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MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

EDITORIAL STAFF

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HOT TOPIC: NEW GUIDELINES - VENOUS THROMBOEMBOLISM (VTE)

The American Society of Hematology (ASH) released the first 6 chapters of their clinical practice guidelines on VTE with an additional 4 chapters under development. Published chapters include diagnosis, prophylaxis in medical patients, optimal management of anticoagulation therapy, heparin-induced thrombocytopenia (HIT), and VTE in pediatrics and pregnant women. Key "strong" recommendations are discussed below.

For hospitalized medical patients, the guidelines recommend risk assessment for VTE and bleeding to help guide decisions regarding VTE prophylaxis. For patients who are at high bleeding risk but require VTE prophylaxis, ASH prefers mechanical prophylaxis. However, in patients with a high VTE risk but acceptable bleeding risk, the guidelines prefer anticoagulants. When anticoagulants are used for VTE prophylaxis, low molecular weight heparin (LMWH) is preferred over direct oral anticoagulants (DOACs). Extending pharmacological prophylaxis post hospital discharge is not advised.

Strategies surrounding diagnosis of VTE focus on establishing an accurate diagnosis while avoiding unnecessary, more invasive testing. In patients with suspected VTE who have a low pre-test probability for VTE, the guidelines recommend a D-dimer test as the initial strategy to rule out a diagnosis of VTE; if results are negative, no further testing is required. For patients at high VTE risk, imaging is warranted. For patients with suspected pulmonary embolism (PE) who require additional testing, clinicians should use a ventilation-perfusion scan (preferred) or computed tomography pulmonary angiography.

For patients on vitamin K antagonist (VKA) therapy and at low to moderate risk of recurrent VTE, ASH recommends against periprocedural bridging with LMWH or unfractionated heparin (UFH) when interruption of VKA therapy for invasive procedures is required. While managing anticoagulation therapy is complex for patients on maintenance VKA therapy, the guidelines recommend patient self-testing (PST) of international normalized ratio (INR) and self-adjustment of VKA dose in patients who are willing and have demonstrated ability to perform this task.

Heparin-induced thrombocytopenia (HIT) is a rare and serious adverse drug reaction that is often misdiagnosed. In patients with suspected HIT, ASH recommends using the clinical 4Ts scoring system to estimate the probability of HIT. Patients with an intermediate or high 4Ts score should then receive an immunoassay. In patients with acute HIT, ASH recommends non-heparin anticoagulants; suggested options include argatroban, bivalirudin, danaparoid, fondaparinux, or a DOAC.

In pregnant women with VTE, ASH recommends use of LMWH over UFH. Although ASH states that more research is needed in pediatric patients, they recommend anticoagulation therapy in

those symptomatic for VTE, with suggested preference of LMWH or VKA. Nonfunctioning or unneeded central venous catheters should be removed after start of anticoagulation therapy. Topics for forthcoming chapters include treatment, cancer, thrombophilia, and prophylaxis in surgical patients.

AAD REVISES MELANOMA GUIDELINES

The American Academy of Dermatology (AAD) updated their 2011 treatment guidelines for the management of primary cutaneous melanoma, incidence of which continues to increase each year. The publication provides recommendations regarding the type of biopsies used to optimize accurate diagnosis and guide management. Accurate staging is also critical, which may incorporate sentinel lymph node biopsy in some patients. Surgery remains the cornerstone of cutaneous melanoma treatment.

The guidelines offer insight on nonsurgical interventions, although these should only be considered if surgery is impractical or contraindicated and for cases of melanoma in situ, lentigo maligna (MIS, LM), which is characterized by larger tumors on the face, scalp, and ears in older patients, resulting in these patients being poor surgical candidates. As a result, off-label use of topical imiquimod may be considered for adjunctive therapy following optimal surgical excision or when surgery is not possible. Radiation therapy may also be considered as second-line therapy for MIS, LM type; however, its use is uncommon in the United States (US).

