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MRx CLINICAL ALERT

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SPOTLIGHT: HEPATITIS C VIRUS (HCV) GUIDELINE UPDATE

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) updated their guidance for testing, managing, and treating HCV infection. The 2 new fixed-dose combination pangenotypic direct-acting antivirals (DAAs) glecaprevir/pibrentasvir (Mavyret™) and sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) have been incorporated into the guidelines. AASLD/IDSA includes Mavyret as one of their recommended regimens in patients with or without compensated cirrhosis and the following characteristics: genotype (GT) 1-6 and treatment-naïve; GT1 and prior treatment with either pegylated-interferon/ribavirin (PEG-IFN/RBV) ± an NS3 protease inhibitor (PI), or a non-NS5A inhibitor / sofosbuvir-containing regimen; GT2 with prior failure of PEG-IFN/RBV ± sofosbuvir; and GT4-6 with prior failure of PEG-IFN/RBV. Vosevi is included in the recommended regimens, regardless of compensated cirrhosis status, in patients with: GT1 and prior failure of an NS5A inhibitor; GT1a and prior failure of a non-NS5A inhibitor / sofosbuvir-containing regimen; and GT3-6 and prior failure of a DAA. Vosevi is also recommended in GT3 patients with compensated cirrhosis who failed prior PEG-IFN/RBV therapy.

A new section titled "HCV Resistance Primer" has been added that discusses polymorphism resistance associated substitutions (RAS) and thresholds of clinical relevance. AASLD/IDSA recommends RAS testing prior to treatment with elbasvir/grazoprevir (Zepatier®), ledipasvir/sofosbuvir (Harvoni®), sofosbuvir/velpatasvir (Epclusa®), and daclatasvir (Daklinza®) + sofosbuvir (Sovaldi®) in select patients.

New sections were also added concerning HCV treatment in unique populations, such as kidney transplant recipients, pregnant women, and children. In kidney transplant patients, regardless of presence of compensated cirrhosis or prior treatment, Mavyret is recommended for GT1-6 and Harvoni is recommended for GT1 and GT4. For pregnant women, AASLD/IDSA recommends HCV screening when known or suspected risks for HCV infection are present. When feasible, antiviral therapy should be provided prior to considering pregnancy to reduce the risk of HCV transmission to future offspring; however, due to limited data in this population, HCV treatment during pregnancy is not recommended. All children born to HCV-infected women should be tested for HCV at or after 18 months of age. Children who are anti-HCV positive after 18 months should be tested with an HCV RNA assay after age 3 years to confirm chronic HCV infection. In addition, siblings of children with mother-to-child transmission acquired chronic HCV should also be tested. All HCV-infected pediatrics ages ≥ 3 years should be treated with a DAA, if available for the child's age group, regardless of disease severity. However, deferring therapy until

IFN-free regimens are available is recommended for those ages 3 to 12 years with chronic HCV. Notably, only Harvoni or Sovaldi + weight-based RBV is recommended in select patients ≥ 12 years of age or weighing ≥ 35 kg. These are the only DAA products approved for use in pediatrics at this time.

HOT TOPIC: FDA APPROVES FIRST BIOSIMILAR FOR CANCER

On September 14, 2017, the Food and Drug Administration (FDA) approved Amgen's bevacizumab-awwb (Mvasi™) as a biosimilar to bevacizumab (Avastin®; Genentech). Bevacizumab-awwb is indicated for the treatment of metastatic colorectal cancer, non-squamous non-small cell lung cancer (NSCLC), glioblastoma, metastatic renal cell carcinoma, and persistent, recurrent, or metastatic cervical cancer. This is the first biosimilar approved by the FDA for the treatment of cancer. According to the FDA, a biosimilar is a biological product approved based on data demonstrating that it is *highly similar* to an FDA-approved biological agent, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Although bevacizumab-awwb (Mvasi) was approved as a biosimilar to bevacizumab (Avastin), these products are not considered interchangeable.

