



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

EDITORIAL STAFF

EDITOR IN CHIEF
Maryam Tabatabai
PharmD

EXECUTIVE EDITOR
Carole Kerzic
RPh

DEPUTY EDITORS
Jill Bot
PharmD, MBA

Stephanie Christofferson
PharmD

Jessica Czechowski
PharmD

Lara Frick
PharmD, BCPS, BCPP

Leslie Pittman
PharmD

Download at:
magellanrx.com

■ FDA RECALL GUIDELINES

The United States (US) Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) published their final guidance on Public Warning and Notification of Recalls. It instructs industry and FDA staff members on the use, content, and conditions for issuing a public recall notification of an FDA-regulated product, including drugs, medical devices, and food.

A firm (e.g., manufacturer, distributor) generally announces a recall within 24 hours of the FDA advising of a serious product-related health risk. The FDA may also directly notify the public via press releases, emails, and online and social media postings, including the weekly FDA Enforcement Report. Typically, the public is informed when the FDA assigns their strongest recall classifications, Class I or Class II, to a product. Class I recalls recognize a product with potential to cause serious health problems or death; Class II recalls are assigned to products that might cause a temporary health problem or pose a slight threat of a serious nature; and Class III recalls are designated to products unlikely to cause any adverse health effects, but violate FDA labeling or manufacturing laws.

A public notification must include: (1) information identifying the recalled product, such as brand name, images, lot/serial number, unique device identification (UDI) number, expiration date, and packaging; (2) geographic areas and dates of distribution of

the affected product; (3) the product defect and potential health threat; (4) the number and nature of complaints or adverse effects reported due to the product defect; (5) the name and contact information of the recalling firm; and (6) instructions for consumers on appropriate actions.

■ BEERS CRITERIA® UPDATE

The American Geriatrics Society (AGS) updated the Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults. The evidence-based criteria identify drugs to be avoided by older adults in most circumstances or certain situations. Key changes include the addition of criteria advising against coprescribing of opioids with benzodiazepines or gabapentinoids. Concurrent use of ciprofloxacin with certain medications (e.g., select macrolides, warfarin, theophylline) is also not recommended. Criteria for some medications were eliminated since their use is not specific to elderly patients, including 8 antiseizure medications, 8 agents for insomnia, and vasodilators for syncope. Discontinued ticlopidine and pentazocine were also removed. H₂-receptor antagonists were excluded since evidence of their risk in patients with dementia is lacking. The AGS no longer provides recommendations for the oncology agents carboplatin, cisplatin, vincristine, and cyclophosphamide, due to their specialized use.

Medications to be used with caution in the elderly include dextromethorphan/quinidine (limited efficacy in dementia), rivaroxaban (risk of gastrointestinal



BENZODIAZEPINE PRESCRIBING TRENDS

The US National Institute of Drug Abuse (NIDA) reported drug overdose deaths involving benzodiazepines increased from 1,135 cases in 1999 to 11,537 cases in 2017; deaths involving benzodiazepine in combination with other synthetic narcotics have risen steadily since 2014. In 2016, the FDA required manufacturers to include Boxed Warnings in benzodiazepine and opioid labeling regarding serious side effects of concurrent use, including respiratory depression and death.

A study published in *JAMA Network Open* (Agarwal, et al) evaluated US benzodiazepine prescribing patterns in adults from 2003 to 2015. Researchers analyzed data from the National Ambulatory Medical Care Survey (NAMCS), an annual cross-sectional survey representing office-based physician visits. The population-based sample of adult outpatient visits revealed a significant increase in benzodiazepine-related visits from 2003 (3.8%) to 2015 (7.4%). During 2005 to 2015, the rate of new prescriptions remained fairly constant (~1%); however, a significant increase was seen with continuing prescriptions (4.2% to 6.4%). Coprescribing benzodiazepines with opioids or other central nervous system (CNS) depressants (nonbenzodiazepine sedative hypnotics, muscle relaxants, and antipsychotics) rose from 1% of visits in 2003 to 2.9% in 2015. Moreover, in 2015, benzodiazepines were coprescribed in 19.2% of visits that also included an opioid.

