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MRx CLINICAL ALERT

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HOT TOPIC: FDA APPROVES AGENT FOR MULTIDRUG RESISTANT HIV

The Food and Drug Administration (FDA) approved Taimed Biologics' ibalizumab-uiyk (Trogarzo™) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in heavily treatment-experienced adults with multidrug resistant (MDR) HIV-1 infection who are failing their current antiretroviral (ARV) regimen. It is estimated that over 1.1 million people in the United States (US) are living with HIV, of which 25,000 have MDR HIV. Ibalizumab-uiyk is the first of a new class of ARV medication, a CD4-directed post-attachment HIV-1 inhibitor. Unlike other ARV agents that inhibit HIV replication, ibalizumab-uiyk prevents entry of HIV into CD4+ T cells. Ibalizumab-uiyk is also the first FDA-approved long-acting ARV agent. It is prescribed in combination with other ARV medications. Ibalizumab-uiyk is administered by a healthcare professional (HCP) via intravenous (IV) infusion; a single loading dose of 2,000 mg is followed by a maintenance dose of 800 mg every 2 weeks.

Safety and efficacy of ibalizumab-uiyk were studied in 40 heavily treatment-experienced HIV-infected patients with MDR HIV-1. At least a 0.5$\log_{10}$ decrease in viral load (primary efficacy measure) was achieved in 83% of participants 1 week after ibalizumab-uiyk was added to their failing ARV regimens. After 24 weeks of ibalizumab-uiyk treatment, 43% of the trial participants achieved HIV RNA suppression (< 50 copies/mL). Adverse reactions were typically mild to moderate in severity and included diarrhea, dizziness, nausea, and rash. However, immune reconstitution inflammatory syndrome, an exacerbation of progressive multifocal leukoencephalopathy, occurred in 1 patient treated with ibalizumab-uiyk, as did severe rash. Drug-drug interactions are not foreseen with ibalizumab-uiyk since it is not eliminated via renal or hepatic routes. Ibalizumab-uiyk was granted Fast track, Breakthrough therapy, Priority review, and Orphan drug designations by the FDA.

ENDOCRINE SOCIETY UPDATES TESTOSTERONE GUIDELINES

The Endocrine Society (ES) published the evidence-based guidelines, "Testosterone Therapy in Men with Hypogonadism," as an update to their 2010 guidance. The ES recommends that a diagnosis of hypogonadism be made only if the patient has symptoms of testosterone deficiency and clearly and consistently low serum testosterone (T) levels. Initial and confirmatory diagnostic tests should include a fasting morning total T level; if the total T level is low normal, measuring a free T concentration is recommended. The cause of confirmed testosterone deficiency should be established. The ES recommends testosterone therapy for men with symptomatic testosterone deficiency after the potential risks and benefits of treatment are discussed with the patient. Testosterone therapy should not be initiated in men who are planning fertility in the near future or who have breast or prostate cancer,

prostate nodules, prostate-specific antigen (PSA) level > 4 ng/mL, or select men with PSA > 3 ng/mL. Clinicians should target T levels in the mid-normal range in men receiving exogenous testosterone. Serum T concentration, hematocrit, and risk for prostate cancer should be monitored during the first year of treatment. The ES does not give preference to any testosterone replacement product but states that choice of formulations should be based on patient preference and drug pharmacokinetics, adverse effect profile, treatment burden, and cost.

FDA WARNS AGAINST USE OF CLARITHROMYCIN IN PATIENTS WITH HEART DISEASE

The FDA is advising that clarithromycin (Biaxin®; Biaxin XL) be prescribed with caution in patients with heart disease. The warning is based on review of a 10-year follow up of the large prospective CLARICOR trial in patients with coronary heart disease (CHD) that reported an unexpected increase in deaths among patients with CHD who received a 2-week course of clarithromycin. The increased risk became apparent after patients had been followed for at least 1 year. Reasons for the increased reports of death are unknown at this time. A warning is included in the clarithromycin labeling regarding the increased risk of heart problems or death in patients with heart disease. Clarithromycin is an oral macrolide antimicrobial used to treat infections of the skin, ears, sinuses, and lungs, as well as other areas of the body. Prescribers are advised to consider other antibiotics in patients with heart disease.

CDC ADVISORY COMMITTEE RECOMMENDS HEPLISAV-B™

The Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immune Practices (ACIP) recommended the adjuvanted recombinant hepatitis B vaccine, Heplisav-B by Dynavax, for prevention against infection due to all known hepatitis B virus (HBV) subtypes. Heplisav-B is approved for use in people 18 years and older. In clinical studies, Heplisav-B's 2-dose regimen resulted in a statistically significantly higher rate of seroprotection against HBV compared to 3 doses of the recombinant HBV vaccine, Engerix-B® (90% versus 70.5%, 8 weeks after the last dose).