GUIDELINES TO TREAT CAR-T THERAPY ADVERSE EFFECTS

In August 2017, the FDA approved the first chimeric antigen receptor T cell (CAR-T) therapy, tisagenlecleucel (Kymriah™). A second, axicabtagene ciloleucel, is expected to be approved in November 2017. CAR-T therapy is designed to treat hematologic malignancies. With CAR-T therapy, a patient's T cells are collected, re-engineered, and infused back into the body to recognize and kill cancerous B cells. While these treatments hold great promise for patients with aggressive hematologic cancers, they come with serious, potentially life-threatening adverse effects. The most notable are cytokine-release syndrome (CRS) and neurotoxicity, also known as CAR-T cell-related encephalopathy syndrome (CRES). CRS is characterized by high fever, hypotension, hypoxia, and multi-organ toxicity; CRES may be evident by confusion, seizures, and encephalopathy. Rarely, fulminant hemophagocytic lymphohistiocytosis (HLH), also called macrophage-activation syndrome (MAS), has occurred.

The CARTOX Working Group, funded in part by the MD Anderson Cancer Center and the National Cancer Institute, proposed guidelines for managing these toxic effects, including pre-treatment, monitoring during and after CAR-T infusion, and identification, grading, and treatment of CRS and CRES. A baseline MRI should be performed to rule out central nervous system (CNS) disease. Hospitalization with close monitoring, including cardiac and neurologic assessments, is recommended for at least 7 days after CAR-T cell infusion, particularly in patients with high tumor burden. Seizure prophylaxis with oral levetiracetam for 30 days beginning the day of CAR-T infusion is recommended. Low-dose lorazepam or haloperidol may be used in agitated patients with careful monitoring. For temperature ≥ 38°C, perform blood and urine cultures and chest X-ray and treat with acetaminophen (preferred) or ibuprofen. If neutropenia is also present, begin empiric broad spectrum antibiotics. Utilize intravenous (IV) fluids to maintain adequate hydration and blood pressure; if persistent hypotension occurs, initiate low-dose vasopressors. Anti-interleukin-6 (IL-6) therapy with tocilizumab (Actemra®) or siltuximab (Sylvant®; off-label) is given according to the CRS, CRES, and HLH/MAS algorithms provided. Corticosteroids can be considered for patients at high risk of severe CRS (grade 3 or 4) or those with persistent grade 2 CRS despite anti-IL-6 therapy.

RISK OF KEYTRUDA® IN MULTIPLE MYELOMA PATIENTS

The FDA released a statement warning patients and healthcare providers about the risks of using the programmed death receptor-1 (PD-1) blocker, pembrolizumab (Keytruda; Merck), in combination with dexamethasone and an immunomodulatory agent (lenalidomide or pomalidomide) for the treatment of multiple myeloma. Of note, pembrolizumab is not approved for use in patients with multiple myeloma. The FDA statement was released after a review of interim data from 2 clinical trials (KEYNOTE-183 and KEYNOTE-185) for the treatment of multiple myeloma that found an increased risk of death for patients receiving pembrolizumab combined with an immunomodulatory agent. All patients in the trials have discontinued treatment with the agent, and trial enrollment has been suspended. This warning does not apply to patients receiving pembrolizumab for an FDA-approved indication, as the safety and efficacy of use in these conditions have been established. Patients taking pembrolizumab for an approved indication should continue taking their medication as prescribed.

The FDA is evaluating all ongoing clinical trials with anti-PD-1/PD-L1 agents in combination with immunomodulatory agents or in hematologic malignancies combined with other classes of drugs to determine whether this is a class effect.

