DECEMBER 2018

# MRx CLINICAL ALERT

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## *HOT TOPIC:* FDA APPROVES THREE NEW BIOSIMILARS

On November 28, 2018, the United States (US) Food and Drug Administration (FDA) approved the first biosimilar to Genentech's CD20-directed antibody rituximab (Rituxan®). Rituximab-abbs (Truxima®), by Celltrion/Teva was approved for the treatment of adults with: (1) relapsed or refractory, low grade or follicular, CD20-positive B cell non-Hodgkin's lymphoma (NHL) as a single agent; (2) previously untreated follicular, CD20-positive, B cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy; or (3) non-progressing (including stable disease), low-grade, CD20-positive, B cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy. Due to the current patent protection for Rituxan, Celltrion/Teva did not seek approval for diffuse large B cell CD20-positive NHL or non-oncologic indications. Like Rituxan, Truxima carries boxed warnings for hepatitis B reactivation and life-threatening effects, such as infusion reactions, mucocutaneous adverse effects, and progressive multifocal leukoencephalopathy (PML). Truxima is only administered via intravenous (IV) infusion by a healthcare professional (HCP) with appropriate medical support.

The FDA also recently approved 2 biosimilars for *eligible* indications of their reference products. Each marks the third biosimilar approved in the US for its respective originator product. Sandoz's adalimumab-adaz (Hyrimoz™), a biosimilar to Abbvie's adalimumab (Humira®), was approved to treat rheumatoid arthritis, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, and ulcerative colitis; its availability is not expected until 2023. Coherus's pegfilgrastim-cbqv (Udenyca™) was approved as a biosimilar to Amgen's pegfilgrastim (Neulasta®) and is indicated to decrease the occurrence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. Market launch of Udenyca is planned for January 3, 2019.

Biosimilars may offer improved access to important biologic medications. Their approval is based on data that demonstrate no clinically meaningful differences between the biosimilar product and its reference product regarding potency, safety, and purity. Data may include structural and functional description, animal studies, human pharmacokinetic and pharmacodynamic studies, immunogenicity, and other safety and efficacy data. No biosimilar approved in the US, however, is deemed interchangeable with its reference product by the FDA.

## HYPERLIPIDEMIA GUIDELINE UPDATE

The American Heart Association (AHA) and American College of Cardiology (ACC), along with several other relevant professional organizations, published updated guidance on optimal lipid management. Foremost, the guidelines emphasize a heart-healthy lifestyle for all ages, including recommendations on diet composition, weight control, and physical activity. Extensive recommendations are also made regarding pharmacologic treatment in several subpopulations.

The AHA/ACC expanded upon the use of the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score introduced in 2013, urging clinicians to consider risk-enhancing factors, such as family history of premature ASCVD, persistent low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL, persistent triglycerides ≥ 175 mg/dL, metabolic syndrome, chronic kidney disease (CKD), history of preeclampsia or premature menopause, chronic inflammatory disorders, and high-risk ethnic groups, among others, when considering antilipid therapy. Coronary calcium score may also be used when uncertainty exists for ASCVD risk level. For primary prevention in patients ages 40 to 75 years with LDL-C 70 to 189 mg/dL, lifestyle management alone is advised in those with low ASCVD risk (10-year risk < 5%). For patients with borderline risk (10-year risk 5% to < 7.5%), moderate-intensity statin therapy may be added if risk enhancers are present. Moderate-intensity statin therapy with a goal to reduce LDL-C by 30% to 49% is recommended in patients with intermediate risk (10-year risk ≥ 7.5% to < 20%). High-intensity statin therapy to reduce LDL-C by ≥ 50% is recommended in high-risk (10-year risk ≥ 20%) patients. Additional details are provided in the guidelines for primary prevention in older adults, pediatrics, and other populations at risk.

