



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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RPh

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TWO NEW AGENTS GET FDA NOD TO PREVENT MIGRAINE

The United States (US) Food and Drug Administration (FDA) approved 2 new calcitonin gene-related peptide (CGRP) inhibitors, fremanezumab-vfrm (Ajovy™; Teva) and galcanezumab-gnlm (Emgality™; Eli Lilly), for the prevention of migraine in adults. The medications target the CGRP neurotransmitter released during a migraine attack. Both can be self-administered by subcutaneous (SC) injection. Fremanezumab-vfrm is available as a 225 mg/1.5 mL single-dose prefilled syringe with dosing regimens of 225 mg once monthly and 675 mg (3 consecutive 225 mg injections) every 3 months. Galcanezumab-gnlm is approved as a 120 mg/mL single-dose prefilled pen and syringe and is given as a 240 mg loading dose (2 consecutive injections), followed by 120 mg every month.

Both fremanezumab-vfrm and galcanezumab-gnlm demonstrated significant reductions in average monthly migraine days (MMD) compared to placebo in patients who experienced episodic migraine (EM) or chronic migraine (CM); CM is defined as ≥ 15 MMD. In the HALO-EM clinical trial (n=875), after 12 weeks, fremanezumab-vfrm led to a reduction in EM by 3.7 and 3.4 days with monthly and quarterly doses, respectively, compared to 2.2 days for placebo. More patients treated with fremanezumab-vfrm achieved $\geq 50\%$ reduction in average MMD compared to placebo (47.7%, 44.4%,

and 27.9%, respectively). Similarly, in the HALO-CM trial (n=1,130), patients with CM who were treated with monthly or quarterly fremanezumab-vfrm or placebo experienced a decrease in average MMD by 5, 4.9, and 3.2 days, respectively, and the proportion of patients with $\geq 50\%$ reduction in MMD was 40.8%, 37.6% and 18.1%, respectively.

In the 6-month EVOLVE-1 and EVOLVE-2 clinical trials (n=1,311) for EM, the approved dose of galcanezumab-gnlm led to respective decreases in mean MMD by 4.7 and 4.3 days compared to 2.8 and 2.3 with placebo. The proportion of patients who achieved $\geq 50\%$ reduction in MMD was 62% and 59% with galcanezumab-gnlm and 39% and 36% with placebo, respectively. In the 3-month REGAIN trial (n=811) for CM, galcanezumab-gnlm resulted in a decrease in mean MMD by 4.8 days versus 2.7 days with placebo; 28% of patients treated with galcanezumab-gnlm had $\geq 50\%$ reduction in MMD compared to 15% with placebo.

Migraine affects over 37 million people in the US. CGRP inhibitors offer a new approach in treating patients who require continuous preventive treatment. Fremanezumab-vfrm is currently available and galcanezumab-gnlm is expected soon. Both will have similar pricing as the first approved CGRP inhibitor, self-administered, monthly erenumab-aooe (Aimovig™). While fremanezumab-vfrm offers a 3-month dosing regimen, Eli Lilly plans to provide a 12-month free-drug access program for galcanezumab-gnlm to select commercially-insured patients.

■ GUIDELINE UPDATE FOR ATRIAL FIB

The American College of Chest Physicians (ACCP) updated the 2012 guidance on the use of antithrombotic therapy for atrial fibrillation (AF). Many risk factors are common in AF and ischemic stroke; therefore, the ACCP promotes an integrated approach to AF management that incorporates stroke prevention. The ACCP advises clinicians to gauge stroke risk using the risk factor-based CHA₂DS₂-VASc score, rather than stratifying patients with AF as low, moderate, or high risk (Strong recommendation). Among key updates (all Strong recommendations), the ACCP suggests no antithrombotic therapy in patients with AF and no valvular heart disease who are at low risk of stroke (e.g., CHA₂DS₂-VASc score of 0 in males and 1 in females), including those with paroxysmal AF. The expert panel suggests the use of oral anticoagulation over either no therapy or therapy with aspirin, with or without clopidogrel, in patients with a single non-sex CHA₂DS₂-VASc stroke risk factor. Similarly, in patients at high risk for stroke (e.g., CHA₂DS₂-VASc \geq 2 in males or \geq 3 in females), the ACCP recommends oral anticoagulation over no therapy or therapy with aspirin (\pm clopidogrel). When oral anticoagulation is recommended, a novel oral anticoagulant (NOAC) is preferred over a vitamin K antagonist (e.g., warfarin). In patients prescribed warfarin, the time in therapeutic range (TTR) should be $>$ 70%. Additionally, the ACCP recommends use of the HAS-BLED score to identify patients at high risk of bleeding (score \geq 3) who will require more frequent monitoring.



