



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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FDA ALERT: RISK OF BLOOD CLOTS WITH TOFACITINIB

The United States (US) Food and Drug Administration (FDA) issued a public safety communication to alert patients and healthcare professionals (HCPs) that an ongoing safety trial found an increased risk of pulmonary embolism (PE) and death when patients with rheumatoid arthritis (RA) were treated with a 10 mg twice daily dose of tofacitinib (Xeljanz[®], Xeljanz XR[®]), compared to patients treated with tofacitinib 5 mg twice daily or a tumor necrosis factor (TNF) inhibitor. Tofacitinib was given in combination with methotrexate. While the 10 mg twice daily dose of tofacitinib is not FDA-approved for RA, it is approved for patients with ulcerative colitis. The trial will continue, but patients who were receiving the 10 mg twice daily dose of tofacitinib will transition to the FDA-approved dose for RA (5 mg twice daily). The FDA is reminding HCPs of the approved RA dose. Patients should not stop taking tofacitinib or change their dose without first talking to their HCP and should seek immediate medical attention if they have symptoms of PE (e.g., sudden shortness of breath, chest pain, hemoptysis, hyperhidrosis).

POSITION STATEMENT ON NEW MIGRAINE THERAPIES

The American Headache Society (AHS) released a position statement on the integration of new migraine treatments into clinical practice. Oral agents with proven efficacy for migraine prophylaxis include select antiepileptics and beta-

blockers and frovatriptan (menstrual migraine only). Select antidepressant and antihypertensive agents have also demonstrated efficacy. Treatment should be started at a low dose and titrated to a target response. Erenumab-aooe (Aimovig[™]), fremanezumab-vfrm (Ajovy[®]), and galcanezumab-gnlm (Emgality[®]) belong to a new class of injectable drugs for migraine prophylaxis: calcitonin gene-related peptide (CGRP) inhibitors. They are administered every 4 or 12 weeks. Compared to oral prophylaxis agents, the CGRP inhibitors do not require slow dose escalation, have a faster onset of therapeutic benefit, and may be better tolerated. They also have little risk for drug interactions and, therefore, may be added to an existing preventative regimen.

The AHS recommends initiating CGRP inhibitors in adults with a diagnosis of migraine (with or without aura) who suffer 8 to 14 monthly headache days or 4 to 7 monthly headache days and have moderate disability. Patients should also be intolerant of or have had an inadequate response to a 6-week trial of at least 2 oral prophylactic agents. For patients with chronic migraine (\geq 15 monthly headache days with \geq 8 being migraine), CGRP inhibitors are recommended if the patient cannot tolerate or has had an inadequate response to a 6-week trial of at least 2 oral prophylactic agents or at least 6 months of onabotulinumtoxinA (Botox[®]) treatment. Response to CGRP inhibitor therapy should be assessed after 3 months (for monthly injections) or 6 months (for quarterly injections),

and therapy should only be continued if clinically meaningful treatment benefit can be documented. The consensus statement also addresses non-pharmacologic preventive therapy, including neuromodulation and biobehavioral therapies, and acute treatment.

■ CONSENSUS PSORIASIS GUIDELINES

The American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) published 2 new guidelines for the treatment of plaque psoriasis (PSO). The documents are the first in a series of 6 guidelines that update and expand upon the 2008 AAD psoriasis guideline. The Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with biologics assess the efficacy and adverse effects of older TNF inhibitors adalimumab, etanercept, and infliximab, as well as agents approved after 2008, including the TNF inhibitor certolizumab, interleukin (IL)-17 inhibitors brodalumab, ixekizumab, and secukinumab, IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab (investigational), and the IL-12/23 inhibitor ustekinumab. With the exception of certolizumab and risankizumab, all FDA-approved biologics are given the highest strength recommendation, Level A, for monotherapy of moderate to severe PSO in adults. The AAD/NPF states that efficacy of certolizumab is likely comparable to the other TNF inhibitors, and risankizumab was given a Level B recommendation for PSO monotherapy. Furthermore, the AAD/NPF advises that any recommendation given to a TNF inhibitor applies to its biosimilar product.