The benzodiazepine visit rate (for 2003, 2015) was stable among psychiatrists (29.6%, 30.2%); however, this rate increased across other specialties, such as medical (3.3%, 6%) and surgical (1%, 4.3%), and particularly among primary care physicians (3.6%, 7.5%). The benzodiazepine visit rate was unchanged when associated with insomnia (26.9%, 25.6%) and had a relatively small increase with anxiety/depression (26.6%, 33.5%) and neurologic conditions (6.8%, 8.7%). The largest increases were seen with back and/or chronic pain (3.6%, 8.5%) and undefined conditions (1.8%, 4.4%). Researchers offer that a possible explanation for this trend is the availability of several options to treat anxiety and insomnia, while the options for pain are limited. This study does not distinguish between appropriate versus inappropriate use of benzodiazepines.

bleeding), and trimethoprim (risk of hyperkalemia with renal impairment in patients on select antihypertension medications). Sodium levels should be carefully monitored with carbamazepine, mirtazapine, oxcarbazepine, tramadol, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants due to a risk for syndrome of inappropriate antidiuretic hormone secretion (SIADH). SSRIs and SNRIs may also increase fall risk. Age criteria around aspirin use have decreased from 80 to 70 years based on new data regarding bleeding risk.

FOCUSED GUIDELINE UPDATE FOR AFib

The American Heart Association (AHA), the American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) released a focused update of the 2014 Guideline on the Management of Patients with Atrial Fibrillation (AF). Key modifications include addition of the novel oral anticoagulant (NOAC) edoxaban (Savaysa®; a factor Xa inhibitor) as an option for stroke prevention. All NOACs (dabigatran [Pradaxa®], apixaban [Eliquis®], edoxaban, rivaroxaban [Xarelto®]) are now preferred over warfarin in NOAC-eligible patients with AF. In NOAC-eligible patients, NOACs were at least noninferior to warfarin in preventing stroke and systemic embolism and have a lower risk of bleeding. Apixaban is preferred in patients with end-stage renal disease or on dialysis; remaining NOACs are not recommended in this population due to lack of evidence. The anticoagulant reversal agents idarucizumab (Praxbind®; reversal for dabigatran) and andexanet alfa (Andexxa®; reversal for rivaroxaban and apixaban) are recommended in the event of life-threatening bleeding or an urgent procedure.

An oral anticoagulant, aspirin, plus a P2Y₁₂ inhibitor are recommended in patients with AF after percutaneous coronary intervention (PCI) with stent placement who are at increased risk of stroke (CHA₂DS₂-VASC risk score ≥ 2) and for whom triple therapy is prescribed. Clopidogrel is preferred over prasugrel (Effient®) in this setting. A transition to dual therapy (oral anticoagulant plus P2Y₁₂ inhibitor) may be considered after 4 to 6 weeks. Dual therapy with dose-adjusted warfarin plus either clopidogrel, ticagrelor (Brilinta®), or dabigatran is also a reasonable option to reduce the risk of bleeding.

Furthermore, new data demonstrates that weight loss provides additional benefit over risk factor modification alone in overweight and obese patients in reducing AF symptoms and severity, as well as the number and cumulative duration of AF episodes. The extent of improvement is directly related to the degree of weight loss.

DRUG INFORMATION HIGHLIGHTS

- Flu Season Update (2018–2019): The Centers for Disease Control and Prevention (CDC) reported increased influenza activity during the week ending 02/23/2019. In the US, New York City and 33 states reported high activity, District of Columbia and 8 states reported moderate activity, while the remainder of the country reported low or minimal activity. The influenza A(H1N1)pdm09 virus was reported most often across the US; however, influenza A(H3N2) predominated in the southeastern, southern-central, and central states, and New York and New Jersey. No nationwide shortages of oral influenza antivirals have been reported.
- Dr. Reddy's Laboratories (DRL; 2018) and Alvogen (2019) received FDA approval for generic versions of Suboxone® (buprenorphine/naloxone) sublingual film. The manufacturer of Suboxone, Indivior, sued both companies for patent infringement. Preliminary ruling in US District Court blocked DRL and Alvogen from marketing their products "at risk"; however, on February 19, 2019, the Supreme Court overturned this decision. Since then, 4 generic versions were launched, including product by DRL, Alvogen, Mylan (pursuant to a settlement agreement; approved 2018), and Sandoz (authorized generic [AG] version).
- The 100 mg/mL single-dose One-Press® patient-controlled injector was approved for Janssen's guselkumab (Tremfya®); a single-dose 100 mg/mL prefilled syringe is also available to treat plaque psoriasis (PSO).
- The FDA approved an oral disintegrating tablet (ODT) formulation of Evekeo® (amphetamine sulfate) to treat attention deficit hyperactivity disorder (ADHD) in patients 6 to 17 years of age. Approved strengths include 5 mg, 10 mg, 15 mg, and 20 mg. Evekeo 5 mg and 10 mg oral tablets are also available to treat ADHD (ages ≥ 3 years), narcolepsy, and exogenous obesity (short-term; ages ≥ 12 years).
- The intermittent shortage of epinephrine auto-injectors persists nationwide in the US. Backorders with periodic shipments to distributors continue for Impax's 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.
- Mylan's Wixela™ Inhub™ (fluticasone propionate/salmeterol) inhalation powder was approved as a generic version of Advair® Diskus® for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Wixela Inhub is approved in the same strengths as Advair Diskus 100 mcg/50 mcg, 250 mcg/50 mcg, and 500 mcg/50 mcg.

