



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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STANDARDS OF MEDICAL CARE IN DIABETES—2019

The American Diabetes Association (ADA) published their annual update for the Standards of Medical Care in Diabetes. Changes were made to align the guidance with the recent type 2 diabetes mellitus (T2DM) consensus report by the ADA and European Association for the Study of Diabetes (EASD). These include use of the diabetes care decision cycle and consideration of important patient factors (e.g., comorbidities, hypoglycemic risk, effects on body weight, side effects, cost, patient preference) when selecting an antidiabetic agent. The ADA prefers a glucagon-like peptide 1 (GLP-1) receptor agonist over insulin in patients with T2DM who require an injectable antidiabetic agent. Use of medications with proven cardiovascular (CV) and renal benefit are also preferred in those with CV and renal disease, respectively. The ADA emphasizes the importance of a diabetes care team approach, particularly in diabetic patients who are pregnant or hospitalized. A new Diabetes Technology section was created for new and existing recommendations on devices, hardware, and software used to manage diabetes, including telemedicine.

The criteria for diagnosing diabetes permits the use of 2 abnormal test results (e.g., fasting plasma glucose and hemoglobin A1c [HbA1c]) from the same blood sample. The 10-year atherosclerotic CV disease (ASCVD) risk

should be part of a patient's overall risk assessment. The ADA regards routine glucose self-monitoring to be of limited additional benefit in patients with T2DM who are not on insulin. Further, glycemic targets should be re-evaluated periodically based on disease progression and patient age.

Regarding lifestyle management, the ADA recommends against a one-size-fits-all meal planning approach in diabetic patients, since eating patterns vary among individuals. Overall, the ADA does encourage decreased consumption of sugar and artificially sweetened beverages. Emphasis is placed on tobacco use as a potential T2DM risk factor. Although, tobacco cessation should be encouraged, the years immediately following smoking cessation may also represent a time of increased risk for diabetes. In addition, the unique pathology and/or needs of pediatric and elderly diabetic patients is addressed with new recommendations. In geriatrics, a simplified insulin regimen should be used based on self-management abilities.

FLU GUIDELINE UPDATE

The Infectious Diseases Society of America (IDSA) updated their 2009 seasonal influenza guidelines. Annual vaccination continues to be the cornerstone for preventing and minimizing the impact of the flu. In the outpatient setting, decisions to prescribe antiviral treatment (oral oseltamivir [Tamiflu®] or inhaled zanamivir [Relenza®] for 5 days, or

single-dose intravenous [IV] peramivir [Rapivab®]) should be based on the patient's clinical presentation and epidemiology factors. If influenza is suspected, antiviral therapy is recommended in patients with severe or progressive illness or at high risk for influenza complications (e.g., immunocompromised, very young, elderly, pregnant, American Indians, native Alaskans). Treatment can also be considered in non-high-risk patients with flu symptoms for ≤ 2 days or who live or work with high-risk individuals.

While diagnostic testing is not required for treatment decision making, it is recommended if the results will influence clinical management. The IDSA recommends use of newer rapid molecular assays to improve influenza detection. Early testing is advised in individuals at high risk of hospitalization or death and in pregnant women. Notably, initiating antiviral treatment should not be delayed pending test results.

In the community setting, preexposure and postexposure prophylaxis (using oseltamivir or zanamivir) is recommended in select individuals at high risk for influenza complications. The IDSA made no recommendations regarding the newly approved antiviral baloxavir marboxil (Xofluza®) since it was approved after the finalization of the guidelines; however, clinical study information on its use was provided.

■ FDA FLUOROQUINOLONE WARNING

The United States (US) Food and Drug Administration (FDA) issued a Safety Alert on the increased risk of rare, but serious, aortic ruptures associated with systemic fluoroquinolone (FQ) antibiotics in select patients. The alert is based on case reports submitted to the FDA Adverse Event Reporting System (FAERS) and 4 published observational studies. While the exact cause is unknown, patients treated with an oral or injectable FQ who had a history of blockages or aneurysm of blood vessels, including the aorta, hypertension, select genetic disorders (e.g., Marfan syndrome, Ehlers-Danlos syndrome), and advanced age were twice as likely to experience aortic aneurysm or dissection. The FDA is advising clinicians to avoid prescribing FQs in these patient populations, if possible. FQ treatment should be stopped immediately if symptoms of aortic aneurysm or dissection occur.