The Joint AAD/NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities addresses extracutaneous manifestations of psoriasis in adults, including co-occurring conditions, mental health, psychosocial wellness, and quality of life. Comorbid conditions discussed include psoriatic arthritis, cardiovascular disease, metabolic syndrome, inflammatory bowel disease (IBD), malignancy, renal and hepatic disease, sleep apnea, chronic obstructive pulmonary disease, uveitis, and psychiatric disorders. Regarding psoriasis treatment, the AAD/NPF advise that TNF inhibitors are relatively contraindicated in psoriasis patients with New York Heart Association (NYHA) class III or IV congestive heart failure. Furthermore, there is an association between psoriasis and IBD, and use of TNF inhibitors to treat IBD can lead to paradoxical psoriasis-like outbreaks; therefore, discontinuation of TNF inhibitor therapy may be needed to resolve the skin eruptions (Level B). In addition, IL-17 inhibitor therapy should be avoided in patients with IBD (Level C).

■ UPDATED GUIDANCE FOR PAH

The American College of Chest Physicians (CHEST) published updated guidelines on pulmonary arterial hypertension (PAH) in adults. The guideline includes 2 new recommendations on combination therapy as well as 2 ungraded consensus-based statements on palliative care. For treatment-naïve PAH patients with World Health Organization (WHO) Functional Class (FC) II or WHO FC III without rapid disease progress or poor prognosis, initial therapy with ambrisentan plus tadalafil to improve 6-minute walking distance (6MWD) is now suggested (weak recommendation, moderate quality evidence). For stable or symptomatic PAH patients on background therapy with ambrisentan, CHEST now suggests the addition of tadalafil to improve 6MWD. An evidence-based, consensus-driven treatment algorithm was developed to guide clinicians through an organized treatment approach.



BEHAVIORAL HEALTH CORNER

ESKETAMINE APPROVED FOR TREATMENT-RESISTANT DEPRESSION (TRD)

The FDA approved Janssen's esketamine nasal spray (Spravato™), in combination with an oral antidepressant, for the treatment of TRD in adults. The N-methyl D-aspartate (NMDA) receptor antagonist was granted Breakthrough Therapy and Priority Review. Esketamine is the *s*-enantiomer of the anesthetic agent ketamine. Product labeling carries Boxed Warnings regarding the risks of sedation, dissociation, abuse and misuse, as well as suicidality. Due to these risks, esketamine must be dispensed only to a certified medical office, where the patient self-administers the dose and is monitored by an HCP for at least 2 hours. The patient should not drive or operate machinery until the following day. Each nasal spray device contains a total of 28 mg of esketamine, delivered as 2 sprays. Initial dosage is 56 mg twice per week for 4 weeks, then 56 mg or 84 mg once weekly for 4 weeks, and 56 mg or 84 mg every 1 or 2 weeks thereafter.

In clinical trials in patients with TRD, when given with oral antidepressant therapy, esketamine demonstrated superior improvement in depressive symptoms at day 28 compared to placebo. In a long-term study, patients treated with esketamine were 51% less likely to relapse than those who received placebo. Esketamine is a Schedule III controlled substance and is only available through a restricted Risk Evaluation and Mitigation Strategy (REMS) program.

