SEPTEMBER 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

GUIDELINE UPDATE FOR HIV MANAGEMENT

The International Antiviral Society – USA (IAS-USA) Panel released updated guidelines for the treatment and prevention of human immunodeficiency virus 1 (HIV-1) infection in adults. One key revision is to center initial antiretroviral treatment (ART) around unboosted regimens with an integrase strand transfer inhibitor (INSTI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs), with consideration for unique patient situations (e.g., comorbidities, pregnancy, cost). The IAS-USA encourages starting ART as soon as possible after diagnosis of HIV infection, even the same day, if feasible, and the patient is willing to commit to therapy. ART should not be delayed while awaiting common pre-treatment test results. Agents that are not recommended for prompt ART initiation are non-nucleoside reverse-transcriptase inhibitors (NNRTIs), due to possible transmitted resistance, and abacavir, without HLA-B*5701 results. The IAS-USA advises against routine CD4+ count testing, if it is > 250 cells/UL and the HIV RNA has been undetectable for 1 year. Further, the IAS-USA recommends an alternative pre-exposure prophylaxis (PrEP) regimen with emtricitabine/tenofovir disoproxil fumarate (Truvada®) in HIV-negative men who have sex with men (MSM) who have infrequent sexual exposure and are at risk for infection. It is an "on-demand" approach in which 2 tablets are taken before exposure, followed by 1 tablet daily for 2 days after exposure; this regimen is not included in the Truvada labeling.

FIRST DRUG FOR HEREDITARY AMYLOIDOSIS

On August 10, 2018, the United States (US) Food and Drug Administration (FDA) approved Alnylam's patisiran (Onpattro™), the first agent to treat adults with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR; formerly known as familial amyloid polyneuropathy), a rare, and often fatal, genetic disorder. In hATTR, mutations in the transthyretin (TTR) gene cause the liver to produce abnormal TTR protein that accumulates as amyloid fibrils in tissues throughout the body, most notably in the nerves and heart, and eventually lead to organ failure. An estimated 3,000 to 3,500 Americans may be candidates for hATTR treatment; although, some experts believe that this number may increase since approval of new agents may lead to the identification of more eligible patients.

Patisiran is part of a new class of drugs called small interfering RNAs (siRNAs) that inhibits production of mutant and wild-type TTR messenger RNA (mRNA) by the liver, thereby reducing the deposit of abnormal TTR in tissues. Patisiran is administered intravenously (IV) over about 80 minutes by a healthcare professional (HCP) every 3 weeks. The dosage is 0.3 mg/kg in patients weighing < 100 kg and is 30 mg for those weighing ≥ 100 kg. In the 18-month APOLLO study, treatment with patisiran in patients with hATTR polyneuropathy (n=225) led to a significant improvement in neuropathy and quality of life (QoL), as measured by a mean change in the modified Neuropathy Impairment Score +7 (mNIS+7) of -34

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points and Norfolk QoL-Diabetic Neuropathy questionnaire (QoL-DN) of -21.1 points, as compared to placebo. Patisiran-treated patients also scored better on assessments of walking, nutritional status, and the ability to perform activities of daily living. The most common adverse effects were upper respiratory tract infections and infusion-related reactions. Deaths reported during the study were consistent with the natural disease history. Durability of response (≥ 36 months) and neuropathy stabilization were demonstrated in open-label extension trials.

Patisiran was granted FDA's Priority review, Breakthrough therapy, and Orphan drug designations. Further, Ionis' investigational once-weekly, subcutaneous (SC) antisense oligonucleotide agent, inotersen, has received Orphan drug status for the treatment of hATTP polyneuropathy by the FDA; its Priority review decision is slated for October 5, 2018. The oral TTR stabilizer tafamidis is in phase 3 trials in the US; it is approved in Europe and Japan. Other treatments for hATTR include liver transplantation and off-label use of the oral non-steroidal anti-inflammatory drug (NSAID), diflunisal.