The CDC recommends HBV vaccination for adults at high risk for HBV infection due to their occupation, lifestyle, living situation, and travel to certain areas, as well as for patients with diabetes, end-stage renal disease, chronic liver disease, or HIV infection. If the CDC agrees with the committee's vote, the updated recommendation will be published in the *Morbidity and Mortality Weekly Report (MMWR)*.

BEHAVIORAL HEALTH CORNER

UPDATED ADVICE FOR PRIMARY CARE (PC) CLINICIANS ON ADOLESCENT DEPRESSION

The American Academy of Pediatrics (AAP) states that adolescent depression is often not diagnosed until the patient reaches adulthood. In response to the lack of timely detection, the AAP published part 1 of their updated "Guidelines for Adolescent Depression in Primary Care (GLAD-PC)." It focuses on depression in patients aged 10 to 21 years and provides strong and very strong recommendations on identification of at-risk youth, assessment and diagnosis, and initial management. The AAP also offers new recommendations on practice preparation for improved care of patients with depression.

The AAP urges PC clinicians to seek education on depression assessment, identification, diagnosis, and treatment, unless previously trained, and to establish collaborative relationships with community mental health resources. Annual depression screening using formal self-reported tools is advised in patients ages ≥ 12 years. Patients with depression risk factors (e.g., family or personal history of depressive episode, trauma, substance use, frequent somatic symptoms) should be monitored over time for the development of depression. Assessment, based on the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* or the *International Classification of Diseases, 10th Revision (ICD-10)*, should be performed in adolescents who have positive results on depression screening, present with an emotional-based chief complaint, or are highly suspect for depression despite a negative screening. Families and patients should receive counseling regarding depression, its treatment options, and associated confidentiality limitations. The AAP recommends PC clinicians develop a treatment plan with patients and families with specific goals regarding functioning in the home, social, and school settings. Furthermore, clinicians should create an emergency communication procedure for handling acute crises and suicidality.

DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2017-2018) for week ending 03/24/18: The CDC reported decreases in influenza activity. Sixteen states continue to experience widespread flu activity. Four states reported high activity, 8 states reported moderate activity, and New York City as well as 38 states reported low or minimal activity. The number of influenza B viruses reported exceeded influenza A viruses. Flu activity may remain elevated for a number of weeks. Availability of brand and generic oseltamivir (Tamiflu®) capsules and oral powder for suspension continues. In addition, the FDA warned the public of the potential for fraudulent and unapproved flu treatments and reminds that there are no over-the-counter (OTC) drugs to prevent or cure the flu.
- A new dosing regimen was granted for nivolumab (Opdivo®) to be given as 480 mg IV every 4 weeks infused over 30 minutes. This new dosing regimen applies to all current indications for nivolumab, except microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer. Nivolumab may still be administered as 240 mg IV every 2 weeks for all indications.
- Boehringer Ingelheim has made a business decision to discontinue distribution of Twynsta® (telmisartan/amlodipine) 80 mg/10 mg fixed-dose tablets. All other strengths will remain available; generic versions of the 80 mg/10 mg tablet are available.
- The FDA approved the first direct-to-consumer (DTC) test for 3 breast cancer genes. The Personal Genome Service Genetic Health Risk (GHR) Report tests for specific BRCA1/BRCA2 breast cancer gene mutations. The specific BRCA1/BRCA2 breast cancer gene mutations detected by this test are most common in people of Ashkenazi Jewish descent; however, these mutations are among over 1,000 known BRCA mutations and are not the most common BRCA1/BRCA2 mutations in the general population. Consumers collect a saliva sample to perform a DNA analysis. Since the test only detects 3 genetic mutations in the BRCA1/BRCA2 breast cancer gene, a negative result does not rule out other BRCA mutations that may increase the risk of breast, ovarian, or prostate cancer. Moreover, most cancer cases are not due to hereditary gene mutations, rather they may be caused by a wide range of factors, such as smoking, obesity, and hormone use. The test will be distributed by 23andMe®.
- Sanofi received approval for Toujeo® Max SoloStar® (insulin glargine 300 units/mL) 3 mL prefilled pen. The new pen delivers up to 160 units per injection, in 2 unit increments, while the original 1.5 mL (450 units) Toujeo Solostar pen provides up to 80 units per injection in 1 unit increments. The 3 mL pen is recommended for patients requiring at least 20 units per day. Launch is expected in the third quarter of 2018.

