



MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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HOT TOPIC: **NEW THERAPY FOR MIGRAINE PREVENTION**

Over 37 million people in the United States (US) suffer from migraines, which can be debilitating, with pain lasting from hours to days. The US Food and Drug Administration (FDA) approved erenumab-aooe (Aimovig™), a first-in-class drug by Amgen/Novartis, for the preventive treatment of migraine in adults. Erenumab-aooe is a monoclonal antibody that blocks the calcitonin gene-related peptide (CGRP) receptor that plays a key role in migraine pathophysiology. The approval was based on 3 placebo-controlled, phase 3 trials (ARISE, STRIVE, LIBERTY) in a total of 2,199 migraineurs. Average baseline monthly migraine days (MMD) was 8 for episodic migraines (ARISE, STRIVE) and 18 for chronic migraines (LIBERTY). Over 3 or 6 months, depending on the study, erenumab-aooe significantly decreased mean MMD of episodic migraines by 1 to 2 days and of chronic migraines by 2.5 days. At least 40% of patients treated with erenumab-aooe experienced ≥ 50% reduction in MMD. Erenumab-aooe can be self-administered by subcutaneous (SC) injection in doses of 70 mg once monthly, although some patients may benefit from a higher 140 mg monthly dose. The most common adverse effects reported with erenumab-aooe were injection site reactions.

Erenumab-aooe is approved as a 70 mg/mL injectable solution in packs of 1 or 2 prefilled syringes or SureClick® auto-injectors. Additional

SC-administered CGRP inhibitors, galcanezumab and fremanezumab, are scheduled to be approved in the US in 2018.

FDA APPROVES FIRST FACTOR Xa ANTIDOTE

The FDA approved Portola's Breakthrough therapy Andexxa® (coagulation factor Xa [recombinant], inactivated-zhzo) for use in patients treated with the oral factor Xa (FXa) inhibitors, rivaroxaban (Xarelto®) or apixaban (Eliquis®), when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The Orphan drug was granted an Accelerated approval based on its effectiveness in healthy individuals; continued approval may depend on its effect on hemostasis in FXa inhibitor-treated patients. The ANNEXA-R and ANNEXA-A clinical trials demonstrated that Andexxa resulted in a median decrease in anti-FXa activity from baseline by 97% and 92% for rivaroxaban and apixaban, respectively. Interim data from the open-label ANNEXA-4 trial reported similar results in patients with major bleeding.

Andexxa is administered only in a healthcare setting. The dose is based on the specific FXa inhibitor prescribed, the FXa inhibitor dose, and time since the last dose. Andexxa is given as an intravenous (IV) bolus (400 mg or 800 mg), followed promptly by a continuous infusion of 4 mg or 8 mg per minute for up to 120 minutes. Reversal of the anticoagulant effect may occur within 2 minutes after completing the bolus dose. Boxed warnings inform that Andexxa has been associated with

thromboembolic or ischemic events, cardiac arrest, and sudden death. Anticoagulant therapy with rivaroxaban or apixaban should be restarted as soon as medically appropriate to reduce the risk of thromboembolic events.

In 2015, idarucizumab (Praxbind®) was approved as a reversal agent for the oral direct thrombin inhibitor dabigatran (Pradaxa®). Until that time, warfarin was the only oral anticoagulant with an antidote (vitamin K1 or prothrombin complex concentrate [Kcentra®]). Andexxa is the first universal FXa-inhibitor reversal agent approved in the US. Phase 2 trials of Andexxa as an antidote to betrixaban (Bevyxxa®), edoxaban (Savaysa®), and enoxaparin (Lovenox®) are ongoing. An early launch of Andexxa is expected in June 2018 with a broader launch planned for early 2019.

■ EPINEPHRINE AUTO-INJECTOR SHORTAGE

Manufacturing delays have resulted in a current nationwide shortage of epinephrine auto-injectors, indicated for the emergency treatment of allergic reactions, including anaphylaxis. Intermittent shortages for Mylan's Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and the authorized generic (AG) versions are reported. Impax's AG version of the discontinued Adrenaclick® is on backorder with no resolution date. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Adamis' Symjepi® 0.3 mg, which was FDA-approved in June 2017, has not entered the US market.



BIOSIMILAR CORNER

FIRST EPOETIN-ALFA BIOSIMILAR APPROVAL

The FDA granted approval to Pfizer's epoetin alfa-epbx (Retacrit®) as the first biosimilar of an erythropoiesis stimulating agent, with reference products of Amgen's Epogen® and Janssen's Procrit®. Indications for Retacrit are the same as Epogen and Procrit and include the treatment of anemia due to chronic kidney disease (CKD), myelosuppressive chemotherapy, and zidovudine for human immunodeficiency virus (HIV)-1 infection, and to reduce the need for allogeneic red blood cell transfusion in patients undergoing noncardiac, nonvascular elective surgeries. While Retacrit has demonstrated no clinically meaningful differences to Epogen or Procrit in terms of safety, purity, and potency, it is not considered to be interchangeable with either product. Retacrit solution for injection may be self-administered IV or SC. It was approved as 1 mL single-dose vials containing 2,000 units, 3,000 units, 4,000 units, 10,000 units, or 40,000 units.