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

- **March 2019:** romosozumab; subcutaneous (SC) sclerostin inhibitor; postmenopausal osteoporosis; Amgen.
- **March 2019:** siponimod; oral sphingosine 1-phosphate receptor modulator; secondary progressive multiple sclerosis; Novartis.
- **March 03, 2019:** esketamine; intranasal N-methyl-D-aspartate (NMDA) receptor antagonist; treatment-resistant depression; Janssen.
- **March 11, 2019:** Dupixent®; dupilumab; SC interleukin (IL)-4 inhibitor; atopic dermatitis (ages 12-17 years); Regeneron.
- **March 11, 2019:** teduglutide, recombinant; SC glucagon-like peptide-2 (GLP-2) analog; pediatric short bowel syndrome; Shire.
- **March 12, 2019:** Tecentriq®; atezolizumab; intravenous (IV) programmed cell death-1 ligand (PD-L1) inhibitor; first-line treatment of triple-negative breast cancer; Genentech.
- **March 14, 2019:** netarsudil/latanoprost; ophthalmic Rho kinase inhibitor/prostaglandin analogue; glaucoma and ocular hypertension; Aerie.
- **March 19, 2019:** brexanolone; IV GABA modulator; postpartum depression; Sage.
- **March 20, 2019:** solriamfetol; oral CNS stimulant; excessive sleepiness related to narcolepsy or sleep apnea; Jazz.
- **March 21, 2019:** olopatadine/mometasone; intranasal H1-histamine antagonist/corticosteroid; allergic rhinitis; Glenmark.
- **March 22, 2019:** sotagliflozin; oral sodium-glucose cotransporter (SGLT) -1 and -2 inhibitor; type 1 diabetes mellitus; Sanofi.
- **March 25, 2019:** diazepam; intranasal benzodiazepine; cluster or acute repetitive seizures (ages ≥ 6 years); Neurelis.
- **March 31, 2019:** aclidinium/formoterol; inhaled long-acting beta₂ adrenergic and muscarinic antagonists; COPD; AstraZeneca.
- **April 1, 2019:** metoclopramide; intranasal dopamine receptor antagonist; diabetic gastroparesis; Evoke.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
sumatriptan (Tosymra®) Promius	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 01/25/2019 • Indicated for the treatment of migraine with or without aura in adults • Serotonin (5-HT_{1B/1D}) receptor agonist (triptan) • Solution: single-dose, disposable unit delivering 10 mg per spray • Recommended dose is a single spray (10 mg) in 1 nostril; may repeat after 1 hour; do not exceed 3 sprays in a 24-hour period
colchicine (Gloperba®) Romeg	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 01/30/2019 • Indicated for prophylaxis of gout flares in adults <ul style="list-style-type: none"> » Safety and effectiveness for acute treatment of gout flares during prophylaxis has not been studied » It is not an analgesic and should not be used to treat pain from other causes • Antihyperuricemic • Oral solution: 0.6 mg/5 mL • Recommended dosage is 0.6 mg once or twice daily
caplacizumab-yhdp (Cabliivi®) Ablynx	<ul style="list-style-type: none"> • BLA approval 02/06/2019; Orphan Drug; Priority Review • Indicated for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy • von Willebrand factor (vWF)-directed antibody fragment • Lyophilized powder for injection: 11 mg in a single-dose vial (SDV) • Recommended dose is 11 mg administered IV by a healthcare professional (HCP) at least 15 minutes before plasma exchange followed by 11 mg SC after completion of plasma exchange on day 1; subsequent daily therapy during plasma exchange and for 30 days past the last plasma exchange is 11 mg SC once daily, which can be self-administered; if after initial treatment course, signs of persistent underlying disease continue, treatment may be continued for a maximum of 28 days • Product availability is expected in late Q1, 2019
triclabendazole (Egaten™) Novartis	<ul style="list-style-type: none"> • NDA approval 02/13/2019; Orphan Drug; Priority Review • Indicated for the treatment of fascioliasis in patients ≥ 6 years of age • Anthelmintic • Oral tablets: 250 mg • Administer orally as 2 doses of 10 mg/kg given 12 hours apart with food; round dose up to the nearest scored tablet portion; may crush and mix with water or applesauce • This product is currently available via the World Health Organization (WHO); Novartis plans to extend their donation program to WHO until 2022; the FDA approval will facilitate the product to be imported into countries where the condition is endemic
antihemophilic factor (recombinant), glycopegylated- exei (Esperoct®) Novo Nordisk	<ul style="list-style-type: none"> • BLA approval 2/19/2019 • Indicated for adults and children with hemophilia A for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding • Extended half-life factor VIII replacement therapy • Lyophilized powder for injection: 500 IU, 1,000 IU, 1,500 IU, 2,000 IU, and 3,000 IU in SDVs; actual factor VIII IU activity is stated on each vial • Recommended IV dosage is weight-based; routine prophylactic dosages are administered every 4 days in patients ages ≥ 12 years, and twice weekly in children < 12 years; product labeling describes dosage calculation for on-demand and perioperative use • Product launch is expected in 2020