NEW TREATMENT FOR ENDOMETRIOSIS

Under a Priority review, the FDA approved Abbvie's oral gonadotropin-releasing hormone (GnRH) receptor antagonist, elagolix (Orilissa™), for the management of moderate to severe pain associated with endometriosis, which affects up to 10% of females 15 to 49 years of age. Elagolix works by suppressing estradiol and progesterone production, resulting in shrinking of endometrial lesions. Elagolix is associated with a dose-dependent decrease in bone mineral density (BMD); therefore, it should be used for a limited duration and avoided in women with confirmed osteoporosis. The recommended dose is 150 mg once daily for up to 24 months, or 200 mg twice daily for up to 6 months. Dose adjustments are necessary in women with moderate hepatic impairment, and the agent should not be used with severe hepatic impairment. Use of elagolix is also contraindicated during pregnancy.

Initial treatment typically includes NSAIDs and continuous hormonal birth control. Progestins, oral androgens (danazol), and GnRH agonists, such as nafarelin nasal spray (Synarel®), and injectable leuprolide (Lupron®) and goserelin (Zoladex®), may also be used. Efficacy of elagolix was demonstrated in 2 double-blind trials that enrolled 1,686 premenopausal women, 18 to 49 years of age, with a surgical diagnosis of endometriosis and moderate to severe endometriosis-related pain. After 3 months, a significantly higher proportion of women treated with elagolix experienced dose-dependent improvements in menstrual pain and non-menstrual pelvic pain, along with a reduction in analgesic use, compared to placebo. Effects were maintained for up to 12 months in extension trials. As with GnRH agonists, elagolix is associated with dose-dependent adverse effects, such as hot flushes and elevated serum lipids; however, unlike other treatments, elagolix does not completely suppress ovulation or cause hormonal flare of endometriosis-related pain.

The Institute for Clinical and Economic Review (ICER) examined data for elagolix. The watch dog concluded that, while the medication appears to offer short-term clinical benefits and a convenient oral formulation, available evidence, including potential risks, are not adequate to determine whether it offers a net health benefit compared to no treatment, or treatment with a GnRH agonist (leuprolide) or a hormonal contraceptive (depot medroxyprogesterone). Additionally, uncertainty exists on its safety and effectiveness with long-term use. ICER concluded that, assuming typical discounts and rebates off its approximate $10,000 annual list price, elagolix meets traditional thresholds for cost-effectiveness when compared to no treatment, but not to other therapies. ICER predicts that elagolix will most likely be an alternative to GnRH agonists. They state that it is reasonable for insurers to require prior authorization based on clinical evidence (e.g., 3-month trial of NSAID and hormonal contraceptives, prescribed by, or in consultation with an obstetrics/gynecology or reproductive endocrinology specialist, limited duration of therapy) to ensure prudent use.

FDA WARNS OF AZITHROMYCIN RISK AFTER STEM CELL TRANSPLANT

The FDA issued a Safety Alert notifying the public of an increased risk of cancer relapse associated with long-term use of the antibiotic azithromycin (Zithromax®, Zmax®) in cancer patients following donor stem cell transplant. This warning is based on results of a clinical trial that revealed an increased rate of relapse in cancers affecting the lymph nodes and blood in patients who were prescribed azithromycin to prevent bronchiolitis obliterans syndrome (BOS), a serious condition caused by inflammation and scarring of the lungs. Azithromycin is indicated to treat infections of the upper and lower respiratory tract, ears, skin, and genitourinary tract, but is not approved to prevent BOS. The FDA is continuing to review additional data. At this time, they advise that HCPs should not prescribe long-term use of azithromycin for prophylaxis of BOS for patients who undergo donor stem cell transplants. Patients should not discontinue treatment without first consulting with their prescriber.