DRUG INFORMATION HIGHLIGHTS

- The intermittent shortage of epinephrine autoinjectors 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 continue 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.
- Eli Lilly announced plans to market an AG version of their antidiabetic agent, insulin lispro (Humalog®). The AG is expected to be available in vials and pens in the US through their subsidiary Imclone Systems at about half the price of the original product.
- The FDA approved a 140 mg/mL prefilled syringe and autoinjector for erenumab-aooe (Aimovig) as an additional formulation to the previously approved 70 mg/mL prefilled syringe and autoinjector. The new concentration will accommodate a 140 mg dose with a single subcutaneous (SC) injection.
- Novartis announced a business decision to permanently discontinue emedastine (Emadine®) 0.05% ophthalmic solution for allergic conjunctivitis. There are no generic versions of this medication.
- Bayer announced a business decision to discontinue marketing the fluoroquinolone moxifloxacin (Avelox®) tablets and the antidiabetic agent acarbose (Precose®) in the US. Generic versions are available.
- Update on consumer level recalls of generic medications to treat hypertension due to potential human carcinogenic impurities: Aurobindo Pharma USA expanded their recall to include 39 lots of valsartan and amlodipine/valsartan tablets, and MacLeod Pharmaceuticals is recalling 1 lot of losartan/hydrochlorothiazide (HCTZ) tablets; both are due to the presence of N-nitrosodiethylamine (NDEA). A new carcinogenic impurity, N-nitroso-N-methyl 4-amino butyric acid (NMBA), was identified causing Camber Pharmaceuticals to recall 87 lots of losartan tablets, Legacy Pharmaceuticals to recall 3 lots of losartan/HCTZ tablets, and Torrent Pharmaceuticals to expand their recall by 60 lots of losartan tablets and 54 lots of losartan/HCTZ tablets. The FDA continues to evaluate the risks to patients and will continue to test all angiotensin receptor blockers (ARBs) for impurities and remove affected products from the market. Meanwhile, to help relieve the drug shortage created by the recalls, the agency is prioritizing the approval process for generic valsartan products, including the recent approval of generic valsartan by Alkem Laboratories.
- Apotex is voluntarily recalling 4 lots of drospirenone and ethinyl estradiol tablets to the patient level. Affected lots may contain defective blisters with incorrect tablet arrangements and/or an empty blister pocket which could lead to an inaccurate dosage and loss of efficacy. No cases of pregnancy have been reported.
- The FDA granted full approval to Bristol-Myers Squibb's PD-1 blocker, nivolumab (Opdivo®), for the treatment of BRAFV600 mutation-positive unresectable or metastatic melanoma as a single agent and in combination with ipilimumab for the treatment of patients with unresectable or metastatic melanoma.

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

- **Quarter 2, 2019:** rituximab, biosimilar to Genentech's Rituxan®; intravenous (IV) anti-CD20 antibody; non-Hodgkin's lymphoma; Pfizer.
- **April 1, 2019:** metoclopramide; intranasal dopamine receptor antagonist; diabetic gastroparesis; Evoke.
- **April 1, 2019:** rizatriptan; sublingual triptan; migraine; Gensco.
- **April 2, 2019:** IV immune globulin; primary immunodeficiency; ADMA.
- **April 18, 2019:** dolutegravir/lamivudine; oral antiretrovirals; human immunodeficiency virus-1 (HIV-1) infection; GlaxoSmithKline.
- **April 25, 2019:** risankizumab; SC IL-23 inhibitor; PSO; Abbvie.
- **April 30, 2019:** fosfomycin; IV antibiotic; complicated urinary tract infection; Nabriva.
- **April 30, 2019:** bupivacaine/meloxicam; anesthetic/non-steroidal anti-inflammatory drug; postsurgical pain; Heron.
- **May 2019:** biosimilar to Abbvie's adalimumab (Humira®); SC TNF inhibitor; Samsung Bioepis.
- **May 5, 2019:** amisulpride; IV atypical antipsychotic; postoperative nausea and vomiting; Acacia.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
methylphenidate (Adhansia XR™) Purdue	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 02/27/2019 • Indicated to treat attention deficit hyperactivity disorder (ADHD) in patients ages ≥ 6 years • Central nervous system (CNS) stimulant • Extended-release capsules: 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, and 85 mg • Recommended starting dose is 25 mg once daily in the morning with or without food; doses > 70 mg in pediatrics and > 85 mg in adults may cause a disproportionate increase in adverse reactions; do not substitute for other methylphenidate products on a mg-per-mg basis. • Schedule CII controlled substance; Boxed Warning for abuse and dependence
trastuzumab-qyyp (Trazimera™) Pfizer	<ul style="list-style-type: none"> • BLA approval 03/11/2019; biosimilar to Genentech's Herceptin® • Indicated for the treatment of human epidermal growth factor receptor 2 (HER2)-overexpressing breast cancer and HER2-overexpressing metastatic gastric 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 based on an FDA-approved trastuzumab product companion diagnostic • HER2/neu receptor antagonist • Injection: 420 mg lyophilized powder for reconstitution in a multiple-dose vial • Recommended dosage is weight-based administered IV, varying by indication • Boxed Warnings for cardiomyopathy, infusion reactions, and pulmonary and embryo-fetal toxicities
netarsudil/ latanoprost (Rocklatan™) Aerie	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 03/12/2019 • Indicated for reduction of elevated intraocular pressure (IOP) in open-angle glaucoma or ocular hypertension • Rho kinase inhibitor/prostaglandin F_{2α} analogue • Ophthalmic solution: netarsudil 0.02%/latanoprost 0.005% 2.5 mL in a 4 mL container • Recommended dosing is 1 drop in the affected eye(s) once daily in the evening • Product availability is expected in April 2019, with a May 1, 2019 launch
brexanolone (Zulresso™) Sage	<ul style="list-style-type: none"> • NDA approval 03/19/2019; Breakthrough Therapy; Priority Review • Indicated for the treatment of postpartum depression in adults • Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator • Injection: 100 mg/20 mL solution in single-dose vial (SDV) • Recommended dosage is initiated at 30 mcg/kg/hr and increased during the first 24 hours to 90 mcg/kg/hr, then decreased over the last 8 hours to 30 mcg/kg/hr; administered IV for a total of 60 hours by a HCP in a certified clinical facility • Launch is expected in late June 2019, following scheduling by the Drug Enforcement Administration (DEA)
solriamfetol (Sunosi™) Jazz	<ul style="list-style-type: none"> • NDA approval 03/20/2019 • Indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA) <ul style="list-style-type: none"> » Not indicated to treat underlying airway obstruction in OSA • Dopamine and norepinephrine reuptake inhibitor (DNRI) • Tablets: 75 mg and 150 mg • Recommended oral dosages <ul style="list-style-type: none"> » Narcolepsy: initiate at 75 mg once daily, may increase to 150 mg once daily » OSA: initiate at 37.5 mg once daily, may increase to 150 mg once daily • Availability is expected after DEA scheduling; anticipated within 90 days of FDA approval

