NOVEMBER 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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HOT TOPIC: NEW FLU MED APPROVED

Influenza places a considerable burden on the United States (US) healthcare system, with up to 35 million cases reported each year. As the 2018-2019 flu season gets underway, the Food and Drug Administration (FDA) granted Priority Review and approval for Genentech/Shionogi's baloxavir marboxil (Xofluza™), the first new novel influenza antiviral in nearly 20 years. The new agent is indicated to treat acute uncomplicated influenza in people ≥ 12 years of age with flu symptoms for ≤ 48 hours. Baloxavir marboxil uses a unique mechanism of action to block the replication of influenza A and B viruses, including Avian strains (H7N9, H5N1). In clinical studies, it was well tolerated and eased flu symptoms in about the same amount of time as the market leader, oral oseltamivir (Tamiflu®), and significantly less time compared to placebo (54 versus 80 hours). Duration of viral shedding was shorter with baloxavir marboxil compared to oseltamivir and placebo (24, 72, and 96 hours, respectively). Furthermore, baloxavir marboxil demonstrated efficacy against select oseltamivir-resistant strains. Baloxavir marboxil, which is approved as 20 mg and 40 mg tablets, is administered as a single oral dose (weight-based, 40 mg or 80 mg), while oseltamivir requires twice-daily dosing for 5 days to treat the flu. In contrast, oseltamivir has a broader indication for influenza treatment in patients ≥ 2 weeks of age and prophylaxis in patients aged ≥ 1 year.

While yearly vaccination is the primary means of preventing and controlling flu outbreaks, treatment with antiviral agents can lessen symptoms, shorten duration of illness, and prevent serious complications.

UPDATED CONSENSUS ON DIABETES MANAGEMENT

The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) updated their 2015 joint position statement on the management of type 2 diabetes mellitus (T2DM). It includes a new decision cycle for patient-centered glycemic management with a goal to prevent diabetes complications and enhance quality of life (QOL). Greater focus is placed on lifestyle management and diabetes self-management education and support. Weight loss strategies include lifestyle, medical nutrition therapy (MNT), medication, and surgical interventions. When T2DM is not controlled with metformin plus lifestyle management, the ADA/EASD recommends addition of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or glucagon-like peptide 1 receptor agonist (GLP1RA) with proven benefit in select patients, such as those with atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), or in patients with clinical heart failure and ASCVD (SGLT2i preferred). An SGLT2i or GLP1RA is recommended when weight management is key. Adjunct treatment with an SLGT2i, GLP1RA, dipeptidyl peptidase 4 inhibitor (DPP4i), or thiazolidinedione (TZD) is

recommended to minimize hypoglycemia. Further, in most patients with T2DM, ADA/EASD recommends use of a GLP1RA over insulin as the first injectable medication.

GUIDANCE UPDATE ON RESISTANT HYPERTENSION

The American Heart Association (AHA) updated the 2008 Scientific Statement on resistant hypertension (RH). The AHA defines RH as above-goal elevated blood pressure (BP) despite concurrent use of 3 antihypertensive drug classes at maximally tolerated doses or BP that requires ≥ 4 medications to achieve a target level. Hypertension is typically treated with a diuretic, a long-acting calcium channel blocker, and a renin-angiotensin system blocker (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB]). The update complements the AHA's revised target BP of ≤ 130/80 mm Hg in patients on antihypertensive therapy; this lower threshold increases the number of patients considered to have RH. Diagnosis of RH should be made based on a 24-hour ambulatory BP measured after medication adherence has been confirmed. RH assessment should consider lifestyle, drug-drug interactions, secondary hypertension, and presence of end organ damage. Recommended treatment for confirmed RH includes optimization of lifestyle interventions, use of a long-acting thiazide-like diuretic (e.g., chlorthalidone, indapamide), and addition of a mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone). If BP remains above target levels, addition of agents with different mechanisms, and possibly referral to a hypertension specialist, are advised.