Key changes around secondary prevention include the identification of a very high-risk group for a recurrent CV event. Very high-risk patients include those with a history of multiple major ASCVD events (e.g., myocardial infarctions [MI], acute coronary syndrome [ACS] events, stroke, symptomatic peripheral arterial disease) or 1 major ASCVD event and multiple high-risk conditions (e.g., age ≥ 65 years, uncontrolled hypertension, diabetes mellitus, smoking, CKD, familial hyperlipidemia). Patients at very high risk may benefit from the addition to maximally tolerated statin therapy of ezetimibe followed by a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

Therapy adherence and response should be assessed with fasting or non-fasting lipid measurement every 4 to 12 weeks following treatment initiation or dose adjustment, with repeated assessment every 3 to 12 months as needed. Notably, the guidelines state that based on mid-2018 list prices, PCSK9 inhibitors have a low cost value in patients with clinical ASCVD and an uncertain value in those without clinical ASCVD on maximally-tolerated statin and ezetimibe therapy.

## CARRIER TUBE CONCERNS FOR EPIPEN®

The FDA alerted patients, caregivers, and HCPs that improperly applied labels of some Epipen® 0.3 mg and Epipen Jr® 0.15 mg (epinephrine) auto-injectors, including authorized generic (AG) versions, may hinder easy removal of the device from the carrier tube. This will not, however, affect proper functioning of the device, which is indicated for the emergency treatment of allergic reactions, including anaphylaxis. Patients and HCPs should inspect epinephrine auto-injectors to ensure quick access to the product in an emergency situation. No adverse events related to this issue have been reported.

## THIRD ANTIDIABETIC AGENT GAINS CARDIOVASCULAR (CV) INDICATION

Janssen's sodium-glucose cotransporter 2 (SGLT2) inhibitor, canagliflozin (Invokana®), used to manage type 2 diabetes mellitus (T2DM), was granted a new indication by the FDA to reduce the risk of major adverse CV events (MACE) in adults with T2DM and established CV disease (CVD); the new indication also applies to the canagliflozin/metformin combination products Invokamet® and Invokamet XR. The SLGT2 inhibitor empagliflozin (Jardiance®) and the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Victoza®) carry similar indications; however, empagliflozin's indication is for risk reduction of CV death only, rather than MACE, which includes CV death, MI, and stroke.

Canagliflozin's new indication is supported by results of the CANagliflozin cardioVascular Assessment Study trials (CANVAS, CANVAS-R), which included 10,134 patients with T2DM and established CVD. Canagliflozin, at daily doses of 100 mg and titrated to 300 mg, based on glycemic control and tolerability, or placebo was added to standard of care for diabetes and ASCVD. After a mean exposure of 149 weeks, compared to placebo, canagliflozin reduced the risk of first occurrence of MACE by 14% overall (Hazard Ratio [HR] 0.86; 95% confidence interval [CI], 0.75 to 0.97). Reductions in all components of MACE were demonstrated; CV death: HR 0.87 (95% CI, 0.72, 1.06), non-fatal MI: HR 0.85 (95% CI, 0.69 to 1.05), and non-fatal stroke: HR 0.9 (95% CI, 0.71 to 1.15).