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

- **April 2018:** trastuzumab (Herzuma); biosimilar to Genentech's Herceptin®; IV anti-HER2 antibody; HER2+ breast, gastric, and gastroesophageal cancers; Celltrion/Teva.
- **April 2018:** trastuzumab (PF05280014); biosimilar to Genentech's Herceptin; IV anti-HER2 antibody; HER2+ breast, gastric, and gastroesophageal cancers; Pfizer.
- **April-May 2018:** filgrastim; biosimilar to Amgen's Neupogen®; injectable leukocyte growth factor; neutropenia/leukopenia; Adello.
- **April-May 2018:** rituximab (Rixathon); biosimilar to Genentech's Rituxan®; IV CD20-directed cytolytic antibody; non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis, antineutrophil cytoplasmic antibodies-associated vasculitis; Novartis/Sandoz.
- **April 6, 2018:** Rubraca®; rucaparib; oral poly (ADP-ribose) polymerase inhibitor; recurrent ovarian cancer (platinum complete/partial response); Clovis.
- **April 13, 2018:** Ryplazim; plasminogen (human); IV enzyme replacement; hypoplasminogenemia; Prometic Life.
- **April 17, 2018:** burosumab; subcutaneous (SC) fibroblast growth factor inhibitor; X-linked hypophosphatemia; Ultragenyx.
- **April 17, 2018:** Tavalisse; fostamatinib; oral Syk kinase inhibitor; immune thrombocytopenic purpura; Rigel.
- **April 24, 2018:** Samsca®; tolvaptan; oral vasopressin antagonist; polycystic kidney disease; Otsuka.
- **April 28, 2018:** Amitiza®; lubiprostone capsule; oral gastrointestinal chloride channel agonist; functional constipation in ages 6-17 years; Mallinckrodt.
- **April 30, 2018:** Azedra; ultratrace iobenguane I-131; IV electron transport inhibitor; neuroendocrine tumors; Progenics.
- **April 30, 2018:** Kymriah™; tisagenlecleucel-T: IV chimeric antigen receptor T cell therapy; diffuse large B cell lymphoma; Novartis.
- **May 4, 2018:** Andexxa; andexanet alfa; IV Factor Xa inhibitor antidote; anticoagulant reversal; Portola.
- **May 4, 2018:** elagolix; oral luteinizing hormone releasing hormone (LHRH); endometriosis; Abbvie.
- **Quarter 2, 2018:** lofexidine; oral alpha adrenergic agonist; substance use disorder; US Worldmeds.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
amantadine extended-release (ER)	Osmolex ER™	The FDA approved the Orphan drug amantadine ER (Osmolex ER) for the treatment of Parkinson's disease and for the treatment of drug-induced extrapyramidal reactions in adults. The recommended starting dose is 129 mg once daily, taken in the morning. The dose may be increased on a weekly basis to a maximum of 322 mg daily. The oral tablets, which contain an ER core surrounded by an immediate-release layer, are approved in 129 mg, 193 mg, and 258 mg strengths.	Osmotica	505(b)(2) NDA approval 02/16/2018
ibrutinib	Imbruvica®	Ibrutinib (Imbruvica), a kinase inhibitor, is now approved in a tablet formulation in 140 mg, 280 mg, 420 mg, and 560 mg strengths. The Orphan drug is also available in 70 mg and 140 mg oral capsules; however, the 140 mg capsule will no longer be available after May 15, 2018. The tablets and capsules carry the same indications for use in select adults with chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström's macroglobulinemia, chronic graft versus host disease, mantle cell lymphoma, and marginal zone lymphoma. Recommended daily dose is 420 mg or 560 mg, depending upon the diagnosis being treated. The new formulation will allow for once daily dosing using a single tablet.	Pharmacyclics	NDA Priority approval 02/16/2018
luliconazole	Luzu™	The Agency approved expanding the use of luliconazole 1% cream (Luzu), a topical antifungal, in patients ≥ 12 years of age for the treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*. It was initially approved for use in adults. Luliconazole is applied to affected areas once daily for 1 to 2 weeks, depending upon diagnosis.	Medicis	sNDA approval 02/20/2018
acetaminophen/ benzhydrocodone	Apadaz™	Approval was given to Apadaz, the fixed-dose combination of acetaminophen (325 mg) and benzhydrocodone (6.12 mg), a prodrug of the opioid agonist hydrocodone. It is indicated for the short-term management (no more than 14 days) of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Apadaz was approved as a Scheduled II controlled substance. The immediate-release oral tablet is dosed as 1 to 2 tablets every 4 to 6 hours as needed for pain; do not exceed 12 tablets in 24 hours.	Kempharm	505(b)(2) NDA Priority approval 02/23/2018
somatropin	Norditropin®	Norditropin, a somatropin product, has new indications for the treatment of pediatric patients with idiopathic short stature (ISS) and growth failure due to Prader-Willi syndrome (PWS). The weekly dosage for ISS is up to 0.47 mg/kg and for PWS is 0.24 mg/kg, divided into equal SC doses given 6 or 7 days per week.	Novo Nordisk	sNDA approval 02/23/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