DRUG INFORMATION **HIGHLIGHTS**

- Influenza update: For the 2017-2018 influenza season, the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend use of the annual flu shot for everyone ages ≥ 6 months. Either a trivalent or quadrivalent inactivated vaccine is recommended for use. The 2017-2018 trivalent vaccine contains: an A/Michigan/45/2015 (H1N1) pdm09-like virus; an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The 2017-2018 quadrivalent vaccine also contains a B/Phuket/3073/2013-like virus. The nasal spray flu vaccine (quadrivalent live attenuated influenza vaccine [LAIV]-4) should not be used during the 2017-2018 flu season. In addition, Afluria® Quadrivalent flu vaccine received an expanded indication for patients as young as 5 years (previously only for use in adults). Afluria Trivalent flu vaccine is also available for use in patients ≥ 5 years.
- The Drug Enforcement Agency (DEA) is proposing to remove naldemedine (Symproic®) from the schedules of the Controlled Substances Act (CSA) pursuant to a petition from the drug sponsor, Shionogi. Naldemedine is a peripherally acting mu-opioid antagonist indicated for the treatment of opioid-induced constipation in adults with chronic non-cancer pain. It is currently a Schedule II controlled substance because it can be derived from opium alkaloids. The basis for the DEA decision is that naldemedine has no potential for abuse and does not meet the finding for control under any CSA schedule, has a currently accepted medical use, and has no potential for physical or psychological dependence.
- The FDA expanded the indication for ipilimumab (Yervoy®), a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, to include select patients ≥ 12 years of age with melanoma. Dosage in adolescents is weight-based, given IV every 3 weeks for 4 doses.
- Zydus' pitavastatin magnesium oral tablet, Zypitamag, an HMG-CoA reductase inhibitor (statin), was approved to treat primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C). The once-daily product is approved as 1 mg, 2 mg, and 4 mg tablets.
- A recent study found the potassium-lowering agent sodium polystyrene sulfonate (Kayexalate®) binds to many orally-administered medications, which may decrease their effectiveness. In order to decrease this risk, the FDA is recommending to separate the dosing of sodium polystyrene sulfonate from other oral medications by ≥ 3 hours.
- Perampanel (Fycompa®) now has an expanded indication for use as monotherapy for the treatment of partial-onset seizures (POS), with or without secondarily generalized seizures, in epileptic patients ≥ 12 years of age. Perampanel is also approved for adjunctive treatment of POS and primary generalized tonic-clonic seizures in epileptic patients ≥ 12 years of age. Dosage is similar for all indications.
- Vimovo® (naproxen/esomeprazole magnesium) received an expanded indication in patients ≥ 12 years of age weighing ≥ 38 kg who require naproxen for the symptomatic relief of juvenile idiopathic arthritis (JIA). The recommended dose in this population is 1 tablet containing naproxen 375 mg/esomeprazole 20 mg twice daily; patients weighing > 50 kg may use the naproxen 500 mg/esomeprazole 20 mg tablet twice daily if additional relief is needed. Vimovo should not be used to treat acute pain and has not been studied for > 6 months in controlled trials.

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

- **October, 2017:** Lyrica CR; pregabalin controlled-release; oral anticonvulsant; postherpetic neuralgia, fibromyalgia; Pfizer.
- **Oct-Nov, 2017:** eptacog beta; IV recombinant coagulation factor VIIa; hemophilia A and B; LFB.
- **October 6, 2017:** Zilretta; intra-articular extended-release triamcinolone acetate; osteoarthritis of the knee; Flexion.
- **October 9, 2017:** MYL1401O; pegfilgrastim (biosimilar to Amgen's Neulasta®); SC leukocyte growth factor; chemotherapy-related neutropenia; Biocon/Mylan.
- **October 13, 2017:** Stelara®; ustekinumab; SC IL-12 and IL-23 inhibitor; plaque psoriasis in ages 12-17 years; Janssen.
- **October 21, 2017:** Simponi Aria®; golimumab; IV tumor necrosis factor (TNF)-alpha inhibitor; ankylosing spondylitis and psoriatic arthritis in adults; Janssen.
- **October 23, 2017:** Soliris®; eculizumab; IV complement inhibitor; myasthenia gravis, neuromyelitis optica; Alexion.
- **October 24, 2017:** Shingrix; IM herpes zoster vaccine; shingles prevention; GlaxoSmithKline.
- **October 25, 2017:** Varubi® (rolapitant); IV substance P/neruokinin 1 (NK1) receptor antagonist; chemotherapy-induced nausea and vomiting; Tesaro.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
fulvestrant	Faslodex®	Estrogen receptor antagonist fulvestrant (Faslodex) has been granted a new indication as monotherapy for the treatment of hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer in postmenopausal women not treated with endocrine therapy. This new indication joins existing indications in HR-positive advanced breast cancer in postmenopausal women with disease progression following endocrine therapy and HR-positive, HER2-negative advanced or metastatic breast cancer in combination with palbociclib in women with disease progression after endocrine therapy.	AstraZeneca	sNDA approval 08/25/2017
gemtuzumab ozogamicin	Mylotarg™	After voluntary removal from the market due to failure to verify clinical benefit and safety concerns, the Orphan drug gemtuzumab ozogamicin (Mylotarg) was approved for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia (AML) in adults and treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients ≥ 2 years. The recent approval includes a lower recommended dose, change in dosing schedule, and a broader patient population. Gemtuzumab ozogamicin, administered via IV infusion, employs weight-based dosing. Regimens are intermittent and based on indication and concomitant treatment.	Pfizer	BLA approval 09/01/2017
bosentan	Tracleer®	The endothelin receptor antagonist bosentan (Tracleer) received Orphan drug status and an expanded indication for use in patients ≥ 3 years of age with idiopathic or congential pulmonary arterial hypertension. A new dispersible tablet formulation for use in adults and pediatrics was also approved as a tutti frutti-flavored 32 mg strength.	Actelion	sNDA approval 09/05/2017
eslicarbazepine	Aptiom®	The anticonvulsant eslicarbazepine (Aptiom) gained an expanded indication to treat POS in patients 4 to 17 years of age, in addition to the existing indication of treating POS in adults. In pediatrics, it is given as a once-daily, weight-based dose and may be titrated according to response and tolerability.	Sunovion	sNDA approval 09/13/2017
brivaracetam	Briviact®	The FDA granted brivaracetam (Briviact), an oral anticonvulsant, approval for use as monotherapy in patients ≥ 16 years of age with POS; previously, it was indicated only as adjunct therapy. Dosage is similar for mono- and adjunctive therapy as 50 mg twice daily to start and titrated based on response and tolerability, not to exceed 200 mg per day.	UCB	sNDA approval 09/14/2017

