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MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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HOT TOPIC: FIRST DRUG COMPRISED OF ACTIVE MARIJUANA DERIVATIVE APPROVED

Under Priority review, the United States (US) Food and Drug Administration (FDA) approved cannabidiol oral solution (Epidiolex®) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome in patients ≥ 2 years of age. It is the only drug approved to treat Dravet syndrome and the FDA designated it as an Orphan drug and Rare pediatric disease drug to treat both serious, difficult-to-treat childhood seizure disorders. Dravet syndrome is diagnosed in approximately 1 in 15,700 individuals in the US and is characterized by frequent prolonged seizures and developmental delays. LGS involves frequent drop seizures and impaired intellectual development. It accounts for 2% to 5% of childhood seizure disorders. LGS is typically first seen between the ages of 3 to 5 years and persists into adulthood. Other medications approved to treat LGS include clobazam, clonazepam, felbamate, lamotrigine, rufinamide, and topiramate.

Cannabidiol (CBD) oral solution is the first agent to garner FDA approval that contains a purified drug substance derived from marijuana. While CBD is a cannabinoid found in marijuana, it is not the primary psychoactive component, nor is it associated with intoxication or euphoria, as seen with tetrahydrocannabidiol (THC). Studies demonstrated CBD has a similar drug-liking and physical dependence potential to placebo in non-dependent adult recreational drug users.

Cannabidiol oral solution was studied in 3 randomized, double-blind, placebo-controlled clinical trials including 516 patients with either LGS or Dravet syndrome. Cannabidiol taken with the patient's current anticonvulsant regimen was shown to be effective in reducing the frequency of seizures when compared with placebo. Over the 12-week treatment period, the reduction in median number of LGS seizures ranged from 37% to 44% with CBD and 17% to 22% with placebo. For Dravet syndrome, seizure reductions were 39% and 13% with CBD and placebo, respectively. Common side effects (≥ 10%) reported with CBD were increased liver transaminases (particularly with concurrent use of valproate and clobazam), somnolence, decreased appetite, diarrhea, rash, fatigue, insomnia, and infections. Epidiolex must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks.

Under the Controlled Substances Act, CBD is a Schedule I controlled substance because it is a chemical component of the cannabis plant. Availability of Epidiolex is anticipated after the US Drug Enforcement Administration (DEA) has made a scheduling determination for the product, which is expected to take place within 90 days of drug approval.

FDA ISSUES STRONGER FLUOROQUINOLONE WARNINGS

The FDA is strengthening warnings for all systemic fluoroquinolone antibiotics related to the risks of significant hypoglycemia and certain mental health side effects. A recent FDA review identified 56 cases of hypoglycemic coma associated with fluoroquinolone use during October 1987 to April 2017. Most patients had risk factors for hypoglycemia (e.g., older age, diabetes, renal impairment). Based on this new information, hypoglycemic coma will be added to the label's existing warnings regarding blood glucose disturbances.

The Agency also found inconsistent labeling regarding psychiatric effects among fluoroquinolone agents. The FDA is requiring that labels of all systemic agents include the following psychiatric adverse effects: disorientation, disturbances in attention, delirium, memory impairment, agitation, and nervousness. The FDA warns that psychiatric adverse reactions may occur after just one dose.

Fluoroquinolone treatment should be discontinued if patients report any central nervous system (CNS) side effects or blood glucose disturbances. Switching to a non-fluoroquinolone antibiotic should be considered if possible. Fluoroquinolones should not be prescribed to treat acute bacterial sinusitis, acute bacterial exacerbations of chronic bronchitis, and uncomplicated urinary tract infections (UTIs) if patients have other treatment options because the risks outweigh the benefits in these patients.