DRUG INFORMATION **HIGHLIGHTS**

- The intermittent nationwide shortage of epinephrine auto-injectors, used for the emergency treatment of allergic reactions, including anaphylaxis, is still ongoing. While Impax's authorized generic (AG) versions of the discontinued Adrenaclick® continue to be on backorder, Mylan reports that they are shipping Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and their respective AGs to some distributors; supply stabilization is not expected until the fourth quarter of 2018. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. To mitigate the shortage impact, the FDA extended the expiration date of specific lots of Epipen 0.3 mg (and its AG) by 4 months beyond the labeled 20-month expiry date. This change is based on stability data provided by Mylan. The FDA has also approved Teva's generic versions of Epipen and Epipen Jr.; product launch date has not been published. Adamis' Symjepi® 0.3 mg was FDA-approved in June 2017, but has not entered the US market; approval of Symjepi 0.15 mg is expected in September 2018.
- The voluntary recall of valsartan and valsartan/hydrochlorothiazide (HCTZ) medications has expanded to include product manufactured by Hetero Labs (labeled as Camber Pharmaceuticals), Torrent Pharmaceuticals, and 3 additional repackagers (A-S Medication Solutions, AvKARE, Remedy Repack). Further, Torrent is recalling all lots of valsartan/amlodipine/HCTZ. The recalls are based on the presence of a probable human carcinogen, N-nitrosodimethylamine (NDMA), likely due to manufacturing changes. Patients with affected product should contact their pharmacist and should continue taking their prescribed medication until a replacement supply is received. No cases of adverse events have been reported.
- The FDA approved Pfizer's filgrastim-aafi (Nivestym™), the second biosimilar to Amgen's filgrastim (Neupogen®). The biosimilar leukocyte growth factor agent is approved for the same indications as the originator product, with the exception of increasing survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic syndrome of acute radiation syndrome).
- Influenza vaccine lots for the 2018-2019 flu season have been released by the FDA and are available for distribution by the manufacturers. Based on epidemiology and antigenic characteristics of recent influenza isolates, modifications were made to the type of virus strains contained in the vaccines for in the 2018-2019 flu season.
- On June 14, 2018, the FDA approved buprenorphine/naloxone buccal film by Mylan and Dr. Reddy's, as generic versions of Indivior's Suboxone® film. That same day, Dr. Reddy's launched the product at risk; however, a subsequent court ruling blocked sales of Dr. Reddy's generic version until patent litigation is resolved, potentially until 2020-2021. Mylan has not launched generic product; terms of a settlement agreement between Indivior and Mylan are not known.
- Based on pharmacokinetic data, labeling for the topical antifungal, tavaborole 5% (Kerydin®), was revised to include treatment of onychomycosis in patients ≥ 6 years of age. Dosing in the this population is the same as in adults.
- Label revisions were approved for metronidazole gel 1.3% (Nuvessa™) to include use in females 12 to 17 years old with bacterial vaginosis (BV). The dosage is 65 mg intravaginally at bedtime in all age groups.