ICER SPOTLIGHT

The Institute for Clinical and Economic Review (ICER) updated the report on targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis (PSO). The tumor necrosis factor-alpha (TNFα) inhibitor certolizumab pegol (Cimzia™), and the interleukin (IL)-23 inhibitors, guselkumab (Tremfya®), tildrakizumab-asmn (Ilumya™), and risankizumab (investigational) were added. ICER determined guselkumab and risankizumab, but not tildrakizumab-asmn and certolizumab pegol, offer a superior net health benefit compared to all subcutaneously (SC) administered TNFα inhibitors. ICER does, however, acknowledge that certolizumab pegol is an important option in pregnant or breastfeeding women. It also states that the mechanism of action of the IL-23 inhibitors may be effective in patients when other therapies have failed. To hasten improved QOL, ICER recommends removing or limiting step therapy around medication coverage, particularly in patients who have switched from another insurer during PSO treatment.

The committee also issued a report evaluating 2 medications recently FDA-approved for hereditary transthyretin amyloidosis (hATTR), a rare, often fatal genetic disorder, characterized by neurologic and cardiac dysfunction. An estimated 3,000 to 3,500 Americans may be candidates for hATTR treatment. The 2 new agents, patisiran (Onpattro™) and inotersen (Tegsedi™), demonstrated significant improvement in neuropathy and QOL. Patisiran is given by a healthcare professional (HCP) as an intravenous (IV) infusion every 3 weeks, and inotersen can be self-administered SC once weekly. Until approval of these agents, hATTR treatments in the US only included liver transplantation and off-label use of the oral non-steroidal anti-inflammatory drug (NSAID), diflunisal. ICER determined that while the new agents provide a substantial net health benefit compared to best supportive care alone, their pricing greatly exceeds cost-effectiveness thresholds; therefore, use of prior authorization strategies is reasonable.

BEHAVIORAL HEALTH CORNER

FDA CONTINUES TO FIGHT OPIOID CRISIS

In an effort to combat the US opioid crisis, the FDA will apply new safety measures for outpatient use of opioid analgesics. Steps taken include the addition of immediate-release formulations to the opioid Risk and Evaluation Mitigation Strategy (REMS). The FDA is expanding the availability of opioid education programs to all HCPs involved in managing a patients pain, including pharmacists and nurses. Information covered will also include use of non-opioid alternatives. Roll-out of this enhanced program is expected by March 2019. While training is not required to prescribe opioids, the FDA is considering mandating it in select circumstances. In addition, the FDA is adding information to all opioid product labels regarding HCP pain management education and new Patient Counseling Guides to assist in patient discussions around risks, safe use, storage, and disposal of opioids. Lastly, the agency is creating a framework to help medical professional societies develop evidence-based, indication-specific guidelines on appropriate opioid prescribing for acute pain, including appropriate duration of therapy.

DRUG INFORMATION **HIGHLIGHTS**

- The intermittent shortage of epinephrine auto-injectors, used for the emergency treatment of allergic reactions, including anaphylaxis, persists nationwide in the US. Impax's authorized generic (AG) version of the discontinued Adrenaclick® continues to be on backorder with additional supply expected in November. Mylan reports that they are shipping Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and their respective AG 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 versions of Epipen and Epipen Jr and Adamis' Symjepi™ (0.3 mg and 0.15 mg) have not entered the US market.
- The FDA issued a Safety Communication to alert patients, caregivers, and HCPs of the proper use of pen needles to inject medicine from pen injectors. The FDA received reports of patients using standard pen needles to administer insulin without removing the inner needle cover, resulting in the insulin not being injected and the risk for hyperglycemia. One case resulted in hospitalization and death. The FDA is reminding HCPs to instruct patients how to use the pen needles and to ensure that the patient can demonstrate proper technique.
- Bristol-Myers Squibb announced that they will stop distribution of their hepatitis C antiviral agent, daclatasvir (Daklinza®) 90 mg tablets in December 2018. The 30 mg and 60 mg tablet remain available.
- Endo Pharmaceuticals announced a voluntary recall of 2 lots of Robaxin® (methocarbamol) 750 mg tablets, 100 count bottle to the consumer level due to a labeling error that misstates the daily dose as 2 to 4 tablets 4 times daily instead of 2 tablets 3 times daily. The error could lead to drug toxicity.
- After reviewing all available postmarketing reports of death and serious adverse events related to the use of the antipsychotic, pimavanserin (Nuplazid®), the FDA did not find any new or unexpected safety risks. The agency did, however, identify potentially harmful prescribing patterns, such as concomitant use with other antipsychotic drugs or drugs that can cause QT prolongation and is reminding HCPs of the potential risks discussed in the product labeling.
- Bristol-Myers Squibb announced the discontinuation of the powder for oral solution formulation of the human immunodeficiency virus-1 (HIV-1) antiretroviral stavudine (Zerit®).
- The FDA approved 75 mg/0.5 mL and 150 mg/1 mL single-dose prefilled syringes of Genentech's omalizumab (Xolair®) for allergic asthma and chronic idiopathic urticaria. Launch is expected in 2018.
- Eyepoint's fluocinolone acetonide intravitreal implant (Yutiq™) was approved to treat chronic non-infectious uveitis of the posterior segment of the eye. The nonbiodegradable system delivers 0.25 mcg/day over 36 months. Launch is expected in Q1, 2019.