abemaciclib	Verzenio™	Abemaciclib (Verzenio), a kinase inhibitor, received a third FDA approved indication for use in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy in postmenopausal women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) advanced or metastatic breast cancer. The recommended dose in combination with an AI is 150 mg orally twice daily, continued until disease progression or unacceptable toxicity occurs. It is available in 50 mg, 100 mg, 150 mg, and 200 mg tablets.	Eli Lilly	NDA Priority approval 02/26/2018
lamivudine/ tenofovir disoproxil fumarate	Cimduo™	Cimduo (lamivudine and tenofovir disoproxil fumarate [TDF]) gained approval for the treatment of HIV-1 infection in combination with other ARV agents in adult and pediatric patients weighing ≥ 35 kg. It contains 2 nucleo(t)side reverse transcriptase inhibitors. Labeling carries a boxed warning for the risk of acute exacerbations of HBV infection. The dose is 1 oral tablet daily regardless of food and is approved as a fixed-dose tablet containing 300 mg lamivudine and 300 mg TDF. Launch of Cimduo is expected in the second quarter of 2018.	Mylan	NDA Priority approval 02/28/2018
lidocaine	Ztlido™	A transdermal anesthetic formulation, Ztlido (lidocaine), was approved for the treatment of pain associated with post-herpetic neuralgia. The patch contains 1.8% of lidocaine and was designed using an adhesive that allows the patch to remain on the skin for 12 hours. Up to 3 patches are applied to the most painful site for up to 12 hours in a 24-hour period. One Ztlido patch provides the same lidocaine exposure as a single Lidoderm® (lidocaine 5%) patch.	Scilex	505(b)(2) NDA approval 02/28/2018
ciprofloxacin	Otiprio®	The fluoroquinolone otic suspension, ciprofloxacin 6% (Otiprio), received a new indication to treat patients ≥ 6 months of age with acute otitis externa (AOE) due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. It is the first single-dose antibacterial approved by the FDA for treating AOE and is administered only by an HCP as a single 0.2 mL (12 mg) dose into the external ear canal of each affected ear. Otiprio was already approved for the treatment of patients ≥ 6 months of age with bilateral otitis media with effusion who are undergoing tympanostomy tube placement.	Otonomy	sNDA approval 03/02/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
lurasidone	Latuda®	Lurasidone (Latuda) was FDA approved for a new indication as monotherapy for the treatment of major depressive episode associated with bipolar I disorder (bipolar depression) in patients 10 to 17 years of age. The recommended starting dose is 20 mg once daily and can be increased up to 80 mg per day. The atypical antipsychotic is also approved for the treatment of adults with bipolar depression as monotherapy and as an adjunct to lithium or valproate, and for the treatment of schizophrenia in patients ≥ 13 years of age. Patients should be monitored for clinical worsening and emergence of suicidal thoughts and behaviors as described in the boxed warning.	Sunovion	sNDA approval 03/05/2018
immune globulin subcutaneous (human) 20% liquid (IGSC)	Hizentra®	The FDA approved a new indication for immune globulin SC (human) 20% liquid (Hizentra) for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment. A Hizentra dosage of 0.2 g/kg body weight once weekly may be initiated 1 week after the last immune globulin intravenous (IGIV) infusion.	CSL Behring	sBLA approval 03/15/2018
brentuximab vedotin	Adcetris®	The CD30-directed antibody-drug conjugate, brentuximab vedotin (Adcetris), received Breakthrough therapy designation and an expanded indication for the treatment of adults with previously untreated stage III or IV classical Hodgkin lymphoma (cHL) in combination with chemotherapy. The recommended dose is 1.2 mg/kg, up to a maximum of 120 mg, given IV over 30 minutes every 2 weeks for a maximum of 12 doses or until disease progression or unacceptable toxicity occurs. Brentuximab vedotin is also approved to treat select patients with cHL after relapse or post stem cell transplant or anaplastic large cell lymphoma (ALCL).	Seattle Genetics	sBLA approval 03/20/2018
tildrakizumab-asmn	Ilumya™	The interleukin-23 antagonist tildrakizumab-asmn (Ilumya) gained approval for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Approved as 100 mg/mL injectable solution, the recommended dose is 100 mg administered SC by an HCP at weeks 0 and 4 and every 12 weeks thereafter.	Sun	BLA approval 03/21/2018

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