BEHAVIORAL HEALTH CORNER

NEW GUIDELINES FOR PERIMENOPAUSAL DEPRESSION

Perimenopause, or menopausal transition, begins about 4 to 8 years before a woman's final menstrual cycle. During this time not only do marked hormone fluctuations occur, leading to symptoms such as hot flashes, sleep disturbances, and mood swings, but women are also at increased risk of developing depressive symptoms and major depressive episodes (MDE). To address the long-standing debate around perimenopausal depression, the North American Menopause Society (NAMS) and the National Network of Depression Centers Women and Mood Disorders Task Group created the first ever guidelines on the evaluation and treatment of the condition. An expert panel systematically reviewed scientific literature published from 1980 to 2015 on depressive disorders and depressive symptoms in peri- and post-

menopausal women. The new guidelines focus on the key areas of epidemiology, clinical presentation, and the therapeutic benefit of antidepressants, hormone therapy (HT), and other therapies (e.g., psychotherapy, exercise, natural health products). The guidelines do not, however, address the effect of HT on menopause-related vasomotor symptoms (VMS) and treatment of major depressive disorder (MDD), both of which are addressed in other medical guidelines.

Depression during midlife in women often appears as classic depressive symptoms in combination with menopausal symptoms (e.g., VMS, sleep disturbance) and psychosocial challenges (e.g., adverse life event, social isolation). Most women who experience an MDE during perimenopause have had a prior episode of depression; however, the risk of depressive symptoms alone is higher during perimenopause regardless of history of major depressive disorder. The diagnosis of perimenopausal depression should consider menopausal stage, co-occurring psychiatric and menopause symptoms, common midlife psychosocial factors, and differential depressive diagnoses. Validated screening tools should be used to evaluate menopause-related mood disorder and health-related quality of life.

The guidelines recommend first-line treatment for perimenopausal MDE with evidence-based antidepressants and psychotherapy. Co-occurring sleep disturbance and night sweats should be addressed as part of the overall treatment regimen. Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) provide benefit in treating major depressive disorder and may relieve menopausal symptoms (VMS, pain). The panel advises that while prior response should guide antidepressant selection when major depressive disorder recurs in midlife, desvenlafaxine is the only agent that has been studied and shown to be effective in peri- and post-menopausal women. Evidence exists that off-label use of estrogen therapy (ET), including continuous hormonal contraception, may provide antidepressant benefit in perimenopausal women, with or without VMS; however, ET was shown to be ineffective in treating depression in postmenopausal women. Lastly, evidence is lacking to support the use of botanical or alternative approaches to treat perimenopausal depression.