■ ICER REPORTS ON BIOLOGIC AGENTS FOR SEVERE ASTHMA

Inhaled corticosteroids and long-acting beta-2-adrenergic agonists are considered the standard of care for asthma. When asthma is severe, treatment can also include

muscarinic agents, leukotriene inhibitors, theophylline, and the biologic therapies benralizumab (Fasenra™), dupilumab (Dupixent®), mepolizumab (Nucala®), omalizumab (Xolair®), and reslizumab (Cinqair®). The Institute for Clinical and Economic Review (ICER) published a final report on the comparative clinical effectiveness and value of these biologic products. Based on current clinical evidence, superiority of 1 product over another has not been established. ICER recommends that medical specialty societies clearly define the response to biologic therapy and the FDA update its guidance on outcomes assessment in asthma therapy with standardized patient populations and comparative trials. To align with the product's added value, ICER recommends that drug manufacturers decrease the price of their biologic agents by $\geq 50\%$. Moreover, ICER states that insurance coverage should provide streamlined access to all biologics for asthma but acknowledges that prior authorization and step therapy are reasonable approaches for payers to ensure the prudent use of these expensive medications.



BEHAVIORAL HEALTH CORNER

DHHS GUIDANCE ON NALOXONE

The Centers for Disease Control and Prevention (CDC) reported 47,600 opioid-related deaths in 2017. In an effort to increase access to naloxone that can reverse the life-threatening respiratory depression associated with opioid overdose, the US Department of Health and Human Services (DHHS) released a statement on its use. To ensure that naloxone is at the right place at the right time, the DHHS recommends clinicians to coprescribe naloxone to patients who are at risk of opioid overdose. This includes patients (1) receiving ≥ 50 morphine milligram equivalents (MME) per day, (2) with respiratory illness, (3) also prescribed a benzodiazepine, or (4) with a non-opioid substance use disorder (e.g., alcohol). Naloxone should also be prescribed to individuals at high risk of experiencing or responding to an opioid overdose, such as a family member or friend of a person with an opioid use disorder, including those who have decreased opioid tolerance (e.g., after release from incarceration or other controlled setting).

The statement by the DHHS reinforces and expands upon prior CDC guidelines and the Surgeon General's call to increase naloxone access. Naloxone comes in a variety of user-friendly formulations, including nasal spray and auto-injection, and is covered by most health insurance plans, or may be attained for free or at low cost by several community programs.

DRUG INFORMATION HIGHLIGHTS

- **Flu Season Update (2018–2019):** The CDC reported increased influenza activity during the week ending 01/26/2019. In the US, New York City and 23 states reported high activity, 10 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 across the US, but H3N2 viruses predominated in the southeast. No nationwide shortages have been reported for oral influenza antivirals. No resistance to neuraminidase inhibitor antivirals, such as oseltamivir, has been detected. The FDA also expanded the indication of Fluzone® Quadrivalent influenza vaccine 0.5 mL dose to include children ages 6 to 35 months.
- 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. Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg continues to be available with no shortages. Teva's generic version of Epipen is available in limited supply since its recent launch; Teva's generic for Epipen Jr is expected to launch in 2019. Adamis' Symjepi® 0.3 mg became available in the US in January 2019 using a phased launch targeting clinics and institutions followed by retail settings. Symjepi 0.15 mg has not entered the US market.
- Bristol-Myers Squibb will complete US market removal of their hepatitis C antiviral Daklinza® (daclatasvir) with discontinuation of 30 mg and 60 mg tablets, effective in June 2019. This follows the discontinuation of the 90 mg tablets as of December 2018. No generics are available for this product.
- Mylan will discontinue Zovirax® (acyclovir) capsules and tablets. Generic formulations are available.
- Torrent Pharmaceuticals is recalling an additional 8 lots of losartan potassium tablets, USP and 6 lots of losartan potassium/hydrochlorothiazide (HCTZ) tablets, USP with active pharmaceutical ingredient (API) manufactured by Hetero Labs Limited. Princeton Pharmaceuticals (DBA Solco Healthcare) is voluntarily recalling 1 lot of irbesartan and 7 lots of irbesartan/HCTZ tablets. The consumer-level voluntary recalls of these and other angiotensin receptor blockers (ARBs) are due to detection of trace levels of a probable human carcinogen, N-nitrosodiethylamine (NDEA).
- Tris Pharma is expanding its retail-level recall of Ibuprofen Oral Suspension Drops, USP, 50 mg per 1.25 mL. Three lots were added due to detection of higher levels of ibuprofen concentration than intended, which could lead to serious adverse effects in infants.
- Portola's prior approval supplement (PAS) for Andexxa® (coagulation factor Xa, inactivated-zhzo) was FDA-approved allowing for a full commercial launch of the product. The rivaroxaban reversal agent was originally granted Accelerated Approval in May 2018 and Orphan Drug and Breakthrough Therapy designations.
- Teva announced FDA approval of Proair® Digihaler™, a breath-actuated albuterol dry powder digital inhaler with built-in sensors that connects to a companion mobile application and provides inhaler use information. Proair Digihaler is indicated to treat or prevent bronchospasm in patients with reversible obstructive airway disease and prevent exercise-induced bronchospasm (EIB) in patients ≥ 4 years old. As with other albuterol products, Proair Digihaler is used on an as-needed basis for reversible obstructive airway disease or prior to exercise. Launch is anticipated in 2019 through a small number of "early experience" programs; a broader national launch is planned in 2020.