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
trastuzumab and hyaluronidase-oyisk (Herceptin Hylecta™) Genentech	<ul style="list-style-type: none"> • BLA approval 02/28/2019 • Indicated for the treatment of HER2-overexpressing breast cancer in adults • Combination of a HER2/neu receptor antagonist and an endoglycosidase • Injectable solution: 600 mg trastuzumab and 10,000 units hyaluronidase per 5 mL solution in an SDV • Recommended dosage is 600 mg/10,000 units (5 mL) administered SC by an HCP over approximately 2 to 5 minutes once every 3 weeks
Expanded Indications	
ibrutinib (Imbruvica®) Janssen	<ul style="list-style-type: none"> • sNDA approval 01/25/2019 • Indicated in combination with obinutuzumab in treatment-naïve patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) • Recommended dosage is 420 mg orally once daily until disease progression or unacceptable toxicity
ospemifene (Osphena®) Duchesnay	<ul style="list-style-type: none"> • sNDA approval 01/25/2019 • Indicated for the treatment of moderate to severe vaginal dryness, a symptom of vulvar and vaginal atrophy, due to menopause • Recommended dosage is one 60 mg tablet once daily with food
pemetrexed (Alimta®) Eli Lilly	<ul style="list-style-type: none"> • sBLA approval 01/30/2019 • Indicated in combination with pembrolizumab and platinum chemotherapy for first-line treatment of metastatic nonsquamous non-small cell lung cancer (NSCLC) with no EGFR or ALK tumor aberrations • Recommended dosage of pemetrexed is 500 mg/m² IV, given with pembrolizumab and platinum chemotherapy on day 1 of each 21-day cycle for 4 cycles; after completion of platinum-based therapy, continue pemetrexed with or without pembrolizumab until disease progression or unacceptable toxicity
pembrolizumab (Keytruda®) Merck	<ul style="list-style-type: none"> • sBLA approval 02/15/2019; Breakthrough Therapy; Orphan Drug • Indicated as adjuvant treatment of melanoma in patients with involvement of lymph node(s) following complete resection • Recommended dosage is 200 mg IV every 3 weeks
trifluridine/tipiracil (Lonsurf®) Taiho Oncology	<ul style="list-style-type: none"> • sNDA approval 02/22/2019; Priority Review • Indicated for the treatment of adults with metastatic gastric or gastroesophageal junction adenocarcinoma previously treated with ≥ 2 lines of chemotherapy that included fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy • Recommended dosage is 35 mg/m² orally twice daily on days 1 through 5 and days 8 through 12 of each 28-day cycle

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.

References:

americangeriatrics.org cdc.gov drugabuse.gov fda.gov federalregister.gov heart.org jamanetwork.com