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

- **November 2018:** lorlatinib; oral tyrosine kinase inhibitor (TKI); non-small cell lung cancer (NSCLC); Pfizer.
- **November 2018:** Signifor® LAR; pasireotide; intramuscular (IM) injection; Cushing's syndrome; Novartis.
- **November 2, 2018:** oliceridine; IV opioid agonist; acute pain; Trevena.
- **November 2, 2018:** pegfilgrastim; biosimilar to Amgen's (Neulasta®); SC granulocyte-colony stimulating factor; neutropenia, leukopenia; Coherus.
- **November 2, 2018:** sufentanil; sublingual (SL) opioid agonist (medically supervised); acute pain; Acelrx.
- **November 9, 2018:** Keytruda®; pembrolizumab; IV programmed cell death 1 (PD-1) inhibitor; hepatocellular carcinoma; Merck.
- **November 13, 2018:** revefenacin; inhaled long-acting muscarinic antagonist; chronic obstructive pulmonary disease (COPD); Theravance.
- **November 16, 2018:** immediate-release oxycodone (abuse-deterrent); oral opioid agonist; pain; Mallinckrodt.
- **November 16, 2018:** rifamycin; oral antibacterial; gastroenteritis; Cosmo.
- **November 20, 2018:** emapalumab; IV type 2 interferon inhibitor; hemophagocytic lymphohistiocytosis; Swedish Orphan Biovitrum.
- **November 26, 2018:** larotrectinib; IV tropomyosin receptor kinase inhibitor; solid tumors; Loxo Oncology.
- **November 28, 2018:** amifampridine; oral potassium channel inhibitor; Lambert-Eaton myasthenic syndrome; Catalyst.
- **November 29, 2018:** gilteritinib; oral TKI; acute myelogenous leukemia; Astellas.
- **November 30, 2018:** bupivacaine collagen sponge; implantable anesthetic; post-surgical pain; Innocoll.
- **November 30, 2018:** rituximab, biosimilar to Genentech's Rituxan®; IV CD20-directed cytolytic antibody; rheumatoid arthritis, chronic lymphocytic leukemia, indolent non-Hodgkin lymphoma, antineutrophil cytoplasmic antibody-associated vasculitis. Teva/Celltrion.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs
latanoprost (Xelpros™) Sun	• 505(b)(2) NDA approval 09/12/2018 • To reduce intraocular pressure in patients with open-angle glaucoma or ocular hypertension • Prostaglandin $F_{2\alpha}$ analog • Ophthalmic emulsion: latanoprost 0.005% (50 mcg/mL) in a 2.5 mL bottle • Administer 1 drop in the affected eye(s) once daily in the evening
moxetumomab pasudotox-tdfk (Lumoxiti™) AstraZeneca	• BLA approval 09/13/2018; Orphan Designation; Priority Review • Treatment of adults with relapsed or refractory hairy cell leukemia who received ≥ 2 prior systemic therapies, including treatment with a purine nucleoside analog • CD22-directed cytotoxin • Lyophilized powder for injection: 1 mg cake or powder in a single-dose vial (SDV) • Administered as 0.04 mg/kg IV over 30 minutes on days 1, 3, and 5 of each 28-day cycle; for a maximum of 6 cycles • Boxed warnings for capillary leak syndrome (CLS) and hemolytic uremic syndrome (HUS)
duvelisib (Copiktra™) Verastem	• NDA approval 09/24/2018; Accelerated Approval; Orphan Drug; Priority Review • Treatment of: » Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies » Relapsed or refractory follicular lymphoma (FL) after ≥ 2 prior systemic therapies • Phosphoinositide 3-kinase (PI3K) inhibitor • Oral capsules: 15 mg and 25 mg • Recommended dose is 25 mg twice daily in 28-day cycles; adjust dose for toxicity • Boxed warnings for fatal and serious toxicities, including infections, diarrhea, colitis, cutaneous reactions, and pneumonitis
dacomitinib (Vizimpro®) Pfizer	• NDA approval 09/27/2018; Orphan Drug; Priority Review • First-line treatment of metastatic NSCLC with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations, as detected by an FDA-approved companion diagnostic test • EGFR kinase inhibitor • Oral tablets: 15 mg, 30 mg, and 45 mg • Recommended dose is 45 mg once daily, until disease progression or unacceptable toxicity occur
amikacin (Arikayce®) Insmed	• 505(b)(2) NDA approval 09/28/2018; approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs; Breakthrough Therapy; Orphan Drug; Priority Review; Qualified Infectious Disease Product • Treatment of adults with limited or no alternative treatment options for *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial regimen in patients without negative sputum cultures after ≥ 6 consecutive months of a multidrug background regimen • Aminoglycoside antibacterial • Liposomal suspension for self-administered oral inhalation: amikacin 590 mg/8.4 mL in a unit-dose glass vial • Dosage is 590 mg once daily by self-administered oral inhalation via Lamira™ nebulizer system; may consider pretreatment with an inhaled bronchodilator • Boxed warning for risk of increased respiratory adverse reactions

