



# MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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### **HOT TOPIC:** **FDA APPROVES FIRST ORAL GLP-1 AGONIST**

The United States (US) Food and Drug Administration (FDA) approved semaglutide tablets (Rybelsus®; Novo Nordisk), the first orally administered glucagon-like peptide-1 (GLP-1) receptor agonist. Based on a Priority Review, it garnered an indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

Safety and efficacy of Rybelsus were evaluated in 8 clinical trials in over 5,800 adults with T2DM. Similar hemoglobin A1c (HbA1c) reductions were demonstrated compared to injectable semaglutide (Ozempic®) and to the injectable GLP-1 agonist liraglutide. Rybelsus also resulted in significant HbA1c improvement over the sodium glucose cotransporter 2 (SGLT2) inhibitor empagliflozin and the oral dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin. Moreover, Rybelsus was effective in patients with moderate renal impairment and did not appear to increase major cardiovascular events. While significant HbA1c reduction was seen when Rybelsus was added to diet and exercise alone, it is not intended for first-line treatment in patients not controlled on diet and exercise alone, due to an uncertain risk of medullary thyroid carcinoma in humans.

Gradual dose escalation improves gastrointestinal tolerability of Rybelsus. The initial dose is 3 mg orally once daily for 30 days, followed by 7 mg

once daily. If glycemic targets are not met after 30 days of the 7 mg dose, the daily dose may be increased to 14 mg. Rybelsus must be taken at least 30 minutes prior to the first food, drink, or other oral medication of the day. Patients on once-weekly injectable Ozempic may switch to Rybelsus up to 7 days after the last Ozempic dose.

### **FDA SAFETY ALERT: HCV AGENTS & LIVER INJURY**

The FDA issued a safety announcement warning the public of rare serious liver injury with the use of Mavyret™ (glecaprevir/pibrentasvir; Abbvie), Vosevi® (sofosbuvir/velpatasvir/voxilaprevir; Gilead), or Zepatier® (elbasvir/grazoprevir; Merck) in patients with advanced liver impairment. None of the agents, which are indicated to treat chronic hepatitis C virus (HCV) infection, are approved for use in patients with moderate to severe hepatic impairment. A total of 63 cases of liver decompensation, including liver failure and death, associated with the use of Mavyret (n=46), Zepatier (n=14), and Vosevi (n=3) were identified in the FDA Adverse Event Reporting System (FAERS) database or in medical literature. Of the 63 cases, at baseline, 13 patients were without cirrhosis, 18 had compensated cirrhosis, 21 had decompensated cirrhosis, and 11 had unknown liver function status. Of the cases that initially reported no cirrhosis or compensated cirrhosis, over half were later found to have evidence of advanced liver disease or pre-existing risk factors at baseline that may have contributed to the development of worsening liver

function. The median time to onset of liver-related events (e.g., hyperbilirubinemia, jaundice, ascites, hepatic encephalopathy) was 22 days (range 2 days to 16 weeks) from initiation of treatment. Eight deaths were reported. Symptoms resolved or liver function values improved in over 60% of the cases after discontinuing the drug. The FDA is advising that healthcare professionals (HCP) continue to prescribe Mavyret, Vosevi, and Zepatier per the FDA-approved labeling for patients without liver impairment or with mild liver impairment (Child-Pugh A). Liver disease severity should be assessed at baseline and monitored closely throughout therapy. Patients should not stop taking their prescribed medication and should contact their HCP if symptoms of worsening liver function occur.

## ■ 2019–2020 INFLUENZA SEASON UPDATE

Updated guidelines for the 2019–2020 influenza season are available from the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP). The 2019–2020 US influenza vaccines contain new influenza A(H1N1)pdm09 and A(H3N2) components. Routine annual influenza vaccination continues to be recommended for all persons aged  $\geq 6$  months without contraindications. A licensed, recommended, age-appropriate vaccine should be used with no vaccine preferred over another, including the intranasal formulation and a new 0.5 mL per dose formulation for children 6 to 35 months of age. Other key guideline updates by the AAP include: all pediatric influenza vaccines for the 2019–2020 season will be quadrivalent vaccines; and children 6 months to 8 years of age receiving the influenza vaccine for the first time or who received only 1 dose before July 1, 2019 should receive 2 doses of the prescribed vaccine, ideally by the end of October. Lastly, any licensed, recommended, age-appropriate influenza antiviral medication can be used in children to treat suspected or confirmed influenza, especially for those at high risk of complications.