CDC UPDATES RECOMMENDATIONS FOR LATENT TUBERCULOSIS TREATMENT

The Centers for Disease Control and Prevention (CDC) updated their recommendations on the treatment of latent tuberculosis infection (LTBI). In 2011, the CDC recommended once-weekly isoniazid and rifapentine for 12 weeks (3HP) administered by directly observed therapy (DOT); however, this regimen was not recommended for use in children < 12 years of age or for patients with human immunodeficiency virus-1 (HIV-1) infection. In 2017, a CDC Work Group conducted a systematic review and meta-analysis of the 3HP regimen and determined that it is as safe and effective as other recommended LTBI regimens and achieves significantly higher treatment completion rates. As a result, the CDC now recommends 3HP for treatment of LTBI in patients ≥ 2 years of age and in patients with HIV-1 infection or acquired immunodeficiency syndrome (AIDS) who are taking antiretroviral medications with acceptable drug-drug interaction profiles with rifapentine. Additionally, the CDC now recommends the 3HP regimen be administered by DOT or self-administered therapy (SAT) in patients ≥ 2 years of age. The CDC acknowledges that additional studies are needed to understand the pharmacokinetics, safety, and tolerance of 3HP in patients ages < 2 years; adherence and safety of 3HP-SAT among patients < 18 years of age; and safety of 3HP during pregnancy.

GUIDELINE UPDATE ON OSTEOPOROSIS SCREENING

Osteoporotic fractures are associated with multiple negative outcomes including limitations in ambulation, chronic pain, disability, loss of independence, and decreased quality of life. With the aging population in the US, the prevalence of primary osteoporosis will likely increase to approximately 12.3 million Americans > 50 years of age by the year 2020. Higher rates of osteoporosis and osteoporotic fractures occur in women compared to men; however, fracture-related mortality is higher among men. Osteoporosis is generally asymptomatic until a fracture occurs; therefore, screening for osteoporosis is the most effective tool in preventing osteoporotic fractures.

In an effort to decrease preventable burden, the US Preventive Services Task Force (USPSTF) released updated guidelines regarding osteoporosis screening to prevent fractures. They recommend screening for osteoporosis with bone measurement testing in all women aged ≥ 65 years and in postmenopausal women < 65 years who are considered to be at increased risk of osteoporosis by a clinical risk assessment tool (Level B recommendations). Evidence is convincing to support the use of subsequent drug therapies to reduce fracture rates in postmenopausal women. A similar effect cannot be presumed to occur in men; therefore, the USPSTF concludes that the current evidence is insufficient to determine the benefit of osteoporosis screening on fracture prevention in men.

USPSTF states there is compelling evidence that bone measurement tests are accurate for predicting osteoporotic fractures. Central dual-energy X-ray absorptiometry (DXA) that measures bone mineral density (BMD) of the hip and lumbar spine is most commonly used to define osteoporosis and guide treatment initiation. Risk assessment tools with moderate accuracy in predicting osteoporosis and related fractures include: the Simple Calculated Osteoporosis Risk Estimation (SCORE), Osteoporosis Risk Assessment Instrument (ORAI), Osteoporosis Index of Risk (OSIRIS), Osteoporosis Self-Assessment Tool (OST), and the Fracture Risk Assessment Tool (FRAX®). Screening interval may be based on age, baseline BMD, and projected time to osteoporosis development.