# DRUG INFORMATION **HIGHLIGHTS**

- The intermittent shortage of epinephrine auto-injectors persists nationwide in the US. Impax's AG versions of the discontinued Adrenaclick® continue to be on backorder with periodic shipments to distributors; they do not have full inventory at this time. Likewise, Mylan reports that they are shipping Epipen 0.3 mg, Epipen Jr 0.15 mg, and their respective AGs intermittently to some distributors; supply stabilization is expected by the end of 2018. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Teva's generic version of Epipen has entered the US market and is available in limited supply; additional supply plus launch of its generic of Epipen Jr are expected in 2019. Adamis' Symjepi® 0.3 mg and 0.15 mg have not entered the US market.
- Flu Season Update (2018–2019): The Centers for Disease Control and Prevention (CDC) reported increased influenza activity during the week ending 11/24/2018. In the US, 2 states reported high activity, 3 states reported moderate activity, while the remainder of the country reported low or minimal activity. The influenza A(H1N1)pdm09 virus was reported most commonly. No nationwide shortages have been reported of oral influenza antivirals.
- The FDA approved Amphastar's Primatene® Mist, an over-the-counter (OTC) epinephrine non-chlorofluorocarbon (CFC) propellant metered dose oral inhaler for the temporary relief of mild symptoms of intermittent asthma in people ≥ 12 years old. It was approved as 11.7 g (160 sprays). Dosage is 1 to 2 sprays every 4 hours (maximum 8 sprays per 24 hours). Primatene Mist was removed from the US market in 2011 as a result of phasing out CFC-containing products. Launch of the new OTC Primatene Mist is anticipated in early 2019.
- The FDA approved Allergan's Liletta®, a levonorgestrel-releasing intrauterine system, for the prevention of pregnancy for up to 5 years per device. Previously, it was approved for use up to 4 years per device.
- New voluntary nationwide consumer-level recalls of antihypertensive medications were issued due to trace levels of a probable human carcinogen, N-nitrosodiethylamine (NDEA). These include 1 lot of Sandoz's losartan potassium/hydrochlorothiazide (HCTZ) 100 mg/25 mg tablets, several lots of irbesartan 75 mg, 150 mg, and 300 mg tablets by Sciegen (labeled as Westminster Pharmaceuticals and Golden State Medical Supply), and all lots of amlodipine/valsartan and amlodipine/valsartan/HCTZ by Teva. Mylan is also recalling all remaining lots of valsartan-containing products within expiry. To date, there have been no reports of adverse events related to recalled product. Please consult the FDA website for detailed information.
- Janssen issued a voluntary recall of 1 lot of Ortho-Novum® 1/35 tablets (lot: 18BM114; expiry: 3/2020) and 2 lots of Ortho-Novum 7/7/7 tablets (lot: 18CM120, 18BM110; expiry: 3/2020) to the pharmacy level. Both products contain norethindrone/ethinyl estradiol. The recalls are due to the absence of appropriate instructions for use of the accompanying dispenser from the patient information. Improper use can lead to patients taking the pills in the incorrect order, potentially resulting in breakthrough bleeding or an unintended pregnancy.
- The FDA approved Teva's generic version of buprenorphine transdermal patch (Butrans®; Purdue). An AG version from Rhodes is also available.

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

- **December 18, 2018:** trastuzumab, biosimilar to Herceptin®; IV HER2/neu antagonist; HER2+ breast cancer, HER2+ gastric/gastroesophageal cancer; Celltrion/Teva.
- **December 19, 2018:** brexanolone; IV GABA modulator; postpartum depression; Sage.
- **December 20, 2018:** solriamfetol; oral central nervous system (CNS) stimulant; excessive sleepiness related to narcolepsy or sleep apnea; Jazz.
- **December 21, 2018:** calaspargase pegol; IV asparagine specific enzyme; acute lymphocytic leukemia (ALL); Shire.
- **December 21, 2018:** prucalopride; oral 5-HT4 serotonin agonist; chronic idiopathic constipation; Shire.
- **December 26, 2018:** CAM2038; buprenorphine depot; SC opioid partial agonist; substance use disorder; Braeburn.
- **December 28, 2018:** astodrimer sodium; intravaginal antibiotic; bacterial vaginosis; Starpharma.
- **December 28, 2018:** Keytruda®; pembrolizumab; IV programmed cell death 1 (PD-1) inhibitor; Merkel cell carcinoma; Merck.
- **Dec 2018–Jan 2019:** itraconazole; oral azole antifungal; systemic fungal infections; Hedgepath.
- **January 5, 2019:** levodopa; inhaled dopamine receptor agonist; Parkinson's disease; Acorda.