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.

RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
cemiplimab-rwlc (Libtayo®) Regeneron	• BLA approval 09/28/2018; Breakthrough Therapy; Priority Review • Treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation • PD-1 inhibitor • Injectable solution: 350 mg/7 mL (50 mg/mL) in a SDV • Recommended dosage is 350 mg infused IV over 30 minutes every 3 weeks until disease progression or unacceptable toxicity occur
testosterone enanthate (Xyosted™) Antares	• 505(b)(2) NDA approval 09/28/2018 • Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone • Androgen steroid • Injectable solution: 50 mg/0.5 mL, 75 mg/0.5 mL, and 100 mg/0.5 mL auto-injectors • Starting dose is 75 mg SC once weekly; adjust dose based on serum testosterone level • Boxed warning for BP increases that can increase the risk of major adverse CV events • Product launch is expected before the end of 2018
sarecycline (Seysara™) Allergan	• NDA approval 10/01/2018 • Treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients ≥ 9 years of age • Tetracycline-derived antibacterial • Oral tablets: 60 mg, 100 mg, and 150 mg • Weight-based dosage is 60 mg for patients 33–54 kg, 100 mg for patients 55–84 kg, and 150 mg for patients 85–136 kg. Efficacy beyond 12 weeks and safety beyond 12 months have not been established • Product launch is anticipated in January 2019
omadacycline (Nuzyra™) Paratek	• NDA approval 10/02/2018; Priority Review; Qualified Infectious Disease Product • Treatment of adult patients with community-acquired bacterial pneumonia (CABP) or acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible microorganisms • Tetracycline-derived antibacterial • Lyophilized powder for injection: omadacycline 100 mg in a SDV • Oral tablet: omadacycline 150 mg (equivalent to 196 mg omadacycline tosylate) • Recommended dosage for CABP and ABSSSI: » Loading dose (day 1): 200 mg IV over 60 minutes OR 100 mg IV over 30 minutes twice on day 1; alternative for ABSSSI *only* is 450 mg orally once daily » Maintenance dose: 100 mg IV over 30 minutes once daily OR 300 mg orally once daily • Product launch is anticipated in quarter 1, 2019
elapegademase-lvlr (Revcovi™) Leadiant	• BLA approval 10/05/2018; Orphan Designation; Priority Review • Treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in adult and pediatric patients • Adenosine deaminase, recombinant, pegylated • Injectable solution: 2.4 mg/1.5 mL (1.6 mg/mL) in a SDV • Recommended initial dosage (based on ideal body weight): » For patients switching from pegademase, bovine (Adagen®): 0.2 mg/kg IM once weekly » For Adagen-naïve patients: 0.4 mg/kg IM weekly, divided in 2 doses