The guidelines also provide recommendations on the management of dermatologic toxicities of treatment, such as those experienced with B-Raf proto-oncogene (BRAF) inhibitors (e.g., dabrafenib, vemurafenib) and checkpoint inhibitors (e.g., atezolizumab, ipilimumab, nivolumab, pembrolizumab). More than 90% of patients treated with BRAF inhibitor monotherapy will develop cutaneous toxicity, and approximately 40% of those treated with checkpoint inhibitors will develop autoimmune-related skin disorders. Notably, BRAF inhibitor use is generally combined with mitogen-activated protein kinase (MEK) inhibitors (e.g., cobimetinib, trametinib), which limits skin toxicity. The frequency of monitoring and management is dependent on the treatment agent; however, a dermatologic assessment every 2 to 4 weeks for the first 3 months of BRAF inhibitor monotherapy is recommended for patients with numerous squamoproliferative neoplasms and within the first month of therapy and as needed for those with adverse skin effects using checkpoint inhibitors.

FDA ALERT ON MS AGENT

The US Food and Drug Administration (FDA) is warning that rare but serious cases of stroke or arterial dissection have occurred in patients with multiple sclerosis (MS) after receiving alemtuzumab (Lemtrada®). Symptoms occurred within 1 to 3 days of taking alemtuzumab. Patients should be warned to seek immediate medical care if they experience stroke-like symptoms.

BEHAVIORAL HEALTH CORNER

ICER EVALUATES EXTENDED-RELEASE (ER) MEDICATIONS FOR OPIOID USE DISORDER (OUD)

The Institute for Clinical and Economic Review (ICER) released an evidence report assessing the comparative clinical effectiveness and value of ER medications for the treatment of OUD, including buprenorphine implant (Probuphine®), naltrexone ER injection (Vivitrol®), and buprenorphine ER injections (Braeburn's investigational CAM2038 and Sublocade™).

Notably, ICER determined that compared to generic sublingual (SL) buprenorphine/naloxone, data for Probuphine are inconclusive because the patients studied may not mirror the general population expected to be candidates for these treatments. Vivitrol has outcomes similar to buprenorphine/naloxone. Limited evidence suggests that CAM2038 may provide better outcomes than buprenorphine/naloxone. No judgement of Sublocade is possible due to lack of comparative trials.

Regarding value, ICER found that, compared to generic SL buprenorphine/naloxone, Probuphine, Vivitrol, and CAM2038 can result in marginal differences in quality-adjusted life years (QALYs), but they have universally higher costs. Limitations of the report include failure to model re-use of medication-assisted therapy for patients who have relapsed or provide insight into the specific drug of choice for illicit use, which may be relevant in this space.

ICER stresses that OUD is a chronic disease requiring long-term treatment and urges stakeholders to lessen the stigma surrounding the condition. Pricing of ER products should parallel their added benefit. Restrictions to prescribing and accessing ER medications should be eliminated.