DRUG INFORMATION HIGHLIGHTS

- The intermittent shortage of epinephrine auto-injectors, used for the emergency treatment of allergic reactions, including anaphylaxis, continues nationwide in the US. Sporadic availability is reported for Impax's authorized generic (AG) version of the discontinued Adrenaclick® and for Mylan's Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and the respective AG. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Teva plans to launch their recently approved generic versions of Epipen and Epipen Jr in the coming months. On September 27, 2018, the FDA approved Adamis' Symjepi® 0.15 mg auto-injector, in addition to Symjepi 0.3 mg that was approved in June 2017; Sandoz plans to make both strengths available in the US as soon as possible.
- The FDA alerted the public of reports of Fournier's gangrene (FG) associated with the antidiabetic class of sodium-glucose cotransporter-2 (SGLT2) inhibitors—canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. The condition is a rare, but serious, necrotizing fasciitis of the genitals and surrounding area. Since the approval of SGLT2 inhibitors in 2013, a total of 12 cases of FG have been confirmed within several months of starting therapy. For all patients, the SGLT2 inhibitor was stopped and surgery required. Symptoms of FG can progress quickly and become life-threatening; therefore, it is important that patients on SGLT2 inhibitor therapy seek immediate medical attention if they experience tenderness, redness, or swelling in the peri-genital area, have a fever above 100.4° F, or a general ill feeling. If FG is suspected, initiate treatment with a broad-spectrum antibiotic, discontinue the SGLT2 inhibitor, and start an appropriate alternative antidiabetic agent.
- Gilead plans to distribute AG versions of hepatitis C antivirals Epclusa® (sofosbuvir 400mg/velpatasvir 100mg) and Harvoni® (ledipasvir 90mg/sofosbuvir 400mg) in the US through a newly created subsidiary, Asegua Therapeutics. Launch is expected in January 2019.
- Teva's buprenorphine 16 mg/naloxone 4 mg sublingual film (Cassipa®) was FDA-approved under an abbreviated 505(b)(2) pathway. It is administered as 1 film daily, only after patient induction, stabilization, and titration to a dose of 16 mg buprenorphine using another marketed product.
- Approval was granted to Vertical's estradiol 1% gel (Divigel®) for the treatment of moderate to severe VMS due to menopause. The medication requires daily administration of 0.25 g to 1 g applied topically to the right or left upper thigh on alternating days.
- Sun Pharmaceutical's cyclosporine 0.09% ophthalmic solution was approved to increase tear production in patients with keratoconjunctivitis sicca (dry eye). Administer 1 drop twice daily into each eye via the single-use vial.
- The ongoing investigation of valsartan-containing products identified an additional impurity, N-nitrosodiethylamine (NDEA), in lots that were already included in the recent recall. NDEA and N-nitrosodimethylamine (NDMA) are known animal, and suspected human carcinogens that are formed during the manufacturing process. Both impurities were found in many batches of valsartan active pharmaceutical ingredient (API) by China's Zhejiang Huahai Pharmaceuticals (ZHP). Subsequently, the FDA froze import of all API and finished product made by ZHP into the US. NDMA was also detected in some valsartan medications made by a second Chinese company, Zhejiang Tianyu Pharmaceuticals. The Agency advises patients with affected valsartan to continue taking their medication until a replacement supply is received.
- Valeant's topical tretinoin 0.05% lotion (Altreno™) gained approval to treat acne vulgaris in patients ≥ 9 years old. Apply a thin layer to affected skin once daily.