## ■ IMMUNE GLOBULIN SHORTAGE

On August 12, 2019, the FDA confirmed that, although the supply of immune globulin (IG) products has increased in recent years, it has not kept up with an increase in demand for these products, resulting in an ongoing shortage of intravenous (IV) and subcutaneous (SC) formulations that could impact patient care in the US. The agency is working with manufacturers and IG applicants to mitigate IG shortages. In addition, the Plasma Protein Therapeutics Association and IG manufacturers are facilitating access to specific products. The FDA urges HCPs, hospitals, and medical systems to create evidence-based strategies

when considering IG dose reductions, treatment delays or prioritization, and alternative therapies, as well as contractual agreements in order to best meet patient needs. The FDA ([fda.gov](http://fda.gov)) and American Society of Health-System Pharmacists ([ashp.org](http://ashp.org)) each maintain a list of IG products in shortage.



## BEHAVIORAL HEALTH CORNER

### VA/DoD SUICIDE RISK ASSESSMENT

Across the US, suicide rates have increased by 25% between 1999 and 2016, and the rate in veterans is 21% higher compared with age- and sex-matched civilians. The US Department of Veterans Affairs (VA) and the US Department of Defense (DoD) released an update to their joint clinical practice guideline for the assessment and management of patients at risk for suicide. The guideline panel developed 3 algorithms and 22 evidence-based recommendations organized into 3 categories: screening and evaluation, risk management and treatment, and other management methods. The panel strongly recommends that mental health and primary care providers assess risk factors as part of a comprehensive suicide risk assessment, including suicidal ideation, prior suicide attempts, psychiatric conditions or symptoms, recent biophysical stressors, and access to firearms. Proper stratification using self-reported measures and clinical interviews is key to providing the proper level of care and preventing potential harm by lack of referral for appropriate treatment. Cognitive behavioral therapy (CBT)-based interventions focused on suicide prevention are strongly recommended for patients with recent histories of self-directed violence. To reduce risk in patients with suicide ideations, providers should offer the following pharmacologic treatments: ketamine infusion in patients with major depression, lithium in those with unipolar or bipolar disorder, and clozapine in patients with schizophrenia or schizoaffective disorder. Evidence also supports use of a crisis response plan between the patient and HCP and removal of items that can be used to cause harm (lethal means safety). The VA/DoD concluded that critical gaps remain in our understanding of effective approaches to identify and treat persons at risk for suicide. Limited data are available regarding appropriate screening tools, drug and non-drug intervention, community-based intervention, and post-acute care monitoring.