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

- **Feb–Apr 2019:** glucagon auto-injector; subcutaneous (SC) glycogenolytic; hyperinsulinemia/hypoglycemia; Xeris.
- **Feb–May 2019:** Cyramza®; ramucirumab; IV vascular endothelial growth factor receptor 2 (VEGFR2) antagonist; hepatocellular carcinoma; Eli Lilly.
- **February 06, 2019:** caplacizumab; IV/SC antithrombotic; thrombotic thrombocytopenic purpura (TTP); Sanofi.
- **February 13, 2019:** iclaprim; IV antibiotic; skin and skin-structure infections; Motif Bio.
- **February 15, 2019:** halobetasol/tazarotene; topical corticosteroid/retinoid; plaque psoriasis (PSO); Bausch Health.
- **February 22, 2019:** Jakafi®; ruxolitinib; oral Janus kinase (JAK) inhibitor; graft-versus-host disease; Incyte.
- **February 22, 2019:** Lonsurf®; trifluridine/tipiracil; oral fixed-dose nucleoside metabolic inhibitor/thymidine phosphorylase inhibitor; gastric cancer; Otsuka.
- **February 25, 2019:** Lotemax® 0.38% gel; loteprednol; ophthalmic corticosteroid; postoperative ocular pain/inflammation; Bausch Health.
- **February 27, 2019:** turoctocog alfa pegol; IV long-acting recombinant factor VIII; hemophilia A; Novo Nordisk.
- **March 03, 2019:** esketamine; intranasal N-methyl-D-aspartate (NMDA) receptor antagonist; major depressive disorder (MDD); Janssen.
- **March 12, 2019:** Tecentriq®; atezolizumab; programmed cell death-1 ligand (PD-L1) inhibitor; first-line treatment of triple-negative breast cancer; Genentech.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
diclofenac epolamine (Licart™) IBSA	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 12/19/2018 • Indicated for topical treatment of acute pain due to minor strains, sprains, and contusions • Nonsteroidal anti-inflammatory drug (NSAID) • Topical system: 1.3% diclofenac epolamine (10 x 14 cm); for topical use only • Recommended dosage is 1 topical system applied to the most painful area once daily • Boxed warnings for CV and gastrointestinal events
levetiracetam (Elepsia™ XR) Sun	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 12/20/2018 • Indicated for adjunctive treatment of partial-onset seizures in patients ≥ 12 years old • Antiepileptic drug • Oral extended-release (ER) tablets: 1,000 mg and 1,500 mg • Initial dose is 1,000 mg once daily; increase by 1,000 mg every 2 weeks, as required, to a maximum of 3,000 mg once daily
ravulizumab-cwvz (Ultomiris™) Alexion	<ul style="list-style-type: none"> • BLA approval 12/21/2018; Orphan Drug; Priority Review • Indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) in adults • Complement inhibitor • Injection: 300 mg/30 mL (10 mg/mL) single-dose vial (SDV) • Recommended loading and maintenance dosages are weight-based • Boxed warning for serious meningococcal infections • Available only through a Risk Evaluation and Mitigation Strategy
tagraxofusp-erzs (Elzonris™) Stemline	<ul style="list-style-type: none"> • BLA approval 12/21/2018; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in patients ≥ 2 years of age • CD123-directed cytotoxin • Injection: 1,000 mcg in 1 mL SDV • Recommended dosage is 12 mcg/kg IV over 15 minutes once daily on days 1 to 5 of a 21-day cycle; dosing period may be extended for up to day 10 of a cycle; continue therapy until disease progression or unacceptable toxicity <ul style="list-style-type: none"> » Premedication with an H1- and H2-histamine antagonists, acetaminophen, and a corticosteroid prior to each infusion is recommended » Administer first cycle in an inpatient setting and subsequent cycles in an inpatient or suitable outpatient ambulatory care setting; observe patient for ≥ 4 hours postinfusion • Boxed warning for capillary leak syndrome
trastuzumab-dttb (Ontruzant®) Samsung Bioepis	<ul style="list-style-type: none"> • BLA approval 01/18/2019; Biosimilar to Genentech's trastuzumab (Herceptin®) • Indicated for adjuvant treatment of HER2-overexpressing breast cancer and HER2-overexpressing metastatic gastric cancer or gastroesophageal junction adenocarcinoma in patients who have not received prior treatment for metastatic disease; see package insert for complete details <ul style="list-style-type: none"> » Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product • HER2/neu receptor antagonist • Injection: 150 mg lyophilized powder for reconstitution in a SDV • Recommended dosage is weight-based administered IV, varying by indication • Boxed warnings for cardiomyopathy, infusion reactions, embryo-fetal toxicity, and pulmonary toxicity