ANDA=AbbreviatedNewDrugApplication;BLA=BiologicsLicenseApplication;NDA=NewDrugApplication;sBLA=SupplementalBiologicsLicenseApplication; sNDA = Supplemental New Drug Application

RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
copanlisib	Aliqopa®	A kinase inhibitor, copanlisib (Aliqopa), was granted Orphan drug designation and accelerated approval for the treatment of adults with relapsed follicular lymphoma (FL). Aliqopa is approved as a 60 mg lyophilized solid for reconstitution. It is administered via IV infusion over 1-hour on days 1, 8, and 15 of a 28-day treatment cycle.	Bayer	NDA Priority approval 09/14/2017
lanreotide	Somatuline® Depot	The somatostatin analog lanreotide (Somatuline Depot) received a new indication for the treatment of adults with carcinoid syndrome; when used, it reduces the frequency of short-acting somatostatin analogue rescue therapy. The recommended dose for this indication is 120 mg SC every 4 weeks. Lanreotide is also indicated to treat adults with acromegaly or gastroenteropancreatic neuroendocrine tumors.	Ispen	sNDA approval 09/15/2017
secnidazole	Solosec™	The FDA approved secnidazole (Solosec), a nitroimidazole antimicrobial, for the treatment of bacterial vaginosis in adult women. Approved as 2 g oral granules in unit-of-use foil packets, it is administered as 1 packet once daily. Granules are not intended to be dissolved in liquid, but may be sprinkled onto applesauce, yogurt, or pudding. Secnidazole was designated as a Qualified Infectious Disease Product. Availability is expected in the first quarter of 2018.	Symbiomix	NDA Priority approval 09/15/2017
fluticasone furoate/ umeclidinium/ vilanterol	Trelegy® Ellipta®	The first single-inhaler triple-therapy was granted FDA approval for the long-term maintenance treatment of chronic obstructive pulmonary disease (COPD). Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) is a fixed-dose combination of an inhaled corticosteroid, an anticholinergic, and a long-acting beta^2-adrenergic agonist. It is indicated in patients who are on a fixed-dose combination of fluticasone furoate/vilanterol (Breo® Ellipta) who require additional bronchodilation or for patients already taking umeclidinium (Incruse® Ellipta) and Breo Ellipta. Trelegy Ellipta is not indicated for the relief of acute bronchospasm or asthma. The inhaler provides 30 doses in 2 blister strips containing fluticasone furoate 100 mcg or umeclidinium/ vilanterol 62.5/35 mcg per blister. It is administered as 1 oral inhalation once daily.	GlaxoSmithKline	NDA approval 09/18/2017

ANDA=AbbreviatedNewDrugApplication;BLA=BiologicsLicenseApplication;NDA=NewDrugApplication;sBLA=SupplementalBiologicsLicenseApplication; sNDA = Supplemental New Drug Application

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