DRUG INFORMATION **HIGHLIGHTS**

- The intermittent shortage of epinephrine auto-injectors persists nationwide in the US. Backorders with periodic shipments to distributors continue for Impax's authorized generic (AG) versions of the discontinued Adrenaclick® and Mylan's Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and their respective AGs. Supply stabilization of Mylan's product was expected by the end of 2018 but a new resolution date is not available. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Teva's generic version of Epipen has entered the US market and is available in limited supply; additional supply plus launch of its generic of Epipen Jr are expected in 2019. Adamis's Symjepi® 0.3 mg and 0.15 mg have not entered the US market.
- Flu Season Update (2018–2019): The Centers for Disease Control and Prevention (CDC) reported increased influenza activity during the week ending 12/22/18. In the US, New York City and 9 states reported high activity, 7 states and Puerto Rico reported moderate activity, while the remainder of the country reported low or minimal activity. The influenza A(H1N1)pdm09 virus was reported most commonly. No nationwide shortages have been reported of oral influenza antivirals.
- Tris Pharma voluntarily recalled 3 lots of Infants' Ibuprofen Concentrated Oral Suspension, USP 50 mg/1.25 mL to the retail level. Affected product potentially contains higher than stated concentrations of ibuprofen. Infants may be more susceptible to a higher potency level of drug and may be at higher risk of permanent non-steroidal anti-inflammatory drug (NSAID)-associated renal injury. To date, there have been no reports of adverse events related to this recall. Affected product was packaged in 0.5 oz bottles and sold as Equate (Walmart), CVS Health, and Family Wellness (Family Dollar).
- On December 14, 2018, the FDA approved trastuzumab-pkrb (Herzuma®) by Teva/Celltrion as the second biosimilar to Genentech's trastuzumab (Herceptin®) for the treatment of HER2-positive breast cancer.
- The FDA approved a new strength of tocilizumab (Actemra®) as a 162 mg/0.9 mL single-dose prefilled autoinjector (ACTPen™) for subcutaneous (SC) use.
- The label for enasideni (Idhifa®), indicated to treat acute myeloid leukemia (AML), carries a warning about the risk of differentiation syndrome; however, the FDA is warning that signs and symptoms of differentiation syndrome may not be recognized. Differentiation syndrome is a side effect which may be life-threatening or fatal if not treated quickly and appropriately. Symptoms including fever, cough, shortness of breath, peripheral edema with rapid weight gain, bone pain, and dizziness. Healthcare providers (HCPs) are reminded of the need for early recognition and aggressive management of differentiation syndrome to lessen the likelihood of serious illness and death.
- New voluntary nationwide consumer-level recalls of antihypertensive medications were issued due to trace levels of a probable human carcinogen, N-nitrosodiethylamine (NDEA). Torrent is voluntarily recalling 2 lots of losartan potassium tablets, USP. Mylan expanded its recall to include all lots of valsartan-containing products within expiry; this includes amlodipine/valsartan, valsartan tablets, and valsartan/hydrochlorothiazide (HCTZ) tablets. Aurobindo is recalling 2 lots of valsartan tablets, 26 lots of amlodipine/valsartan tablets, and 52 lots of valsartan/HCTZ tablets.
- Allergan will discontinue the antihypertension medication Byvalson® (nebivolol/valsartan). No generic versions are available.
- Pragma Pharmaceuticals announced discontinuation of Moxatag® (amoxicillin) 775 mg tablets, indicated to treat tonsillitis and pharyngitis.
- Based on a business decision, Teva will discontinue both strengths of Orap® (pimozide) tablets; generic versions of the antipsychotic medication are available.

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

- **January 2019:** romosozumab; SC sclerostin inhibitor; osteoporosis; Amgen.
- **January 14, 2019:** Cabometyx®; cabozatinib; oral tyrosine kinase inhibitor; hepatocellular carcinoma (HCC); Exelixis.
- **January 18, 2019:** sactuzumab govitecan; intravenous (IV) anti-trop2 antibody; breast cancer; Immunomedics.
- **January 29, 2019:** apomorphine; SL dopamine receptor agonist; Parkinson's disease motor fluctuation; Sumitomo Dainippon.
- **January 30, 2019:** cladribine; oral antimetabolite; relapsing-remitting MS; Merck.
- **January 31, 2019:** samidorphan/buprenorphine; SL opioid agonist/partial agonist; major depressive disorder; Alkermes.
- **February 06, 2019:** caplacizumab; IV/SC antithrombotic; thrombotic thrombocytopenic purpura (TTP); Sanofi.