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

- **October 2018:** Invokana®, Invokamet®/XR; canagliflozin, canagliflozin/metformin-XR; cardiovascular outcomes with type 2 diabetes; Janssen.
- **October 5, 2018:** amisulpride; intravenous (IV) atypical antipsychotic; postoperative emesis; Acacia.
- **October 5, 2018:** halobetasol propionate; topical corticosteroid; plaque psoriasis; Valeant.
- **October 6, 2018:** inotersen; SC protein synthesis inhibitor; hereditary transthyretin (hATTR) amyloidosis with polyneuropathy; Akcea.
- **October 20, 2018:** Dupixent®; dupilumab; SC interleukin-4 (IL-4) inhibitor; eosinophilic asthma; Regeneron.
- **October 26, 2018:** estradiol/progesterone; oral hormone therapy; menopausal VMS; TherapeuticsMD.
- **October 26, 2018:** Xyrem®; sodium oxybate; oral central nervous system depressant; pediatric narcolepsy with cataplexy; Jazz.
- **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.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs	
lamivudine/ nevirapine/ zidovudine Micro Labs	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 08/13/2018 • Indicated for use alone as a complete regimen or in combination with other antiretroviral (ARV) agents for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults and pediatric patients weighing ≥ 35 kg • Combination of 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs), lamivudine and zidovudine, and 1 non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), nevirapine • Oral fixed-dose tablets: lamivudine 150 mg/nevirapine 200 mg/zidovudine 300 mg • During the first 14 days, the dosage is 1 fixed-dose tablet once daily followed by a daily oral dose of lamivudine 150 mg and zidovudine 300 mg 12 hours later. If tolerated (no rash), the recommended maintenance dose is 1 fixed-dose tablet orally twice daily. • Boxed warnings advise of life-threatening hepatotoxicity, severe hepatomegaly, exacerbations of hepatitis B virus (HBV) infection, skin reactions, hematologic toxicity, myopathy, and lactic acidosis
stiripentol (Diacomit®) Biocodex	<ul style="list-style-type: none"> • NDA approval 08/20/2018; Orphan Drug; Priority Review • Indicated for the treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; there is no data to support monotherapy • Anticonvulsant that acts via gamma-aminobutyric acid (GABA)_A receptor-mediated effects and increases serum concentrations of clobazam and its active metabolite by inhibiting cytochrome P450 activity • Oral capsule and oral powder for suspension: 250 mg and 500 mg • Administer as 50 mg/kg/day, by mouth in 2 or 3 divided doses • Launch is anticipated in early January 2019
cenergermin-bkbj (Oxervate™) Dompé farmaceutici	<ul style="list-style-type: none"> • BLA approval 08/22/2018; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated for the treatment of neurotrophic keratitis • Recombinant human nerve growth factor (rhNGF) • Ophthalmic solution: 0.002% (20 mcg/mL) in a multiple-dose vial • Administer as 1 drop into the affected eye(s) 6 times per day at 2-hour intervals, for 8 weeks • Launch is planned in early 2019
lanadelumab-flyo (Takhzyro™) Shire	<ul style="list-style-type: none"> • BLA approval 08/23/2018; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated for prophylaxis of hereditary angioedema (HAE) attacks in patients ≥ 12 years of age • Plasma kallikrein inhibitor (monoclonal antibody) • Injectable solution: 300 mg/2 mL in a single-dose vial (SDV) • Administer 300 mg SC every 2 weeks; dosing every 4 weeks may be considered if the patient is attack-free for > 6 months; may self-administer
eravacycline (Xerava™) Tetraphase	<ul style="list-style-type: none"> • NDA approval 08/27/2018; Priority Review • Indicated for the treatment of complicated intra-abdominal infections in patients ≥ 18 years of age; it is not indicated for treatment of complicated urinary tract infections (cUTI) • Tetracycline antibiotic • Lyophilized powder for injection: 50 mg of eravacycline (equivalent to 63.5 mg eravacycline dihydrochloride) in a SDV • Administer as 1 mg/kg IV over approximately 60 minutes every 12 hours for 4 to 14 days; adjust dose for severe hepatic impairment (Child-Pugh C) and/or concomitant use of a strong cytochrome P450 isoenzyme 3A4 inducer

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RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
New Drugs <i>continued</i>	
antihemophilic factor (recombinant) pegylated-aucl (Jivi®) Bayer	<ul style="list-style-type: none"> • BLA approval 08/30/2018 • Indicated for use in previously treated adults and adolescents (≥ 12 years old) with hemophilia A for: <ul style="list-style-type: none"> » On-demand treatment and control of bleeding episodes; » Perioperative management of bleeding; and » Routine prophylaxis to reduce the frequency of bleeding episodes; it is not indicated for use in previously untreated patients or for von Willebrand disease • Recombinant DNA-derived, factor VIII concentrate • Lyophilized powder for injection: approximately 500 IU, 1,000 IU, 2,000 IU, and 3,000 IU in SDV • Recommended dosages: <ul style="list-style-type: none"> » For the control of bleeding and perioperative management, the required dose is based on body weight, desired factor VIII rise, and reciprocal of expected recovery » The recommended initial regimen for routine prophylaxis is 30 to 40 IU/kg twice weekly; dosing regimen may be adjusted to 45 to 60 IU/kg every 5 days, based on bleeding episodes
doravirine (Pifeltro™) Merck	<ul style="list-style-type: none"> • NDA approval 08/30/2018 • Indicated in combination with other ARV agents for the treatment of HIV-1 infection in adults with no prior ARV treatment history • Non-nucleoside reverse transcriptase inhibitor (NNRTI) • Oral tablet: 100 mg • Administer 1 tablet once daily with or without food; dosage adjustment of 1 tablet taken twice daily required with concomitant rifabutin use
doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo™) Merck	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 08/30/2018 • Indicated as a complete regimen for the treatment of HIV-1 infection in adult patients with no ARV treatment history • Combination of the NNRTI, doravirine, and 2 NRTIs, lamivudine and tenofovir disoproxil fumarate (TDF) • Fixed-dose oral tablet: doravirine 100 mg/lamivudine 300 mg/TDF 300 mg • Administer as 1 tablet once daily with or without food; dosage adjustments with renal impairment and concomitant use of rifabutin may be needed • Boxed warning advises severe acute exacerbations of HBV occurred in patients coinfecting with HIV-1 and HBV who have discontinued lamivudine or TDF; initiation of anti-HBV therapy may be warranted
riluzole (Tiglutik™) ITF Pharma	<ul style="list-style-type: none"> • 505(b)(2) NDA approval 09/05/2018; Orphan Drug • Indicated for the treatment of amyotrophic lateral sclerosis (ALS) • Benzothiazole agent • Oral suspension: 5 mg/mL in 300 mL multi-dose bottle • Administer 50 mg (10 mL) every 12 hours at least 1 hour before or 2 hours after a meal • Anticipated availability is mid-October 2018