Retacrit is the tenth FDA-approved biosimilar. It may become the fourth biosimilar available in the US, possibly at a significantly discounted price compared to its reference products.



BEHAVIORAL HEALTH CORNER

FIRST NON-OPIOID APPROVED TO TREAT OPIOID WITHDRAWAL

FDA granted approval under a Priority review to US Worldmeds' lofexidine (Lucemyra™) for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. It represents the first non-opioid medication approved in the US to treat opioid withdrawal symptoms. Lofexidine is an oral central alpha 2-adrenergic receptor agonist. Since lofexidine does not stop opioid cravings, it is not a treatment for opioid use disorder (OUD); however, it can be used as part of a broader, long-term treatment plan for managing OUD.

Lofexidine was studied in 2 randomized, double-blind trials in adults physically dependent on opioids and undergoing abrupt opioid discontinuation. Patients received lofexidine or matching placebo for 7 (study 1, n=602) or 5 days (study 2, n=264). A significantly greater proportion of subjects on lofexidine completed the treatment period (study 1: lofexidine 40% versus placebo 28%; study 2: lofexidine 49% versus placebo 33%). Based on the patient-reported, 30-point Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop), significantly greater symptom improvement was seen with lofexidine (mean difference from placebo for study 1: -2.3 for 2.16 mg/day dose and -2.7 for 2.88 mg/day dose; study 2: -1.9 for 2.88 mg/day dose). The most common side effects included hypotension, bradycardia, somnolence, and dizziness.

The recommended lofexidine starting dose is three 0.18 mg tablets taken orally 4 times daily during peak withdrawal symptoms, typically lasting 5 to 7 days. Continue for up to 14 days. Gradually discontinue the drug over 2 to 4 days to reduce the risk of marked increase in blood pressure. While lofexidine therapy was initiated at inpatient sites in clinical trials, the product labeling instructs if lofexidine is prescribed in an outpatient setting, the patient should be capable of monitoring and recognizing signs and symptoms of hypotension and bradycardia.

Launch of lofexidine is expected in August 2018.

DRUG INFORMATION HIGHLIGHTS

- Novartis' chimeric antigen receptor T cell (CAR-T) therapy tisagenlecleucel (Kymriah™) received a new indication for the treatment of adults with relapsed or refractory (r/r) large B cell lymphoma after ≥ 2 lines of systemic therapy including diffuse large B cell lymphoma (DLBCL), high-grade B cell lymphoma, and DLBCL arising from follicular lymphoma. It is not for treatment of primary central nervous system lymphoma. Initial approval for tisagenlecleucel was granted in August 2017 to treat patients ≤ 25 years of age with r/r B cell precursor acute lymphoblastic leukemia. The new indication is supported by the open-label, phase 2 JULIET trial. Among 68 evaluable patients with r/r DLBCL treated with tisagenlecleucel, 32% attained a complete response and 18% achieved a partial response. The median time to first response was 0.9 months. At a median of 9.4 months, median duration of response and overall survival were not estimable. Cytokine release syndrome (CRS) and ≥ grade 3 neurologic adverse events were reported in 78% and 18% of patients, respectively. No treatment-related deaths occurred. Tisagenlecleucel is the second CAR-T therapy to gain approval as a 1-time treatment for B cell lymphomas, following approval of Gilead/Kite's axicabtagene (Yescarta™) in October 2017.
- On May 25, 2018, Janssen stopped US distribution of simeprevir (Olysio™), used to treat hepatitis C virus (HCV) infection. The decision was based on declining use of simeprevir due to the availability of other effective therapies for HCV infection and significant changes in HCV treatment guidelines.
- Effective January 1, 2019, Abbvie will voluntarily discontinue sales of co-packaged extended-release dasabuvir/ombitasvir/paritaprevir + ritonavir (Viekira XR®) and ombitasvir/paritaprevir + ritonavir (Technivie®) in the US due to changes in HCV treatment practices. Viekira XR and Technivie are approved for treatment of select adults with HCV genotype 1 and genotype 4, respectively. Physicians should not write new prescriptions for these agents after June 30, 2018.
- FDA is warning that the anticonvulsant lamotrigine (Lamictal®) can cause hemophagocytic lymphohistiocytosis (HLH), a rare and serious reaction that results in overactivity of the immune system that can lead to hospitalization and death, particularly if treatment is delayed. Patients who develop fever or rash should be promptly evaluated and lamotrigine should be discontinued if HLH cannot be ruled out. Since its approval in 1994, lamotrigine has been associated with 8 confirmed cases of HLH. The product label will be updated to include this warning.
- Acadia issued a press release about safety risks associated with pimavanserin (Nuplazid®). Since the launch of the atypical antipsychotic, over 1,800 serious, including fatal, cases were reported through the FDA Adverse Event Reporting System (FAERS). Reports occurred most often in elderly patients with advanced Parkinson's disease who had many comorbid conditions and were taking several concomitant medications. Acadia and the FDA are continuing to collect and review postmarketing data. Pimavanserin's current labeling carries a boxed warning for increased mortality in elderly patients with dementia-related psychosis.

