FEBRUARY 2020

# MRx CLINICAL ALERT

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## HEPATITIS C VIRUS (HCV) GUIDELINE UPDATE

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) revised the guidelines for the management of HCV infection. Throughout the guidelines, the AASLD/IDSA removed recommendations around less effective, complex, alternative regimens and drugs that have been discontinued in the United States (US). Other key changes were made in several sections throughout the guidelines.

The AASLD/IDSA expanded the recommendation of universal and risk-based HCV screening to include those born outside the baby boomer era (1945 to 1965). This is particularly important for those ages 20 to 39 years, a population with a higher incidence of injection drug use. A 1-time, routine, opt-out HCV screening is now recommended for all individuals ages ≥ 18 years. For persons ages < 18 years, the recommendations focus on behaviors or exposures associated with HCV infection and include a single test in individuals with current or past at-risk behavior; periodic repeat HCV testing in those with ongoing increased at-risk behavior; and annual testing for persons who inject drugs and for human immunodeficiency virus (HIV)-positive men who have unprotected sex with men.

Regarding initial treatment of chronic HCV infections with oral direct-acting antivirals (DAAs), the AASLD/IDSA added the recently approved, shorter 8-week regimen for glecaprevir/pibrentasvir (Mavyret®) in patients with any genotype (GT) with compensated cirrhosis. New simplified treatment regimens for treatment-naïve patients without cirrhosis with any GT include glecaprevir/pibrentasvir for 8 weeks and sofosbuvir/velpatasvir (Epclusa®) for 12 weeks. The AASLD/IDSA also updated treatment recommendations after failure with sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) or glecaprevir/pibrentasvir with several options as detailed in the guidance.

Other areas with revisions include the management of acute HCV infection, wherein new recommendations advise starting treatment as soon as possible without waiting for spontaneous resolution. The same treatment regimens are recommended for chronic and acute HCV infections. In addition, recently approved DAA regimens for children ages 3 to 11 years were incorporated and include ledipasvir/sofosbuvir (Harvoni®) in patients with GT 1, 4, 5, or 6 and sofosbuvir plus ribavirin in patients with GT 2 or 3. Lastly, new information was added for the use of DAAs in the setting of organ transplantation from HCV-positive donors to HCV-negative recipients. To treat iatrogenic HCV infection and retain allograft function, the AASLD/IDSA advises initiating a preemptive pangenotypic DAA regimen as early as possible after transplantation. Options include glecaprevir/pibrentasvir for 8 weeks or sofosbuvir/velpatasvir for 12 weeks to treat any GT, and ledipasvir/sofosbuvir for 12 weeks in patients with GT 1, 4, 5, or 6. Ultimately, the use

of organs from HCV-positive donors may reduce organ wait time and lower mortality of patients on transplant waiting lists; however, informed consent is recommended due to the various risks associated with use of an organ from an HCV-positive donor.

## ICER: FINAL REPORT FOR ADD-ON THERAPIES FOR TYPE 2 DIABETES

In December 2019, the Institute for Clinical and Economic Review (ICER) released their final report, including policy recommendations, for add-on therapies for type 2 diabetes mellitus (T2DM). The report compares the effectiveness and value of the first orally available glucagon-like peptide 1 receptor agonist (GLP-1RA) semaglutide (Rybelsus®) to the injectable GLP-1RA liraglutide (Victoza®), the oral dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin (Januvia®), and the oral sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin (Jardiance®). Based on data from 12 clinical trials that focus on glycemic effect, cardiovascular (CV) outcomes, and potential harms, ICER concluded that treatment with oral semaglutide resulted in a greater reduction in hemoglobin A1c (HbA1c) compared to empagliflozin, sitagliptin, and liraglutide at 52 weeks. Oral semaglutide also reduced body weight more than liraglutide and sitagliptin, but less than empagliflozin. In addition, ICER found that while oral semaglutide resulted in a numerically lower rate of major adverse cardiovascular events (MACE) compared to placebo, the difference was not statistically significant. An ICER network meta-analysis (NMA) revealed that oral and injectable semaglutide reduced the incidence of MACE compared to sitagliptin; however, no statistically significant differences were found compared to liraglutide or empagliflozin. Treatment with empagliflozin also reduced the risk of hospitalization for heart failure in the NMA. Subsequent to the ICER report, in January 2020, injectable semaglutide (Ozempic®) received a new indication to reduce the risk of CV death in adults with T2DM and established CV disease (CVD). It joins liraglutide and the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin (and their metformin combinations) as antidiabetic agents FDA-approved to reduce the CV effects of diabetes.