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
inotersen (Tegsedi™) Ionis	• NDA approval 10/05/2018; Orphan Designation; Priority Review • Treatment of adults with polyneuropathy of hATTR • Transthyretin-directed antisense oligonucleotide • Injectable solution: 284 mg/1.5 mL in a single-dose prefilled syringe • Recommended dose is 284 mg SC once weekly • Boxed warnings for thrombocytopenia and glomerulonephritis • Available only through a restricted distribution program; launch is anticipated in 2018
Expanded Indications	
tocilizumab SC (Actemra®) Genentech	• sBLA approval 09/12/2018 • Treatment of systemic juvenile idiopathic arthritis (SJIA) in patients aged 2 to 17 years as monotherapy or in combination with methotrexate • Pediatric weight-based dosing: 162 mg SC every 2 weeks for patients < 30 kg and 162 mg once weekly for patients ≥ 30 kg
perampanel (Fycompa®) Eisai	• sNDA approval 09/27/2018 • Treatment of partial onset seizures, with or without secondary generalized seizures, including patients ≥ 4 years old • Dosing is consistent with other indications: 2 mg orally once daily at bedtime, with 2 mg weekly adjustments based on clinical response and tolerability
adalimumab (Humira) Abbvie	• sBLA approval 09/28/2018 and 10/05/2018 • Treatment of: » Noninfectious intermediate, posterior, and panuveitis in patients aged ≥ 2 years (09/28/2018) » Hidradenitis suppurativa (HS) in patients as young as 12 years (10/05/2018) • Recommended dosage: » Uveitis: 10 mg for patients 10-14 kg, 20 mg for patients 15-29 kg, and 40 mg for patients ≥ 30 kg, administered SC every other week » HS: for adolescents ≥ 60 kg, the dose is 160 mg on day 1, 80 mg on day 15, and 40 mg every week thereafter starting on day 29; for adolescents 30 to < 60 kg, the dose is 80 mg SC on day 1, then 40 mg every other week starting on day 8
carfilzomib (Kyprolis®) Onyx	• sNDA approval 09/28/2018 • Approved for addition of a once-weekly dosing regimen in combination with dexamethasone, for the treatment of relapsed or refractory multiple myeloma in patients who have received 1 to 3 lines of therapy • Recommended dosage is 20/70 mg/m^2 infused IV over 30 minutes once weekly
emicizumab-kxwh (Hemlibra®) Genentech	• sBLA approval 10/04/2018 • Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients, ages newborn through adults, without factor VIII inhibitors • Loading dose is 3 mg/kg SC once weekly for 4 weeks; maintenance dose is 1.5 mg/kg once weekly, OR 3 mg/kg every 2 weeks, OR 6 mg/kg every 4 weeks; the new maintenance regimens also apply to patients with factor VIII inhibitors
rivaroxaban (Xarelto®) Janssen	• sNDA approval 10/11/2018 • For use in combination with aspirin to reduce the risk of major CV events (CV death, myocardial infarction, and stroke) in patients with chronic coronary artery disease or peripheral artery disease • Dosage is 2.5 mg twice daily, plus aspirin (75 mg to 100 mg) once daily

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References: diabetes.org fda.gov heart.org icer-review.org