DRUG INFORMATION **HIGHLIGHTS**

- The nationwide shortage of epinephrine auto-injectors, for the emergency treatment of allergic reactions, including anaphylaxis, appears to be subsiding. While Impax's authorized generic (AG) version of the discontinued Adrenaclick® continues to be on backorder, Mylan reports that they are shipping large amounts of Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and their respective AGs, to distributors. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Adamis' Symjepi® 0.3 mg, FDA-approved in June 2017, has not entered the US market; further, approval of the 0.15 mg version of Symjepi is expected in September 2018.
- The FDA announced a voluntary recall of several valsartan-containing medications due to the presence of N-nitrosodimethylamine (NDMA), a probable human carcinogen. The impurity is likely due to manufacturing changes. Affected product includes valsartan and valsartan/hydrochlorothiazide by Teva (labeled as Major or Actavis) and Prinston (labeled as Solco). Product by repackagers, including A-S Medication Solutions, Avkare, and Remedy Repack, is also impacted. Patients with affected product should contact their pharmacist and continue taking their prescribed medication until a replacement supply is received.
- Aralez has permanently discontinued aspirin/omeprazole (Yosprala®) fixed-dose oral tablets in the US due to changing market dynamics.
- Two vaccines for the prevention of herpes zoster (shingles) are available in the US for use in people aged ≥ 50 years. They include a live attenuated virus vaccine (Zostavax®), administered as a single subcutaneous (SC) dose, and a recombinant zoster vaccine (Shingrix®), which is administered as a 2-dose intramuscular (IM) series, with the second dose given anytime from 2 to 6 months after the first. During the 4 months following the introduction of Shingrix in October 2017, the CDC received 13 reports of administration errors involving Shingrix. Errors included incorrect route of administration, inappropriate age of recipient, patient receipt of vaccine counseling statement for Zostavax instead of Shingrix, failure of instructing patients to return for the second Shingrix dose, administration of Shingrix instead of the intended varicella vaccine (Varivax®), improper storage, and failure to reconstitute the vaccine prior to administration. In many cases, providers may have confused administration instructions for Shingrix with instructions for Zostavax. In order to prevent Shingrix administration errors, vaccine providers should be aware of prescribing information, storage requirements, preparation guidelines, and recommendations for both herpes zoster vaccines. Moreover, due to high levels of demand for Shingrix, GlaxoSmithKline has implemented order limits resulting in shipping delays to providers. These order limits are expected to continue throughout 2018.

