication as a single agent for the first-line treatment of patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation, or for metastatic NSCLC in patients whose tumors express PD L1 (Tumor Proportion Score [TPS] ≥1%), as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations<br>• New indication in combination with axitinib for the first-line treatment of patients with advanced RCC<br>• Recommended dosage (for both indications) is 200 mg via IV infusion every 3 weeks |
| ivabradine (Corlanor®) Amgen | • NDA approval 04/22/2019; Orphan Drug; Priority Review<br>• New indication for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged ≥ 6 months who are in sinus rhythm with an elevated heart rate<br>• Recommended starting dose is 0.05 mg/kg twice daily with food; adjust dose based on heart rate; maximum dose is 0.2 mg/kg (ages 6 months to < 1 year) or 0.3 mg/kg (ages ≥ 1 year), up to 7.5 mg twice daily<br>• A new 5 mg/5 mL oral solution was FDA-approved with similar adult and pediatric indications as the oral tablets (5 mg and 7.5 mg) |

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**References:**

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