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

- **June 2018:** moxidectin; oral antiparasitic; onchocerciasis; Medicines Development for Global Health.
- **June 2018:** promethazine/hydrocodone/acetaminophen; oral antihistamine/opioid agonist/analgesic; acute pain while reducing opioid-induced nausea and vomiting; Charleston.
- **June 2018:** Rituxan®; rituximab; IV CD20 antibody; pemphigus vulgaris; Genentech.
- **June 4, 2018:** pegfilgrastim, biosimilar to Amgen's Neulasta®; SC colony-stimulating factor; neutropenia/leukopenia; Mylan/Biocon.
- **June 18, 2018:** halobetasol/tazarotene; topical corticosteroid/retinoid; plaque psoriasis; Valeant.
- **June 18, 2018:** tafenoquine; oral antiparasitic; malaria prevention; 60 Degrees.
- **June 20, 2018:** Cinryze®; IV C1 esterase inhibitor; hereditary angioedema prophylaxis (aged ≥ 6 years); Shire.
- **June 25, 2018:** Avastin®; bevacizumab; IV VEGF-inhibitor; ovarian cancer (1st-line); Genentech.
- **June 25, 2018:** plazomicin; IV aminoglycoside; urinary tract infection, septicemia/bacteremia; Achaogen.
- **June 27, 2018:** epidiolex; oral cannabidiol; Dravet syndrome, Lennox-Gastaut syndrome; GW.
- **June 28, 2018:** Keytruda®; pembrolizumab; IV programmed cell death-1 inhibitor; cervical cancer; Merck.
- **June 29, 2018:** binimetinib + encorafenib; oral MEK + BRAF kinase inhibitors; BRAF-positive melanoma; Array.
- **June 29, 2018:** aripiprazole lauroxil nanocrystal dispersion; intramuscular (IM) atypical antipsychotic; schizophrenia; Alkermes.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
fosnetupitant/ palonosetron	Akynzeo®	Injectable fosnetupitant/palonosetron (Akynzeo), a combination serotonin-3 (5-HT ₃) receptor antagonist, and substance P/neurokinin-1 (NK-1) receptor antagonist, was approved in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Fosnetupitant is a prodrug of netupitant. After reconstitution of the 235 mg/0.25 mg lyophilized powder, Akynzeo is administered as a 30-minute IV infusion approximately 30 minutes prior to the start of chemotherapy. Akynzeo is also available as an oral capsule (netupitant/palonosetron). The injectable formulation became available in May 2018.	Mylan	NDA approval 04/19/2018
tolvaptan	Jynarque™	The FDA granted Orphan status and approval to tolvaptan (Jynarque), a selective vasopressin V ₂ -receptor antagonist, to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD). Jynarque oral tablets are available in 28-day combination strength packs of 45 mg/15 mg, 60 mg/30 mg and 90 mg/30 mg. To lessen the incidence of nocturia, the higher of 2 strengths is taken first thing in the morning and the lower strength is taken 8 hours later. Jynarque has the same active ingredient as Samsca®, approved to treat hyponatremia in select patients. Jynarque is dispensed as part of the Jynarque Risk Evaluation and Mitigation Strategies (REMS) program. Use with Samsca would be outside the REMS program prescribing.	Otsuka	NDA Priority approval 04/23/2018
fluticasone furoate/ umeclidinium/ vilanterol	Trelegy™ Ellipta®	The Agency approved an expanded indication of the once-daily, triple combination inhalation of fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) to reduce COPD exacerbations in patients with a history of exacerbations. The indication no longer specifies current use of fluticasone furoate/vilanterol (Breo® Ellipta®) or umeclidinium + fluticasone furoate/vilanterol prior to prescribing Trelegy Ellipta.	GlaxoSmithKline	sNDA approval 04/24/2018
mirabegron	Myrbetriq®	The beta-3 adrenergic agonist, mirabegron (Myrbetriq), was approved for use in combination with the muscarinic antagonist solifenacin (Vesicare®) for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency. Each product is approved for OAB monotherapy. The initial dose of mirabegron is 25 mg orally once daily alone or in combination with oral solifenacin 5 mg once daily.	Astellas	sNDA approval 04/27/2018