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

- **September 2018:** dacomitinib; oral tyrosine kinase inhibitor; non-small cell lung cancer (NSCLC); Pfizer.
- **September 2018:** Promacta®; eltrombopag; oral thrombopoietin receptor agonist; aplastic anemia (1st-line); Novartis.
- **Sep-Oct 2018:** moxetumomab pasudotox; IV anti-CD22 antibody; hairy cell leukemia; AstraZeneca.
- **September 5, 2018:** Tecentriq®; atezolizumab; IV programmed cell death ligand 1 (PD-L1) inhibitor; NSCLC (1st-line); Genentech.
- **September 7, 2018:** Nucala®; mepolizumab; SC interleukin-5 (IL-5) inhibitor; eosinophilic chronic obstructive pulmonary disease (COPD); GlaxoSmithKline (GSK).
- **September 14, 2018:** fremanezumab; SC calcitonin gene-related peptide (CGRP) inhibitor; migraine prevention; Teva.
- **September 21, 2018:** Ruconest®; IV recombinant human C1 esterase inhibitor; hereditary angioedema (HAE) attack prophylaxis; Pharming.
- **September 27, 2018:** galcanezumab; SC CGRP inhibitor; migraine prevention; Eli Lilly.
- **September 28, 2018:** liposomal amikacin; inhaled aminoglycoside antibiotic; nontuberculous mycobacteria lung infections; Insmed.
- **September 28, 2018:** Fycompa®; perampanel; oral anticonvulsant; partial-onset seizures and primary generalized tonic-clonic seizures in ages 2-11 years; Eisai.
- **October 2, 2018:** omadacycline; oral/IV aminomethylcycline antibiotic; skin/skin-structure infections, community-acquired pneumonia; Paratek.
- **October 4, 2018:** Hemlibra®; emicizumab-kxwh; SC factor VIIIa mimetic; hemophilia A without inhibitors; Genentech.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
enzalutamide	Xtandi®	The androgen receptor inhibitor, enzalutamide (Xtandi), was granted an expanded indication to include patients with non-metastatic castration-resistant prostate cancer (CRPC); it was already approved for metastatic CRPC. The recommended dosage is four 40 mg capsules once daily. Patients should be concurrently treated with a GnRH analog or have had a bilateral orchiectomy.	Astellas	sNDA Priority approval 07/13/2018
darunavir/ cobicistat/ emtricitabine/ tenofovir alafenamide	Symtuza™	FDA-approval was awarded to the quadruple fixed-dose combination of Symtuza. It consists of the protease inhibitor, darunavir 800 mg, the CYP3A inhibitor, cobicistat 150 mg, and 2 nucleoside analog reverse transcriptase inhibitors, emtricitabine 200 mg and tenofovir alafenamide 10 mg. Symtuza is indicated as a complete regimen to treat HIV-1 infection in adults with no prior ART, or who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable regimen for ≥ 6 months and have no known substitutions associated with resistance to darunavir or tenofovir. The recommended oral dose is 1 tablet once daily with food.	Janssen	NDA approval 07/17/2018
ribociclib	Kisqali®	The kinase inhibitor, ribociclib (Kisqali), received 2 expanded indications to treat women with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer. The indications include combination use with (1) an aromatase inhibitor in pre/peri/post-menopausal women as an initial endocrine-based therapy; and (2) fulvestrant in postmenopausal women following disease progression on endocrine therapy or as initial endocrine-based therapy. The initial dose of ribociclib in combination with either agent is 600 mg for 21 consecutive days, followed by 7 days off treatment until disease progression or unacceptable toxicity.	Novartis	sNDA approval 07/18/2018
somatropin	Zomacton®	Somatropin (Zomacton), a recombinant human growth hormone, gained 4 supplemental pediatric indications including use for idiopathic short stature (ISS), short stature homeobox-containing gene (SHOX), Turner syndrome (TS), and small for gestational age (SGA). The weekly dosage is divided into 3, 6, or 7 days per week. The dosage for TS is up to 0.375 mg/kg/week, ISS is up to 0.37 mg/kg/week, SHOX deficiency is 0.35 mg/kg/week, and SGA is up to 0.47 mg/kg/week.	Ferring	sNDA approval 07/19/2018
ivosidenib	Tibsovo®	The Agency approved the Orphan drug ivosidenib (Tibsovo), an isocitrate dehydrogenase-1 (IDH1) inhibitor, to treat adults with relapsed or refractory acute myeloid leukemia (AML) and a susceptible IDH1 mutation. This is the first drug to target this specific mutation. Available as 250 mg oral tablets, it is dosed as 2 tablets once daily. A companion diagnostic test to detect IDH1 gene mutation was also approved.	Agios	NDA Priority approval 07/20/2018