RECENT FDA APPROVALS

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs
glasdegib (Daurismo™) Pfizer	• NDA approval 11/21/2018; Orphan Drug; Priority Review • Indicated for use in combination with low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in patients ≥ 75 years old or who have comorbid conditions that preclude the use of intensive chemotherapy • Hedgehog pathway inhibitor • Oral tablets: 25 mg and 100 mg • Recommended dose is 100 mg orally once daily • Boxed warning advises of embryo-fetal death or severe birth defects
larotrectinib (Vitrakvi®) Loxo	• NDA approval 11/26/2018; Accelerated Approval; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated for the treatment of adult and pediatric patients with solid tumors that (1) have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, (2) are metastatic or surgical resection is likely to result in severe morbidity, and (3) have no satisfactory alternative treatments or have progressed following treatment » An FDA-approved test to detect NTRK gene fusion is not currently available » Continued approval may depend on results of confirmatory trials • Tropomyosin receptor kinase (TRK) inhibitor • Approved as 25 mg and 100 mg oral capsules and 20 mg/mL oral solution • Recommended dosage: » Adult and pediatric patients with body surface area (BSA) ≥ 1 m^2 is 100 mg twice daily » Pediatric patients with BSA < 1 m^2 is 100 mg/m^2 orally twice daily » Continue therapy until disease progression or unacceptable toxicity occur
amifampridine (Firdapse®) Catalyst	• NDA approval 11/28/2018; Breakthrough Therapy; Orphan Drug; Priority Review • Indicated for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults • Voltage-gated potassium channel blocker • Oral tablet: 10 mg, functionally scored • Recommended starting dosage is 15 mg to 30 mg orally daily in divided doses (3 to 4 times daily); dosage can be increased by 5 mg daily every 3 to 4 days; maximum dose of 80 mg daily (maximum single dose is 20 mg) • Product launch is expected in early Q1, 2019
gilteritinib (Xospata®) Astellas	• NDA approval 11/28/2018; Orphan Drug; Priority Review • Indicated for the treatment of adult patients who have relapsed or refractory AML with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test; an expanded indication was also approved for a companion diagnostic, to include use with gilteritinib • Multi-kinase inhibitor affective against FLT3 and AXL • Oral tablet: 40 mg • Recommended dose is 120 mg (3 tablets) once daily for a minimum of 6 months unless disease progression or unacceptable toxicity occur
dexamethasone (Dextenza®) Ocular Therapeutix	• NDA approval 12/03/2018 • Corticosteroid indicated for the treatment of ocular pain following ophthalmic surgery • Ophthalmic insert containing a 0.4 mg dose of dexamethasone • Dextenza is inserted into the lower lacrimal punctum canaliculus by a HCP; a single dose delivers 0.4 mg dexamethasone for up to 30 days; the insert is resorbable and does not require removal

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; Q = Quarter; 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

DRUG NAME MANUFACTURER	DESCRIPTION
	New Drugs *continued*
itraconazole (Tolsura™) Mayne	• NDA approval 12/11/2018 • Indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised adults: blastomycosis histoplasmosis, and aspergillosis (in patients intolerant of or refractory to amphotericin B) » Not indicated to treat onychomycosis » Not interchangeable or substitutable for other itraconazole products • Azole antifungal • Oral capsule: 65 mg using SUBA (Super-BioAvailable) drug delivery • Recommended dosage is 130 mg to 260 mg daily with food; see prescribing information for dosing in life-threatening situations • Boxed warnings for congestive heart failure and drug interactions • Product launch is expected in January 2019
prucalopride (Motegrity™) Shire	• NDA approval 12/14/2018 • Indicated for the treatment of chronic idiopathic constipation (CIC) in adults • Serotonin-4 (5-HT_4) receptor agonist • Oral tablets: 1 mg and 2 mg • Recommended dosage is 2 mg once daily; 1 mg once daily is recommended in patients with severe renal impairment • Product launch is expected in 2019
calaspargase pegol-mknl (Asparlas™) Servier	• BLA approval 12/20/2018; Orphan Drug • Indicated as part of a multi-agent chemotherapeutic regimen for the treatment of acute lymphoblastic leukemia (ALL) in patients ages 1 month to 21 years • Asparagine specific enzyme • Injection: 3,750 units/5 mL single-dose vial (SDV) for further dilution • Recommended dose is 2,500 units/m^2 IV no more frequently than every 21 days
levodopa (Inbrija™) Acorda	• NDA approval 12/21/2018 • Indicated for the intermittent treatment of OFF episodes (motor fluctuations) in patients with Parkinson's disease treated with carbidopa/levodopa • Aromatic amino acid • Inhalation powder: capsules contain 42 mg levodopa; for use with the Inbrija inhaler only • Inhale the contents of 2 capsules (84 mg) as needed for OFF symptoms, up to 5 times daily (maximum daily dose is 420 mg); for oral inhalation only, do not swallow Inbrija capsule • Availability is expected in Q1, 2019 through specialty pharmacies
ravulizumab-cwvz (Ultomiris™) Alexion	• BLA approval 12/21/2018; Orphan Drug; Priority Review • Indicated for the treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH) • Complement inhibitor • Injection: 300 mg/30 mL SDV • Recommended dosing is weight-based as described in the product label • Boxed warnings for serious meningococcal infections; available only through Risk Evaluation and Mitigation Strategy (REMS) restricted program