# DRUG INFORMATION HIGHLIGHTS

- The FDA released a statement on the agency's ongoing efforts to resolve the safety issue with angiotensin II receptor blocker (ARB) medications used to treat hypertension. The FDA emphasized that the risk and scope of exposure to potentially carcinogenic nitrosamine impurities in these agents is likely much lower than their initial estimate. Initial estimates of malignancy risk were based on a scientific assessment of the highest possible exposure; however, the majority of patients were likely exposed to a much smaller amount of the impurities, and not all ARBs were affected, leading to a much lower risk than initially projected. The agency is enhancing oversight of manufacturing data and expanding their evaluation of other products. Currently, 43 nitrosamine-free ARB medications are available in the US. In addition, due to this impurity, Torrent expanded their recall with 3 more lots of losartan tablets and 2 lots of losartan/hydrochlorothiazide tablets.
- The FDA also alerted the public that low levels of N-nitrosodimethylamine (NDMA) were detected in some medicines containing the histamine-2 blocker ranitidine. The FDA is investigating the cause and will take appropriate action. The agency is not advising patients to stop taking ranitidine at this time, but patients may seek an alternative product. In the US, Sandoz halted distribution and recalled all lots of generic ranitidine 150 mg and 300 mg capsules. Sales of brand Zantac® and generic ranitidine were suspended by CVS, Rite Aid, Walgreens, and Walmart as well as generic versions by GlaxoSmithKline, Dr. Reddy's, and Strides. Apotex issued a voluntary recall of all lots of ranitidine 75 mg and 150 mg tablets labeled by Rite Aid, Walgreens, and Walmart.
- The American College of Rheumatology along with the Spondylitis Association of America and Spondyloarthritis Research and Treatment Network published updated guidance for the treatment of ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (SpA). New treatment options for axial SpA necessitated updating the 2015 guidelines. Recommendations for AS and nonradiographic axial SpA are similar. Non-steroidal anti-inflammatory drugs (NSAIDs) remain as first-line therapy. Tumor necrosis factor (TNF) inhibitors are recommended in patients with active disease, despite NSAID treatment. Secukinumab and ixekizumab are recommended for patients with active disease who have heart failure or demyelinating disease as a contraindication to a TNF inhibitor, as well as primary nonresponders to a TNF inhibitor. Conversely, secukinumab and ixekizumab are not recommended in patients with irritable bowel disease or recurrent uveitis. Tofacitinib is considered a potential second-line option for patients with non-infectious contraindications to TNF inhibitor therapy. In patients with stable AS or nonradiographic axial SpA, discontinuation of biologic therapy is not recommended, nor is switching to a biosimilar agent.
- Takeda issued a voluntary recall for all doses of Natpara® (parathyroid hormone) for injection due to a potential for particulates from the rubber septum to detach into the cartridge upon repeated puncture. Takeda is communicating directly with HCPs, patients, and specialty pharmacies regarding the actions required as a result of the recall.

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

- **October 2019:** cefiderocol; IV cephalosporin antibiotic; complicated urinary tract infection; Shionogi.
- **Oct-Dec 2019:** adalimumab, biosimilar to Humira®; SC TNF inhibitor; rheumatoid arthritis; Pfizer.
- **Oct-Dec 2019:** influenza quadrivalent vaccine high-dose (Fluzone®); intramuscular virus vaccine; influenza prevention; Sanofi.
- **October 3, 2019:** pegfilgrastim, biosimilar to Neulasta®; SC colony stimulating factor; neutropenia; Novartis.
- **October 4, 2019:** afamelanotide; intradermal alpha-melanocyte stimulating hormone analog; erythropoietic porphyria; Clinuvel.
- **October 4, 2019:** emtricitabine/tenofovir alafenamide (Descovy®); oral antiretroviral (ARV); human immunodeficiency virus-1 (HIV-1) pre-exposure prophylaxis (PrEP); Gilead.
- **October 7, 2019:** teriparatide, *follow-on* to Forteo®; SC parathyroid hormone analog; osteoporosis/osteopenia; Pfenex.
- **October 14, 2019:** rivaroxaban (Xarelto®); oral factor Xa inhibitor; deep vein thrombosis prophylaxis in medically ill patients; Janssen.
- **October 17, 2019:** asenapine; transdermal atypical antipsychotic; schizophrenia; Hisamitsu.
- **October 17, 2019:** diroximel fumarate; oral immunomodulator; relapsing multiple sclerosis; Biogen.
- **October 18, 2019:** ravulizumab-swvz (Ultomiris®); IV complement inhibitor; hemolytic uremic syndrome; Alexion.
- **October 18, 2019:** ustekinumab (Stelara®); IV/SC interleukin-23 inhibitor; ulcerative colitis; Janssen.
- **October 24, 2019:** delafloxacin (Baxdela®); IV/oral fluoroquinolone antibiotic; community-acquired bacterial pneumonia (CABP); Melinta.

## RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
lefamulin (Xenleta™) Nabriva	<ul style="list-style-type: none"> <li>• NDA approval 08/19/2019; Priority Review, Qualified Infectious Disease Product</li> <li>• Indicated for CABP caused by susceptible microorganisms in adults</li> <li>• Pleuromutilin antibiotic</li> <li>• Injection: 150 mg/15 mL single-dose vial</li> <li>• Tablets: 600 mg</li> <li>• Recommended dosage is 150 mg via IV infusion over 60 minutes every 12 hours for 5 to 7 days (may switch to oral therapy to complete the treatment course); 600 mg orally every 12 hours for 5 days, taken 1 hour before a meal or 2 hours after a meal</li> <li>• Boxed warnings for serious infections and malignancies</li> </ul>
istradefylline (Nourianz™) Kyowa Kirin	<ul style="list-style-type: none"> <li>• NDA approval 08/27/2019</li> <li>• Indicated for adjunctive treatment to levodopa/carbidopa in adults with Parkinson's disease</li> <li>• Adenosine receptor antagonist</li> <li>• Tablets: 20 mg and 40 mg</li> <li>• Recommended dosage is 20 mg orally once daily; may increase to a maximum of 40 mg once daily; in patients who smoke ≥ 20 cigarettes per day (or the equivalent of another tobacco product), recommended dosage is 40 mg once daily</li> </ul>
metformin extended-release (Riomet ER™) Sun	<ul style="list-style-type: none"> <li>• 505(b)(2) NDA approval 08/29/2019</li> <li>• Indicated as adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥ 10 years of age with T2DM</li> <li>• Biguanide</li> <li>• Suspension: pellets and diluent containing 47.31 grams metformin for reconstitution</li> <li>• Recommended dosage is 500 mg (5 mL) orally once daily, taken with the evening meal; may increase by 500 mg weekly, up to 2,000 mg (20 mL) once daily</li> <li>• Boxed warning for lactic acidosis</li> </ul>
glucagon (Gvoke™) Xeris	<ul style="list-style-type: none"> <li>• 505(b)(2) NDA approval 09/10/2019</li> <li>• Indicated for the treatment of severe hypoglycemia in adults and pediatric patients aged ≥ 2 years with diabetes</li> <li>• Antihypoglycemic agent</li> <li>• Injectable: 0.5 mg/0.1 mL and 1 mg/0.2 mL, both approved in single-dose auto-injectors (HypoPen™) and prefilled syringes</li> <li>• Recommended dosage is 1 mg for adults and children weighing ≥ 45 kg and 0.5 mg for children weighing &lt; 45 kg administered SC in the lower abdomen, outer thigh, or outer upper arm; if no response after 15 minutes, may repeat dose, using a new device, while waiting for emergency assistance</li> </ul>
tenapanor (Ibsrela®) Ardelyx	<ul style="list-style-type: none"> <li>• NDA approval 09/12/2019</li> <li>• Indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults</li> <li>• Sodium/hydrogen exchanger 3 (NHE3) inhibitor</li> <li>• Tablets: 50 mg</li> <li>• Recommended dosage is 50 mg orally twice daily taken immediately prior to breakfast or the first meal of the day and immediately prior to dinner</li> <li>• Boxed warning for risk of serious dehydration in pediatric patients</li> <li>• Ardelyx is seeking a partner for commercial marketing</li> </ul>