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RECENT FDA APPROVALS *continued*

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
dabrafenib + trametinib	Tafinlar® + Mekinist®	The FDA expanded the combination use of dabrafenib (Tafinlar) + trametinib (Mekinist) for treatment of BRAF V600E or V600K mutation-positive melanoma, as detected by an FDA-approved test, with lymph node involvement following complete surgical resection. The combined use also received a new indication for patients with locally advanced or metastatic anaplastic thyroid cancer (ATC) and with no satisfactory locoregional treatment options. Both agents are considered Breakthrough therapies and Orphan drugs. They are also used together to treat of BRAF V600E mutation-positive metastatic non-small cell lung cancer (NSCLC).	Novartis	sNDA approval 04/30/2018 (melanoma) sNDA Priority approval 05/04/2018 (ATC)
pregabalin	Lyrica®	Pregabalin (Lyrica) received an expanded indication as adjunctive therapy in the treatment of partial onset seizures (POS) to include patients aged 4 to 16 years. Pediatric daily dosing is weight-based in 2 or 3 divided oral doses. Pregabalin extended-release (Lyrica CR®) is not indicated to treat POS. Both formulations are also indicated to treat neuropathic pain.	Pfizer	sNDA approval 05/03/2018
polyethylene glycol 3350 with electrolytes	Plenvu®	Approval was granted for a new low-volume polyethylene glycol 3350 (Plenvu) for colonoscopy preparation in adults. The osmotic laxative is consumed as 2 doses as either a 1-day or 2-day regimen. The kit contains 3 pouches of active product and a mixing container. Unlike traditional preparations, each dose of Plenvu can be mixed in as little as 16 ounces of water and consumed over 30 minutes. Each dose is followed by an additional 16 ounces of clear liquids. Product launch is expected in the third quarter of 2018.	Salix	505(b)(2) NDA approval 05/04/2018
daratumumab	Darzalex®	The Orphan drug daratumumab (Darzalex) gained a new indication for combined use with bortezomib, melphalan, and prednisone to treat patients newly diagnosed with multiple myeloma (MM) who are ineligible for autologous stem cell transplant. This is the first indication for the CD38-directed cytolytic antibody that does not require prior treatment of MM. The dosage for newly diagnosed MM is 16 mg/kg given IV weekly for 6 doses, then every 3 weeks for 16 doses, and then every 4 weeks thereafter.	Janssen	sBLA approval 05/07/2018
brivaracetam	Briviact®	Brivaracetam (Briviact) tablet and oral solution were granted an expanded indication for the treatment of POS to include patients ages 4 to 15 years; the POS indication for the IV formulation only includes patients ≥ 16 years. For POS, the oral pediatric weight-based dose is given twice daily.	UCB	sNDA approval 05/10/2018
fingolimod	Gilenya®	The FDA expanded the fingolimod (Gilenya) indication for treatment of relapsing multiple sclerosis (RMS) to include patients as young as 10 years. The daily pediatric dose is 0.5 mg in patients weighing > 40 kg and 0.25 mg in those weighing ≤ 40 kg. The FDA granted Breakthrough therapy designation for this indication.	Novartis	sNDA Priority approval 05/11/2018

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RECENT FDA APPROVALS *continued*

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
tocilizumab	Actemra®	Tocilizumab (Actemra), an interleukin-6 inhibitor, was approved for SC injection to treat active polyarticular juvenile idiopathic arthritis (PJIA) in patients ≥ 2 years of age as monotherapy or in combination with methotrexate. Actemra IV is already approved in this population. The PJIA dose in pediatrics is 162 mg SC every 3 weeks in patients weighing < 30 kg and every 2 weeks for those ≥ 30 kg. The first SC dose may be given at the time of the next scheduled IV dose. Patients or caregivers may administer the SC dose with proper training.	Genentech	sBLA approval 05/11/2018
emtricitabine/ tenofovir disoproxil fumarate (TDF)	Truvada®	The fixed-dose combination of emtricitabine/TDF (Truvada) received an expanded pre-exposure prophylaxis (PrEP) indication to include adolescents weighing ≥ 35 kg who are at risk of HIV-1 infection, in combination with safer sex practices. The PrEP dosage is emtricitabine 200 mg/TDF 300 mg once daily. Truvada is also indicated in pediatric patients weighing ≥ 17 kg for the treatment of HIV-1 infection in combination with other antiretroviral agents.	Gilead	sNDA approval 05/15/2018

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References:

amgen.com fda.gov headaches.org investors.portola.com ir.acadia-pharm.com ir.valeant.com janssenmd.com pfizer.com