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

- **August 2018:** tafenoquine; oral antiparasitic; malaria prevention; 60 Degrees.
- **August 2018:** ulipristal; oral progestin; uterine fibroids; Allergan.
- **Aug-Oct 2018:** Ilaris®; canakinumab; SC interleukin (IL)-1 inhibitor; atherosclerosis (secondary prevention); Novartis.
- **August 7, 2018:** Orkambi®; lumacaftor/ivacaftor; oral cystic fibrosis (CF) transmembrane conductance regulator (CFTR) corrector/potentiator; CF ages 2–5 years; Vertex.
- **August 10, 2018:** patisiran; intravenous (IV) antisense oligonucleotide; familial amyloid polyneuropathy; Alnylam.
- **August 13, 2018:** migalastat; oral chemical chaperone; Fabry disease; Amicus.
- **August 15, 2018:** Kalydeco®; ivacaftor; oral CFTR potentiator; CF ages 12 to < 24 months; Vertex.
- **August 16, 2018:** Opdivo®; nivolumab; IV programmed cell death 1 (PD-1) inhibitor; small cell lung cancer; Bristol-Myers Squibb.
- **August 22, 2018:** stannsoporfin; IM heme oxygenase inhibitor; hyperbilirubinemia; Infacare.
- **August 24, 2018:** lanadelumab; SC plasma kallikrein inhibitor; hereditary angioedema attack prophylaxis; Shire.
- **August 24, 2018:** Lenvima®; lenvatinib; oral tyrosine kinase inhibitor (TKI); hepatocellular carcinoma (1st-line); Eisai.
- **August 28, 2018:** eravacycline; IV/oral fluorocycline antibiotic; intra-abdominal infections; Tetraphase.
- **August 29, 2018:** lorlatinib; oral TKI; anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC); Pfizer.
- **August 30, 2018:** volanesorsen; SC antisense apolipoprotein inhibitor; familial chylomicronemia syndrome; Akcea.
- **August 31, 2018:** damoctocog alfa pegol; IV pegylated recombinant coagulation factor VIII; hemophilia A; Bayer.
- **August 31, 2018:** dasotraline; oral dopamine/norepinephrine reuptake inhibitor; attention deficit hyperactivity disorder (ADHD); Sunovion.
- **September 4, 2018:** mogamulizumab; IV anti-CCR4 antibody; cutaneous T-cell lymphoma; Pfizer.
- **September 5, 2018:** Tecentriq®; atezolizumab; IV programmed cell death ligand 1 (PD-L1) inhibitor; NSCLC (1st-line); Genentech.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
pembrolizumab	Keytruda®	Accelerated approvals for 2 new indications were granted for pembrolizumab (Keytruda): (1) for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1, as determined by an FDA-approved test; and (2) the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL), or who have relapsed after ≥ 2 prior lines of therapy; it is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy. Continued approval for both indications may depend on confirmatory trial results. The adult dosage for both indications is 200 mg IV every 3 weeks infused over 30 minutes. The dose for pediatrics with PMBCL is 2 mg/kg (up to 200 mg) IV every 3 weeks. The PD-1 inhibitor has several other indications for malignant conditions. The agent received Breakthrough therapy and Orphan drug designations for PMBCL.	Merck	sBLA approval 06/12/2018 (Cervical cancer) and sBLA Priority approval 06/13/2018 (PMBCL)
bevacizumab	Avastin®	Bevacizumab (Avastin) received Orphan drug designation and approval for the treatment of stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer after initial surgical resection in combination with carboplatin and paclitaxel, followed by bevacizumab monotherapy. For this indication, bevacizumab dosage is 15 mg/kg IV every 3 weeks with carboplatin and paclitaxel for 6 to 8 cycles, followed by 15 mg/kg every 3 weeks as a single agent. Bevacizumab was already approved for other subsets of women with these cancers, in addition to various other malignancies.	Genentech	sBLA approval 06/13/2018
moxidectin	no trade name	Moxidectin, a macrocyclic lactone anthelmintic, was approved by the FDA as an Orphan drug for the treatment of river blindness (onchocerciasis) in patients ≥ 12 years old. Moxidectin does not kill adult *Onchocerca volvulus;* rather, it inhibits the release of microfilariae from the adult worm. The safety and efficacy of repeat administration has not been studied. The medication is available in 2 mg tablets and dosed as a single, oral dose of 8 mg (4 tablets).	Medicines Development for Global Health	NDA Priority approval 06/13/2018
C1 esterase inhibitor (human)	Cinryze®	The FDA approved an expanded indication of the Orphan drug, human C1 esterase inhibitor (Cinryze), for routine prophylaxis against angioedema attacks to include pediatric patients ages 6 through 11 years with hereditary angioedema (HAE). Previously, the medication was indicated for routine prophylaxis in patients ≥ 12 years of age. For patients 6 to 11 years old, the initial dose is 500 units IV every 3 to 4 days infused at a rate of 1 mL/minute; the dose may be adjusted up to 1,000 units every 3 to 4 days, according to individual response.	Viropharma	sBLA approval 06/20/2018