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
Expanded Indications	
rimabotulinumtoxin B (Myobloc®) US Worldmeds	<ul style="list-style-type: none"> <li>• sBLA approval 08/20/2019</li> <li>• New indication for the treatment of chronic sialorrhea (excessive drooling) in adults</li> <li>• Recommended dosage is 1,500 to 3,500 units per session, divided among the parotid and submandibular glands and injected no more frequently than every 12 weeks; administer 500 to 1,500 units per parotid gland and 250 units per submandibular gland</li> </ul>
cobicistat (Tybost®) Gilead	<ul style="list-style-type: none"> <li>• sNDA approval 08/22/2019</li> <li>• Expanded indication to increase systemic exposure of atazanavir in combination with other ARV agents in the treatment of HIV-1 infection to include pediatric patients weighting ≥ 35 kg; previously, only approved for use in adults</li> <li>• Recommended dosage in pediatric patients is 150 mg orally once daily in combination with atazanavir</li> </ul>
ixekizumab (Taltz®) Eli Lilly	<ul style="list-style-type: none"> <li>• sBLA approval 08/23/2019</li> <li>• New indication for the treatment of adults with AS</li> <li>• Recommended dosage is 160 mg (two 80 mg injections) SC at week 0, followed by 80 mg every 4 weeks</li> </ul>
nintedanib (Ofev®) Boehringer Ingelheim	<ul style="list-style-type: none"> <li>• sNDA approval 09/06/2019; Orphan Drug, Priority Review</li> <li>• New indication to slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease</li> <li>• Recommended dosage is 150 mg orally twice daily with food</li> </ul>
mepolizumab (Nucala) GlaxoSmithKline	<ul style="list-style-type: none"> <li>• sBLA approval 09/12/2019</li> <li>• Expanded indication as an add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype to include patients 6 to 11 years of age; previously, only approved for this indication in patients ≥ 12 years of age</li> <li>• Recommended dosage in this new age group is 40 mg SC every 4 weeks</li> </ul>
apalutamide (Erleada®) Janssen	<ul style="list-style-type: none"> <li>• sNDA approval 09/17/2019; Priority Review</li> <li>• Expanded indication for the treatment of metastatic castration-sensitive prostate cancer</li> <li>• Recommended dosage is 240 mg (four 60 mg tablets) orally once daily</li> </ul>
pembrolizumab (Keytruda®) Merck  +  lenvatinib (Lenvima®) Eisai	<ul style="list-style-type: none"> <li>• sBLA approval 09/17/2019; Accelerated Approval</li> <li>• New indication for the combination use of pembrolizumab and lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation</li> <li>• Recommended dosage of pembrolizumab is 200 mg IV over 30 minutes every 3 weeks; recommended dosage of lenvatinib is 20 mg orally once daily; continue combination therapy until disease progression, unacceptable toxicity, and pembrolizumab for up to 24 months in patients without disease progression</li> </ul>
doravirine (Pifeltro™) Merck	<ul style="list-style-type: none"> <li>• sNDA approval 09/19/2019</li> <li>• Expanded indication for the treatment of HIV-1 infection for use in combination with other ARVs to include replacement of a current stable ARV regimen in adults who are virologically suppressed (HIV-1 RNA &lt; 50 copies/mL) and have no known substitutions associated with resistance to doravirine</li> <li>• Recommended dosage is 1 tablet (100 mg) orally once daily</li> </ul>

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## RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
<b>Expanded Indications <i>cont.</i></b>	
doravirine/ lamivudine/ tenofovir disoproxil fumarate (TDF) (Delstrigo™) Merck	<ul style="list-style-type: none"> <li>• sNDA approval 09/19/2019</li> <li>• Expanded indication for the treatment of HIV-1 infection for use in combination with other ARVs to include replacement of a current stable ARV regimen in adults who are virologically suppressed (HIV-1 RNA &lt; 50 copies/mL) and have no known substitutions associated with resistance to any component of the product</li> <li>• Recommended dosage is 1 tablet (100 mg doravirine/300 mg lamivudine/300 mg TDF) orally once daily</li> </ul>
daratumumab (Darzalex®) Janssen	<ul style="list-style-type: none"> <li>• sBLA approval 09/26/2019</li> <li>• Expanded indication to include use in combination with bortezomib, thalidomide, and dexamethasone to treat multiple myeloma in newly diagnosed adults who are eligible for autologous stem cell transplant (ASCT)</li> <li>• Recommended dosage is 16 mg/kg (actual body weight) IV; for induction therapy, administer weekly during weeks 1 to 8 (8 doses), followed by every 2 weeks during weeks 9 to 16 (4 doses); stop for high-dose chemotherapy and ASCT; then administer every 2 weeks during weeks 1 to 8 of consolidation therapy (4 doses)</li> </ul>
glecaprevir/ pibrentasvir (Mavyret) Abbvie	<ul style="list-style-type: none"> <li>• sNDA approval 09/26/2019</li> <li>• Expanded indication for an 8-week duration for adults and children ages ≥ 12 years or weighing ≥ 45 kg who have chronic HCV infection with any genotype (1, 2, 3, 4, 5, or 6) and compensated cirrhosis and who have not received previous HCV treatment; previous duration in treatment-naïve patients with compensated cirrhosis was 12 weeks</li> <li>• Recommended dosage is 3 fixed-dose tablets (300/120 mg) orally once daily for 8 weeks</li> </ul>

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