## RECENT FDA APPROVALS

| DRUG NAME<br>MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** |
| talazoparib<br>(Talzenna®)<br>Pfizer | • NDA approval 10/16/2018; Priority Review<br>• Treatment of adults with known or suspected deleterious germline BRCA-mutated (*gBRCAm*) HER2-negative locally advanced or metastatic breast cancer, as determined by an FDA-approved companion diagnostic<br>» The FDA approved the companion diagnostic BRACAnalysis CDx® test by Myriad Genetics<br>• Oral capsules: 0.25 mg and 1 mg<br>• Recommended dose is 1 mg once daily, with or without food, until disease progression or unacceptable toxicity occur; consider dose reduction for adverse reactions and moderate renal impairment |
| estradiol/<br>progesterone<br>(Bijuva™)<br>TherapeuticsMD | • 505(b)(2) NDA approval 10/28/2018<br>• Indicated in women with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause<br>• Fixed-dose combination of an estrogen and progesterone<br>• Oral capsule: 1 mg estradiol/100 mg progesterone<br>• Take 1 capsule orally each evening with food<br>• Boxed warnings include:<br>» Not recommended for the prevention of CVD or dementia; increased risks of stroke, deep vein thrombosis (DVT), pulmonary embolism (PE), MI, and invasive breast cancer; increased risk of probable dementia in postmenopausal women ≥ 65 years of age<br>» For estrogen-only therapy, an increased risk of endometrial cancer in women with a uterus<br>• Product launch is anticipated in Q2, 2019 |
| clobazam<br>(Sympazan™)<br>Aquestive | • 505(b)(2) NDA approval 11/02/2018<br>• Indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age<br>• Oral film: 5 mg, 10 mg, and 20 mg (berry flavored)<br>• Initial dosage is 5 mg per day in patients weighing ≤ 30 kg and 10 mg per day in patients > 30 kg; titrate to 20 mg and 40 mg per day, respectively, as tolerated |
| lorlatinib<br>(Lorbrena®)<br>Pfizer | • NDA approval 11/02/2018; Accelerated Approval; Orphan Drug; Priority Review<br>• Indicated to treat patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on: crizotinib and at least 1 other ALK inhibitor for metastatic disease; alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease<br>• Third-generation ALK tyrosine kinase inhibitor (TKI)<br>• Oral tablets: 25 mg and 100 mg<br>• Recommended dosage is 100 mg orally once daily until disease progression or unacceptable toxicity |

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; 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; Q = Quarter.

## *RECENT FDA APPROVALS continued*

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** *continued* |
| sufentanil (Dsuvia™) Acelrx | • 505(b)(2) NDA approval 11/02/2018<br>• Indicated for use in adults in a certified medically supervised healthcare setting (e.g., hospitals, surgical centers, emergency departments) for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate<br>• Limitations of use include: not for home use; not for use in children; discontinue therapy before patients leave the certified medically supervised healthcare setting; not for use > 72 hours; HCP administration only; reserve for use in patients for whom alternative treatment options have not been tolerated (or are not expected to be tolerated) or have not provided adequate analgesia (or are not expected to provide adequate analgesia)<br>• Sufentanil is an opioid agonist with relative selectivity for mu-opioid receptors<br>• Sublingual (SL) tablet: 30 mcg in a disposable, single-dose applicator (SDA)<br>• Recommended dosage is 30 mcg SL as needed with a minimum of 1 hour between doses; do not exceed 12 tablets in 24 hours<br>• Boxed warnings include accidental exposure, life-threatening respiratory depression, addiction, abuse, misuse, cytochrome P450 3A4 interaction, risk from concomitant use with benzodiazepines and other CNS depressants; available only through a Risk Evaluation and Mitigation Strategy (REMS) program<br>• Product launch is anticipated in Q1, 2019 |
| revefenacin (Yupelri™) Theravance | • NDA approval 11/09/2018<br>• Indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)<br>• Long-acting muscarinic antagonist (anticholinergic)<br>• Inhalation solution: 175 mcg/3 mL in a unit-dose vial for nebulization<br>• Inhale 175 mcg (1 vial) once daily via nebulizer |
| rifamycin (Aemcolo™) Cosmo | • NDA approval 11/16/2018; Priority Review; Qualified Infectious Disease Product<br>• Indicated to treat adults with traveler's diarrhea caused by noninvasive strains of *Escherichia coli*, not complicated by fever or blood in the stool<br>• Broad spectrum antibiotic with negligible gastrointestinal absorption<br>• Delayed-release tablet: 194 mg rifamycin<br>• Dosage is 2 tablets (388 mg) orally twice daily for 3 days<br>• Product launch is anticipated in Q1, 2019 |
| emapalumab-lzsg (Gamifant™) Novimmune | • BLA approval 11/20/2018; Breakthrough therapy; Orphan Drug; Priority Review; Rare Pediatric Disease Designation<br>• Indicated to treat adult and pediatric (newborn and older) patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or intolerance with conventional HLH therapy<br>• Interferon gamma blocking antibody<br>• Injectable solution: 5 mg/mL in 2 mL and 10 mL single-dose vials<br>• Initial dose is 1 mg/kg IV over 1 hour twice per week; may increase dose based on clinical and laboratory criteria; administer therapy until stem cell transplant or unacceptable toxicity |