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
tafenoquine	Krintafel™	Breakthrough therapy and Orphan drug status, and approval were granted to tafenoquine (Krintafel), an 8-aminoquinoline antimalarial drug. It is indicated for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients ≥ 16 year of age, who are receiving appropriate antimalarial therapy for acute infection. It is dosed as two 150 mg tablets orally, with food, as a single dose.	GSK	NDA Priority approval 07/20/2018
risperidone ER	Perseris™	An extended-release (ER) injectable suspension formulation of the atypical antipsychotic, risperidone (Perseris), was approved for the treatment of schizophrenia in adults. It is approved as kits containing 2 syringes prefilled with risperidone powder, 90 mg or 120 mg, and a delivery system. The recommended dosage is 90 mg or 120 mg by monthly intramuscular (IM) injection by an HCP. Patients should be established on oral risperidone prior to initiating Perseris, but simultaneous oral supplementation is not recommended. Perseris is not therapeutically equivalent to the injectable long-acting risperidone, Risperdal Consta®.	Indivior	NDA 505(b)(2) approval 07/27/2018
lusutrombopag	Mulpleta®	Lusutrombopag (Mulpleta), an oral thrombopoietin receptor agonist, received approval for use in adults with chronic liver disease to be used prior to a procedure. It was approved as 3 mg tablets, with a recommended dose of 3 mg once daily for 7 days, starting 8 to 14 days before a scheduled procedure. The procedure should occur 2 to 8 days after the last dose.	Shionogi	NDA Priority approval 07/31/2018
tbo-filgrastim	Granix®	The FDA granted an expanded indication for the leukocyte growth factor, tbo-filgrastim (Granix), for use in patients ages 1 month to 17 years to reduce the duration of severe neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. The dosing is consistent across all age groups at 5 mcg/kg/day as a SC injection. In addition to the prefilled syringes, already available, a vial formulation was approved in the following strengths: 300 mcg/1 mL and 480 mcg/1.6 mL.	Sicor	sBLA approval 07/31/2018
immune globulin IV, human - ifas	Panzyga®	Approval was granted for another human-derived, IV formulation of immune globulin (Panzyga). Prepared as a 10% liquid in 6 bottle sizes ranging from 10 mL to 300 mL, Panzyga is approved for primary humoral immunodeficiency (PI) in patients ≥ 2 years of age, and for chronic immune thrombocytopenia (ITP) in adults. The recommended dose for PI is 300 to 600 mg/kg IV every 3 to 4 weeks, and 1 g/kg IV daily for 2 consecutive days for ITP.	Octapharma	BLA approval 08/02/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
methylphenidate ER	Jornay PM™	Methylphenidate ER capsule (Jornay PM) was approved to treat attention deficit hyperactivity disorder (ADHD) in patients ≥ 6 years of age. The capsules exhibit both delayed- and extended-release properties, and are approved in strengths of 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg. The dosage is 1 capsule once daily in the evening, either swallowed whole or the contents sprinkled onto applesauce. Jornay PM is not substitutable on a mg-per-mg basis with other methylphenidate products. Its launch is expected in the first half of 2019.	Ironshore	NDA 505(b)(2) approval 08/08/2018
mogamulizumab-kpkc	Poteligeo®	The CC chemokine receptor type 4 (CCR4)-directed monoclonal antibody, mogamulizumab-kpkc (Poteligeo), received Breakthrough therapy and Orphan drug status and was approved to treat adults with relapsed or refractory mycosis fungoides or Sézary syndrome after at least 1 prior systemic therapy. It was approved as a 20 mg/5 mL solution in a single-dose vial. It is administered by an HCP as 1 mg/kg IV over at least 60 minutes on days 1, 8, 15, and 22 of the first 28-day cycle and on days 1 and 15 of each subsequent cycle. The launch of Poteligeo is planned in quarter 4, 2018.	Kyowa Kirin	BLA Priority approval 08/08/2018
tafenoquine	Arakoda™	A second formulation of tafenoquine (Arakoda) was approved as 100 mg oral tablets for the prophylaxis of malaria in patients aged ≥ 18 years. The recommended single course of therapy is administered as 3 phases consisting of a loading dose of 200 mg once daily for 3 days prior to travel to malarious areas, followed by a maintenance dose of 200 mg once weekly, starting 7 days after the last loading dose, and then a one-time terminal prophylaxis dose of 200 mg taken 7 days after the last maintenance dose.	60 Degrees	NDA Priority approval 08/08/2018
migalastat	Galafold™	The alpha-galactosidase A (alpha-Gal A) pharmacological chaperone, migalastat (Galafold), was approved to treat adults with a confirmed diagnosis of Fabry disease with an amenable galactosidase alpha gene (GLA) variant. It is available as 123 mg oral capsules, and the dosage is 123 mg every other day, taken at the same time of day on an empty stomach.	Amicus	NDA Priority approval 08/10/2018
segesterone acetate/ ethinyl estradiol	Annovera™	FDA-approval was awarded for a vaginal progestin/estrogen combination contraceptive ring containing segesterone acetate 103 mg and ethinyl estradiol 17.4 mg (Annovera). It is indicated for use in females of reproductive potential to prevent pregnancy. Annovera is inserted vaginally and remains in place continuously for 21 days followed by a 7-day vaginal system-free interval. One vaginal system provides contraception for thirteen 28-day cycles (1 year). Annovera has not been adequately evaluated in females with a body mass index of > 29 kg/m^2. Commercial availability is expected in quarter 3, 2019.	The Population Council	NDA 505(b)(2) approval 08/10/2018

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