Based on the evidence, ICER determined that adding oral semaglutide to background therapy provides a positive net health benefit overall and a substantial net health benefit compared with adding sitagliptin. The evidence did not reveal a net health benefit of adding oral semaglutide over adding liraglutide or empagliflozin. Nevertheless, ICER acknowledged that use of oral semaglutide may lessen therapy burden compared to injectable liraglutide and, therefore, may improve patient outcomes. Regarding cost-effectiveness, ICER determined that oral semaglutide's estimated annual net price of $6,103 is within their value-based price benchmark ($6,000 to $6,400). They also estimate that oral semaglutide may be an appealing option in up to half of eligible T2DM patients.

# BEHAVIORAL HEALTH CORNER

## FDA ALERT: GABAPENTINOIDS

The FDA issued a drug safety communication warning that serious breathing difficulties may occur in patients treated with gabapentinoids (e.g., gabapentin [Neurontin®, Gralise®, Horizant™], pregabalin [Lyrica®, Lyrica® CR]) who also have respiratory risk factors. These risk factors include concomitant use of opioid analgesics or central nervous system (CNS) depressants, conditions that impair lung function, and advanced age. The FDA received 49 case reports of respiratory depression associated with a gabapentinoid from 2012 to 2017, including 12 deaths. All patients who died from respiratory depression associated with a gabapentinoid were found to have at least 1 additional respiratory risk factor. The FDA is requiring that a warning for the risk of respiratory depression be added to the labeling for all gabapentinoids and clinical trials be conducted to further evaluate the abuse potential and risk of respiratory depression. The approved indications vary among these agents and include treatment of neuropathic pain/neuropathy conditions and partial onset seizures.Therapy with a gabapentinoid should be started at the lowest dose. Patients who are elderly, have an underlying respiratory condition, or are on a concurrent opioid or CNS depressant should be monitored for respiratory depression and sedation.

## FDA WARNING LETTER: VIVITROL®

The FDA issued a warning letter to Alkermes for misbranding naltrexone (Vivitrol) by omitting warnings from promotional materials, including the medication's most serious vulnerability for opioid overdose, a potentially fatal risk. The agency has requested that the company immediately cease advertising practices that misbrand Vivitrol and institute a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages. Vivitrol is an extended-release (ER) injectable formulation of the opioid antagonist naltrexone indicated for the prevention of relapse to opioid dependence as well as the treatment of alcohol dependence. It should be prescribed as part of a comprehensive management program that includes psychosocial support.

# DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2019–2020): The Centers for Disease Control and Prevention (CDC) reported occurrences of influenza-like illnesses (ILI) continue to be high for the week ending on January 25, 2020. Nationwide, B/Victoria viruses have been the primary circulating viruses this season, but during recent weeks, they were surpassed by the A(H1N1)pdm09 viruses. District of Columbia, New York City, Puerto Rico, and 41 states reported high ILI activity, while 7 states reported moderate ILI activity, and 2 states reported insufficient data to calculate ILI. At last report, 5.7% of patient visits have been due to ILI, which is above the national baseline of 2.4%.
- Appco/ANI and Denton are voluntarily recalling all quantities and lots within expiry of their ranitidine capsules (150 mg and 300 mg) to the consumer level due to the presence or potential presence of N-nitrosodimethylamine (NDMA) levels above the FDA's acceptable daily intake level (96 ng/day). To date, no adverse events have been reported. The companies are advising consumers to stop using affected products, return supply to the place of purchase, and speak to their physician or pharmacist about alternative treatment options. In addition, Denton has ceased distribution of its product.
- Aurobindo voluntarily recalled 1 lot of mirtazapine tablets to the consumer level due to a label error; bottles labeled as 7.5 mg may contain 15 mg tablets. Taking a higher dose than prescribed may increase the risk for adverse effects.
- Mylan issued a voluntary recall of 3 lots of nizatidine capsules (150 mg and 300 mg) due to the detection of NDMA in the active pharmaceutical ingredient (API) manufactured by Solara.
- The CDC is closely monitoring the outbreak of a novel coronavirus (2019-nCoV) causing respiratory illness. Initially detected in China, the illness has spread globally, including 11 cases reported as of February 5, 2020 in the US. Symptoms include fever, cough, and shortness of breath. There is currently no vaccination or antiviral treatment against 2019-nCoV.
- The FDA approved fremanezumab (Ajovy®) 225 mg/1.5 mL autoinjector for the preventive treatment of migraine in adults. The medication was already approved in this strength as a prefilled syringe. Teva plans to make the autoinjector available in the coming months.
- The American College of Rheumatology (ACR) and the Arthritis Foundation (AF) released guidelines for the management of osteoarthritis (OA) of the hand, hip, and knee. Regarding pharmacologic treatment, the guidelines provide strong recommendations for the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) for knee OA; oral NSAIDs for knee, hip, and hand OA; and intraarticular glucocorticoid injections for knee or hip OA. The guidelines give conditional recommendations for topical NSAIDs, intraarticular glucocorticoids, and chondroitin sulfate for hand OA; topical capsaicin for knee OA; and acetaminophen, duloxetine, and tramadol for knee, hip, and hand OA.
- Taro is voluntarily recalling 1 lot of lamotrigine 100 mg tablets due to possible cross-contamination with enalapril maleate, which is used to treat hypertension and is manufactured in the same facility. While no adverse reports have been reported, chronic exposure to enalapril maleate could increase the risk of adverse effects, particularly in children and pregnant women.