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	
insulin degludec/ liraglutide (Xultophy®) Novo Nordisk	<ul style="list-style-type: none"> • sNDA approval 02/27/2019 • Indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; no longer requires prior use of basal insulin or liraglutide (Victoza®) • Recommended dosing is 10 units given SC once daily in basal insulin/glucagon-like peptide 1 (GLP-1) receptor agonist naïve patients; 16 units SC once daily for treatment-experienced patients
insulin glargine/ lixisenatide (Soliqua®) Sanofi-Aventis	<ul style="list-style-type: none"> • sNDA approval 02/27/2019 • Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus; no longer requires prior use of basal insulin or lixisenatide (Adlyxin®) • Recommended dosing is 15 units to 60 units SC once daily within the hour prior to the first meal of the day
atezolizumab (Tecentriq®) Genentech	<ul style="list-style-type: none"> • sBLA approval 03/08/2019; Accelerated Approval; Priority Review • Indicated in combination with paclitaxel protein-bound for the treatment of adults with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express programmed death-ligand 1 (PD-L1) • Recommended dosage is 840 mg IV over 60 minutes, followed by 100 mg/m² paclitaxel protein-bound; administered on days 1 and 15 for each 28-day cycle with paclitaxel protein-bound administered on days 1, 8, and 15
dupilumab (Dupixent®) Regeneron	<ul style="list-style-type: none"> • sBLA approval 03/11/2019; Breakthrough Therapy • Indication for moderate-to-severe atopic dermatitis was expanded to include patients 12 to > 18 years of age not adequately controlled with topical prescription therapies or when those therapies are not advisable • Recommended dosage is weight-based: <ul style="list-style-type: none"> » For patients < 60 kg: initial dose is 400 mg (two 200 mg injections) SC, followed by 200 mg every other week » For patients ≥ 60 kg: initial dose is 600 mg (two 300 mg injections) SC, followed by 300 mg every other week
fulvestrant (Faslodex®) AstraZeneca	<ul style="list-style-type: none"> • sNDA approval 03/11/2019 • Indicated for hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer in postmenopausal women, in combination with ribociclib, as initial endocrine-based therapy or following disease progression on endocrine therapy • Recommended dosage is 500 mg intramuscularly (IM) into the gluteal area slowly as two 5 mL injections, on days 1, 15, 29, and once monthly thereafter
ceftazidime/ avibactam (Avycaz®) Allergan	<ul style="list-style-type: none"> • sNDA approval 03/14/2019; Qualified Infectious Disease Product • Indications for the treatment of complicated urinary tract infections and complicated intra-abdominal infections were expanded to include patients 3 months to < 18 years of age • Recommended dosages for both indications administered IV every 8 hours <ul style="list-style-type: none"> » Ages 2 years to 18 years: 62.5 mg/kg to a maximum of 2.5 grams » Ages 6 months to < 2 years: 62.5 mg/kg » Ages 3 months to < 6 months: 50 mg/kg

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