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

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
desmopressin acetate	Nocdurna®	The first sublingual (SL) tablet of desmopressin acetate (Nocdurna), a vasopressin analog, was approved for the treatment of adult nocturia due to nocturnal polyuria for patients who awaken ≥ 2 times per night to void. Labeling carries a Boxed warning informing of the risk of hyponatremia. Desmopressin acetate was approved in 27.7 mcg and 53.3 mcg SL tablets. It is dosed as 27.7 mcg SL once daily (women) or 55.3 mcg SL once daily (men), 1 hour before bedtime. A nasal spray formulation (Noctiva®) was previously approved to treat nocturia. Other formulations exist that are approved for other indications. The SL formulation is expected to be available in the second half of 2018.	Ferring	NDA approval 06/21/2018
plazomicin	Zemdri™	The aminoglycoside plazomicin (Zemdri) was approved by the FDA to treat adults with complicated UTI, including pyelonephritis, caused by susceptible organisms including *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* and *Enterobacter cloacae*. Its use should be reserved for patients with limited or no alternative treatment options. Plazomicin is administered by a healthcare professional (HCP) as 15 mg/kg every 24 hours IV over 30 minutes in patients with a creatinine clearance ≥ 90 mL/minute. The recommended duration of therapy is 4 to 7 days. Dosage is adjusted based on renal function. Plazomicin is available as 500 mg/10 mL in a single-dose vial.	Achaogen	NDA Priority approval 06/25/2018
binimetinib + encorafenib	Mektovi® + Braftovi™	The kinase inhibitors, binimetinib and encorafenib, were approved for use in combination to treat unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test. Encorafenib is not indicated for the treatment of wild-type BRAF melanoma. The recommended doses are binimetinib 45 mg orally twice daily and encorafenib 450 mg orally once daily. Binimetinib is available as 15 mg tablets and encorafenib is available as 50 mg and 75 mg capsules. Both agents have received Orphan drug designation. The companion diagnostic, ThxID® BRAF kit, was also approved.	Array	NDA approval 06/27/2018
glycopyrronium tosylate	Qbrexza™	The topical anticholinergic, glycocopyrronium tosylate (Qbrexza), was approved as a single-use, pre-moistened 2.4% medicated cloth, for the treatment of primary axillary hyperhidrosis in patients ≥ 9 years old. A cloth is applied once daily to both axillae. Launch is expected in October 2018.	Dermira	NDA approval 06/28/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
pimavanserin	Nuplazid®	A new 34 mg capsule formulation and 10 mg tablet strength of Nuplazid (pimavanserin), an atypical antipsychotic, have been approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. The capsule will deliver a single dosing unit to reduce pill burden. The 10 mg tablet was approved to accommodate patients requiring dosage adjustments. The 17 mg tablet strength, that previously provided the 34 mg dose and dose adjustments, has been removed from the labeling. The 34 mg capsule and 10 mg tablet are estimated to be available in August 2018.	Acadia	NDA and sNDA approval 06/28/2018
aripiprazole lauroxil	Aristada Initio™	The FDA approved aripiprazole lauroxil (Aristada Initio), a long-acting atypical antipsychotic, as a single IM injection for use in combination with a single oral aripiprazole dose (30 mg), for the initiation of Aristada® (any dose) when used for schizophrenia in adults with established tolerability to oral aripiprazole. Previously, the standard initiation of Aristada included 21 consecutive days of oral aripiprazole starting with the first Aristada dose. Aristada Initio provides an alternative option allowing the first dose of Aristada to be given on the same day as Aristada Initio or up to 10 days thereafter. Aristada and Aristada Initio are not interchangeable due to differing pharmacokinetics. Aristada Initio is approved as a prefilled, single-use, IM injection of aripiprazole 675 mg; it is not meant for repeat dosing. The medication is injected into the deltoid or gluteal muscle by an HCP.	Alkermes	sBLA approval 07/02/2018
incobotulinumtoxinA	Xeomin®	An expanded indication was granted for incobotulinumtoxinA (Xeomin), an acetylcholine release inhibitor and neuromuscular blocking agent, to include the treatment of chronic sialorrhea (excessive drooling) in adults. For chronic sialorrhea, the recommended total dose is 100 units per treatment session consisting of 30 units per parotid gland, and 20 units per submandibular gland, administered by an HCP no sooner than every 16 weeks.	Merz	sBLA approval 07/03/2018
nivolumab + ipilimumab	Opdivo + Yervoy®	The FDA granted Breakthrough therapy and Accelerated approval for nivolumab, a PD-1 blocking antibody, plus low-dose ipilimumab (Yervoy), a recombinant, human monoclonal antibody, to treat patients ≥ 12 years of age with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed after treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The recommended dosing schedule is nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day every 3 weeks for 4 doses. Nivolumab is then continued alone as 240 mg IV every 2 weeks until disease progression or unacceptable toxicity.	Bristol-Myers Squibb	sBLA Priority approval 07/11/2018

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References:

cdc.gov fda.gov uspreventiveservicestaskforce.org

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