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

- **Feb–Mar 2020:** paclitaxel (nanodispersion); intravenous (IV) mitotic inhibitor; breast cancer; Sun.
- **Feb–Mar 2020:** empagliflozin (Jardiance); oral SGLT2 inhibitor; type 1 diabetes mellitus (T1DM); Boehringer Ingelheim.
- **February 14, 2020:** levonorgestrel/ethinyl estradiol; transdermal hormonal contraceptive; Agile.
- **February 20, 2020:** rimegepant; oral calcitonin gene-related peptide (CGRP) inhibitor; migraine treatment; Biohaven.
- **February 21, 2020:** eptinezumab; IV CGRP inhibitor; migraine prevention; Lundbeck.
- **February 21, 2020:** bempedoic acid; oral ATP citrate lyase (ACL) inhibitor; dyslipidemia; Esperion.
- **February 26, 2020:** amisulpride; IV dopamine 2/3 antagonist; postoperative nausea and vomiting; Acacia.
- **February 26, 2020:** bempedoic acid/ezetimibe; fixed-dose oral ACL inhibitor/intestinal cholesterol absorption inhibitor; dyslipidemia; Esperion.
- **March 1, 2020:** naloxone; intranasal opioid antagonist; opioid overdose; Insys.
- **March 9, 2020:** exenatide subdermally implanted mini-pump; continuous subcutaneous (SC) GLP-1RA; T2DM; Intarcia.

## RECENT FDA APPROVALS

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** |
| avapritinib (Ayvakit™) Blueprint Medicines | • NDA approval 01/09/2020; Breakthrough Therapy, Orphan Drug, Priority Review<br>• Indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations<br>• Tyrosine kinase inhibitor<br>• Tablets: 100 mg, 200 mg, and 300 mg<br>• Recommended dosage is 300 mg orally once daily, at least 1 hour before or 2 hours after a meal |
| cocaine hydrochloride (Numbrino™) Lannett | • 505(b)(2) NDA approval 01/10/2020<br>• Indicated for the induction of local anesthesia of the mucous membranes when performing diagnostic procedures and surgeries on or through the nasal cavities in adults<br>• Ester local anesthetic<br>• Nasal solution: 4% in single-use 4 mL and multiple-use 10 mL bottles<br>• Recommended dosage is dependent on the nasal surface area to be anesthetized and the type of procedure, ranging from 40 mg to 160 mg applied to the nasal mucosa by a healthcare provider (HCP)<br>• Boxed warning for high potential for abuse and dependence<br>• Schedule II controlled substance<br>• Do not substitute for other nasal cocaine products unless determined to be substitutable<br>• Product availability is expected in 1Q 2020 |
| diazepam (Valtoco®) Neurelis | • 505(b)(2) NDA approval 01/10/2020; Orphan Drug<br>• Indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (e.g., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ages ≥ 6 years<br>• Benzodiazepine<br>• Nasal spray: 5 mg, 7.5 mg, or 10 mg in 0.1 mL of solution in a ready-to-use nasal spray device for patient or caregiver use<br>• Recommended dosage is dependent on the patient's age and weight, ranging from 5 mg (one 5 mg device) to 20 mg (two 10 mg devices); a second dose may be administered if needed ≥ 4 hours after the first dose; do not exceed 2 doses per single episode; maximum treatment is 1 episode every 5 days, and up to 5 episodes per month; for intranasal use only<br>• Boxed warning regarding risk from concurrent use with opioids<br>• Schedule IV controlled substance |
| ferric derisomaltose (Monoferric™) Pharmacosmos | • NDA approval 01/16/2020<br>• Indicated for the treatment of iron deficiency anemia in adults who have an intolerance to oral iron, have had an unsatisfactory response to oral iron, or who have non-hemodialysis dependent chronic kidney disease<br>• Iron replacement therapy<br>• Injection: 100 mg iron/mL in 1 mL, 5 mL, and 10 mL single-dose vials (SDV)<br>• Recommended dosage is 1,000 mg in patients weighing ≥ 50 kg and 20 mg/kg actual body weight in those weighing < 50 kg; treatment course is a single dose administered by IV infusion over ≥ 20 minutes; repeat dose upon recurrence of iron deficiency anemia |