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	
oxcarbazepine ER (Oxtellar XR®) Supernus	<ul style="list-style-type: none"> • sNDA approval 12/13/2018 • Indicated for the treatment of partial-onset seizures in patients ≥ 6 years of age; previously it was indicated only in the adjuvant setting and safety and efficacy beyond short-term use was not established in pediatrics • Recommended initial dose for adults is 600 mg orally once daily (300 mg to 450 mg in elderly); adult dosage may be increased based on clinical response and tolerability to a maintenance dose of 1,200 mg to 2,400 mg once daily; pediatric dosing is 8 to 10 mg/kg orally once daily; adjust pediatric dose based on clinical response and tolerability up to 600 mg daily
olaparib tablets only (Lynparza®) AstraZeneca	<ul style="list-style-type: none"> • sNDA approval 12/19/2018; Orphan Drug • Indicated for the maintenance treatment of adults with deleterious or suspected deleterious germline or somatic <i>BRCA</i>-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy • Recommended dosage is 300 mg orally twice daily until disease progression or unacceptable toxicity
tacrolimus ER (Envarsus XR®) Veloxis	<ul style="list-style-type: none"> • sNDA approval 12/19/2018 • Indicated to prevent organ rejection in <i>de novo</i> kidney transplant patients in combination with other immunosuppressants • Recommended dosage is 0.14 mg/kg/day once daily on an empty stomach, at the same time of day
dasatinib (Sprycel®) Bristol-Myers Squibb	<ul style="list-style-type: none"> • sNDA approval 12/21/2018 • Indication was expanded to include patients as young as 1 year old for the treatment newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) in combination with chemotherapy • Recommended dosage in pediatrics is weight-based with daily doses ranging from 40 mg to 100 mg; use is not recommended in patients ≤ 10 kg
glycerol phenylbutyrate (Ravicti®) Horizon	<ul style="list-style-type: none"> • 505(b)(2) sNDA approval 12/21/2018; Orphan Drug • Indicated as a nitrogen-binding agent for chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone • Recommended dosage range is 4.5 to 11.2 mL/m²/day and is individualized based on body surface area, plasma ammonia, residual urea synthetic capacity, dietary protein requirements, and diet adherence
cabozantinib s-malate (Cabometyx®) Exelixis	<ul style="list-style-type: none"> • sNDA approval 01/14/2019; Orphan Drug • Indicated for the treatment of hepatocellular carcinoma (HCC) in patients who have previously been treated with sorafenib • Recommended dosage is 60 mg orally, once daily ≥ 1 hour before or ≥ 2 hours after eating

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