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RECENT FDA APPROVALS *continued*

DRUG NAME MANUFACTURER	DESCRIPTION
Expanded Indications	
ivacaftor (Kalydeco®) Vertex	<ul style="list-style-type: none"> • sNDA approval 08/15/2018; Orphan Drug • Approved to include use in children with cystic fibrosis (CF), 12 to < 24 months old, who have ≥ 1 mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor, based on clinical and/or <i>in vitro</i> assay data • Dosage in children weighing 7 kg to < 14 kg is one 50 mg granule packet every 12 hours; in children ≥ 14 kg dosage is one 75 mg granule packet every 12 hours
lenvatinib (Lenvima®) Eisai	<ul style="list-style-type: none"> • sNDA approval 08/15/2018; Orphan Drug • Indicated for the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC) • Dosage is based on actual body weight (< 60 kg: 8 mg; ≥ 60 kg: 12 mg) taken orally once daily until disease progression or unacceptable toxicity
lumacaftor/ivacaftor (Orkambi®) Vertex	<ul style="list-style-type: none"> • sNDA approval 08/15/2018; Orphan Drug • Indication expanded to include use in children 2 to 5 years of age with CF who have 2 copies of the <i>F508del</i> CFTR mutation • Dosage in children < 14 kg is one lumacaftor 100 mg/ivacaftor 125 mg granule packet every 12 hours, and in children ≥ 14 kg is one lumacaftor 150 mg/ivacaftor 188 mg granule packet every 12 hours; take with fat-containing food
sodium picosulfate, magnesium oxide, and anhydrous citric acid (Prepopik®) Ferring	<ul style="list-style-type: none"> • 505(b)(2) sNDA approval 08/15/2018 • Indicated for colon cleansing as a preparation for colonoscopy in adults and pediatrics ages ≥ 9 years • Two doses (1 packet per dose) are required for a complete colonoscopy preparation either as a split-dose (preferred) or day-before dosing regimen
nivolumab (Opdivo®) Bristol-Myers Squibb	<ul style="list-style-type: none"> • sBLA approval 08/16/2018; Accelerated Approval; Priority Review • Indicated for the treatment of metastatic small cell lung cancer (SCLC) in patients whose cancer has progressed after platinum-based chemotherapy and ≥ 1 other line of therapy • Administer as 240 mg IV over 30 minutes every 2 weeks until disease progression or unacceptable toxicity
pembrolizumab (Keytruda®) Merck	<ul style="list-style-type: none"> • sBLA approval 08/20/2018; Accelerated Approval • Indicated in combination with pemetrexed and platinum chemotherapy for first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations • Administer 200 mg every 3 weeks, IV over 30 minutes
ibrutinib (Imbruvica®) Janssen	<ul style="list-style-type: none"> • sNDA approval 08/24/2018 • Indicated for the treatment of Waldenström's macroglobulinemia • Administer 420 mg orally once daily until disease progression or unacceptable toxicity as a single agent, or in combination with rituximab

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