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## *RECENT FDA APPROVALS continued*

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **Expanded Indications** |
| dupilumab (Dupixent®) Sanofi | • sBLA approval 10/19/2018<br>• Indicated as add-on maintenance treatment in patients aged ≥ 12 years with moderate to severe asthma and an eosinophilic phenotype or with oral corticosteroid dependent asthma; it not indicated for the relief of acute bronchospasm or status asthmaticus<br>• Initial dose for asthma is 400 mg (two 200 mg injections) followed by 200 mg every other week or an initial dose of 600 mg (two 300 mg injections) followed by 300 mg every other week; use 600 mg initial and 300 mg maintenance doses in patients with oral corticosteroids-dependent asthma, or with comorbid moderate-to-severe atopic dermatitis<br>• A 200 mg/1.14 mL injectable solution in a single-dose prefilled syringe was also approved |
| sodium oxybate (Xyrem®) Jazz | • sNDA approval 10/26/2018<br>• Indication expanded to include treatment of cataplexy or excessive daytime sleepiness to patients ≥ 7 years of age with narcolepsy<br>• Administer orally twice nightly (at bedtime and 2.5 to 4 hours later); the recommended starting dose, titration regimen, and maximum total nightly dose are weight-based |
| pembrolizumab (Keytruda) Merck | • sBLA approval 10/30/2018 and 11/09/2018<br>• Approval on 10/30/2018 for the indication of first-line treatment of patients with metastatic squamous NSCLC, in combination with carboplatin and either paclitaxel or nab-paclitaxel<br>• Accelerated Approval on 11/09/2018 for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib<br>• Administer 200 mg IV over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression |
| elotuzumab (Empliciti®) Bristol-Myers Squibb | • sBLA approval 11/06/2018<br>• Indicated in combination with pomalidomide and dexamethasone (EPd) for the treatment of multiple myeloma in adults who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor<br>• Recommended dose is 10 mg/kg administered IV every week for the first 2 cycles and 20 mg/kg every 4 weeks thereafter until disease progression or unacceptable toxicity |
| sweet vernal, orchard, perennial rye, timothy, and Kentucky blue grass mixed pollens allergen extract (Oralair™) Stallergenes | • sBLA approval 11/09/2018<br>• Indication expanded to include persons 5 to 9 years of age as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the 5 grass species included in the product<br>• Sublingual dosing in patients 5 to 9 years of age is 100 index of reactivity (IR) on day 1, 2 times 100 IR on day 2, and 300 IR thereafter |
| eltrombopag (Promacta®) Novartis | • sNDA approval 11/16/2018; Breakthrough Therapy; Orphan Drug; Priority Review<br>• Indicated for first-line treatment of adult and pediatric patients ≥ 2 years of age with severe aplastic anemia in combination with standard immunosuppressive therapy<br>• Dosage in patients 2 to 5 years of age is 2.5 mg/kg once daily; 6 to 11 years is 75 mg once daily; and ≥ 12 years is 150 mg once daily; duration of therapy is 6 months for all ages |

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**References:**

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