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RECENT FDA APPROVALS continued

DRUG NAME MANUFACTURER	DESCRIPTION
	Expanded Indications
brentuximab vedotin (Adcetris®) Seattle Genetics	• sBLA approval 11/16/2018; Breakthrough Therapy; Priority Review • Indicated in combination with CHP chemotherapy (cyclophosphamide, doxorubicin, prednisone) for adults with previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T cell lymphomas (PTCL), including angioimmunoblastic T cell lymphoma and PTCL not otherwise specified • Recommended dose is 1.8 mg/kg up to a maximum of 180 mg in combination with chemotherapy; administer every 3 weeks with each cycle of chemotherapy for 6 to 8 doses
venetoclax (Venclexta®) Genentech	• sNDA approval 11/21/2018; Accelerated Approval; Breakthrough Therapy; Priority Review • Indicated in combination with a hypomethylating agent (azacitidine or decitabine) or low-dose cytarabine (LDAC) for the treatment of patients with newly-diagnosed AML who are ≥ 75 years old or have comorbidities that preclude use of intensive induction chemotherapy » Continued approval may depend on results of confirmatory trials • Dosing of the medication requires a ramp-up approach: 100 mg on day 1; 200 mg on day 2; 400 mg on day 3; thereafter, 400 mg when given in combination with azacitidine or decitabine or 600 mg when given in combination with LDAC; continue until disease progression or unacceptable toxicity occur
atezolizumab (Tecentriq®) Genentech	• sBLA approval 12/06/2018; Priority Review • Indicated in combination with bevacizumab, paclitaxel, and carboplatin for the first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations • Recommended dose of atezolizumab is 1,200 mg IV over 60 minutes followed by bevacizumab, paclitaxel, and carboplatin every 3 weeks for a maximum of 4 to 6 cycles of chemotherapy; thereafter, administer atezolizumab 1,200 mg IV, followed by bevacizumab, every 3 weeks until disease progression or unacceptable toxicity; atezolizumab infusion may be delivered over 30 minutes if initial 60 minute infusion is tolerated
tenofovir disoproxil fumarate (Viread®) Gilead	• sNDA approval 12/11/2018 • Indication for the treatment of chronic hepatitis B virus (HBV) infection was expanded to include patients 2 to 11 years of age weighing ≥ 10 kg • Recommended dose for patients unable to swallow a tablet and weighing ≥ 10 kg is 8 mg/kg oral powder (maximum of 300 mg) taken once daily with food; dosing for patients able to swallow a tablet and ≥ 17 kg is 1 tablet (150 mg, 200 mg, 250 mg, or 300 mg based on body weight) once daily without regard to food
romiplostim (Nplate®) Amgen	• sBLA approval 12/14/2018; Orphan Drug • Indication for the treatment of immune thrombocytopenia (ITP) for ≥ 6 months with insufficient response to corticosteroids, immunoglobulins, or splenectomy was expanded to include patients as young as 1 year of age • Recommended initial dose is 1 mcg/kg; dose is adjusted based on platelet count response
pembrolizumab (Keytruda®) Merck	• sBLA approval 12/19/2018; Accelerated Approval; Breakthrough Therapy; Priority Review • Indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma • Recommended dose in adults is 200 mg and pediatrics is 2 mg/kg (up to 200 mg) given IV over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months if no disease progression

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References:

aad.org cdc.gov fda.gov hematology.org icer-review.org