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## *RECENT FDA APPROVALS continued*

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** *continued* |
| teprotumumab-trbw (Tepezza™) Horizon | • BLA approval 01/21/2020; Orphan Drug<br>• Indicated for the treatment of thyroid eye disease<br>• Insulin-like growth factor-1 (IGF-1) inhibitor<br>• Injection: 500 mg lyophilized powder for reconstitution in a SDV<br>• Recommended dosage is 10 mg/kg by IV infusion for 1 dose, followed by 20 mg/kg IV infusion every 3 weeks for 7 additional doses |
| tazemetostat (Tazverik™) Epizyme | • NDA approval 01/23/2020; Accelerated Approval, Orphan Drug, Priority Review<br>• Indicated for the treatment of patients ages ≥ 16 years with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection; continued approval may depend on confirmatory trial results<br>• Methyltransferase inhibitor<br>• Tablet: 200 mg<br>• Recommended dosage is 800 mg (4 tablets) taken orally twice daily with or without food |
| empagliflozin/ linagliptin/ metformin ER (Trijardy XR™) Boehringer Ingelheim/Eli Lilly | • NDA approval 01/27/2020<br>• Indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and to reduce the risk of CV death in adults with T2DM and established CVD<br>• SGLT2 inhibitor, DPP-4 inhibitor, and biguanide<br>• Fixed-dose combination tablets: 5 mg/2.5 mg/1,000 mg, 10 mg/5 mg/1,000 mg, 12.5 mg/2.5 mg/1,000 mg, and 25 mg/5 mg/1,000 mg<br>• Recommended starting dose is based on the patient's current antidiabetic regimen<br>• Boxed warning for lactic acidosis |
| octreotide (Bynfezia Pen™) Sun | • 505(b)(2) NDA approval 01/28/2020<br>• Indicated for the:<br>» Reduction of growth hormone (GH) and IGF-1 [somatomedin C] in adults with acromegaly who have had inadequate response to or cannot be treated with surgical resection, pituitary irradiation, or bromocriptine mesylate at maximally tolerated doses<br>» Treatment of severe diarrhea/flushing episodes associated with metastatic carcinoid tumors in adults<br>» Treatment of profuse watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas) in adults<br>• Somatostatin analogue<br>• Injection: 2,500 mcg/mL as 2.8 mL in a single-patient-use pen<br>• Recommended dosages:<br>» Acromegaly: initial dose is 50 mcg SC 3 times a day; maintenance dose is typically 100 mcg SC 3 times a day, but may be as high as 500 mcg SC 3 times a day<br>» Carcinoid tumors: 100 to 600 mcg/day SC in 2 to 4 divided doses<br>» VIPomas: initial dose is 200 to 300 mcg daily SC in 2 to 4 divided doses for 2 weeks; titrate dose to achieve desired response (150 to 750 mcg/day) |

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## *RECENT FDA APPROVALS continued*

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **New Drugs** *continued* |
| peanut *(Arachis hypogaea)* allergen powder-dnfp (Palforzia™) Aimmune | • BLA approval 01/31/2020; Breakthrough Therapy<br>• Indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanuts in patients with a confirmed diagnosis of peanut allergy; to be used in conjunction with a peanut-avoidant diet<br>• Immunotherapy<br>• Oral powder: 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg capsules and 300 mg sachet<br>• Recommended dose is administered orally as initial escalation (0.5 mg to 6 mg) in patients 4 to 17 years of age; up-dosing (3 mg to 300 mg; increase dose in 2-week intervals) and maintenance dose (300 mg) may be continued in patients ages ≥ 4 years; initial escalation dose and the first dose of each new up-dosing level are administered in a certified healthcare setting; mix contents of the capsule or sachet with soft solid food; consume the entire dose; maximum 1 dose per day<br>• Boxed warning for anaphylaxis<br>• Patients should be prescribed and educated on use of injectable epinephrine<br>• Product is available only through a Risk Evaluation and Mitigation Strategy (REMS); launch is expected in 1Q 2020 |
| | **Expanded Indications** |
| rituximab-abbs (Truxima®) Celltrion | • sBLA approval 12/18/2019<br>• New indications for rheumatoid arthritis (RA) in combination with methotrexate in adults with moderate to severe active RA who had an inadequate response to ≥ 1 tumor necrosis factor (TNF) antagonist therapy and for the treatment of granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) and microscopic polyangiitis (MPA) in adults in combination with glucocorticoids; the biosimilar was previously approved for non-Hodgkin's lymphoma and chronic lymphocytic leukemia<br>• Recommended dosage for RA is two 1,000 mg IV infusions separated by 2 weeks (1 course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks<br>• Recommended dosage for GPA and MPA is 375 mg/m$^2$ once weekly for 4 weeks (induction dose), followed by two 500 mg IV infusions separated by 2 weeks, subsequently followed by a 500 mg IV infusion every 6 months thereafter, based on clinical evaluation (for those who have achieved disease control following induction) |
| insulin aspart (Fiasp®) Novo Nordisk | • sNDA approval 12/19/2019<br>• Expanded indication for improving glycemic control in patients with diabetes mellitus to include pediatric patients, including for the use as continuous SC insulin infusion; previously it was approved in adults only<br>• Recommended dosage is individualized and adjusted based on the route of administration, patient's metabolic needs, blood glucose levels, and glycemic goal |
| micafungin (Mycamine®) Astellas | • sNDA approval 12/20/2019<br>• Expanded indication for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses *without* meningoencephalitis, and/or ocular dissemination in pediatric patients < 4 months of age; previously approved only in patients ≥ 4 months of age for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses; it is also approved for the treatment of other *Candida* infections<br>• Recommended dosage is weight-based at 4 mg/kg once daily administered IV over 1 hour |

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## *RECENT FDA APPROVALS continued*

| DRUG NAME MANUFACTURER | DESCRIPTION |
|---|---|
| | **Expanded Indications** *continued* |
| olaparib (Lynparza®) AstraZeneca | • sNDA approval 12/27/2019<br>• New indication for the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated metastatic pancreatic adenocarcinoma whose disease has not progressed on ≥ 16 weeks of a 1st-line platinum-based chemotherapy regimen; previously received approval for select patients with ovarian and breast cancer<br>• Recommended dosage is 300 mg orally twice daily, with or without food, continued until disease progression or unacceptable toxicity |
| pembrolizumab (Keytruda®) Merck | • sBLA approval 01/08/2020<br>• New indication for patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy<br>• Recommended dosage is 200 mg IV over 30 minutes every 3 weeks until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression |
| infliximab-qbtx (Ixifi™) Pfizer | • sBLA approval 01/14/2020<br>• Expanded indication for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients ≥ 6 years of age with moderately to severely active ulcerative colitis (UC) who have had an inadequate response to conventional therapy; previously only indicated for adults for the treatment of UC<br>• Recommended dosage for the biosimilar is 5 mg/kg as an IV induction regimen at 0, 2, and 6 weeks followed by maintenance dosing of 5 mg/kg every 8 weeks |
| fidaxomicin (Dificid®) Merck | • sNDA approval 01/24/2020<br>• Expanded indication for the treatment of *Clostridioides difficile*-associated diarrhea (CDAD) to include pediatric patients ages ≥ 6 months; it was previously only approved for use in adults<br>• Recommended dosage in pediatric patients is weight-based (up to 200 mg) given orally twice daily for 10 days |

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**References:**

fda.gov cdc.gov hcvguidelines.org icer-review.org rheumatology.org