AUGUST 2017

MRx CLINICAL ALERT

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HOT TOPIC: FDA APPROVES PANGENOTYPIC SALVAGE THERAPY FOR CHRONIC HEPATITIS C VIRUS (HCV)

On July 18, 2017, the Food and Drug Administration (FDA) granted priority approval to Gilead's breakthrough therapy, Vosevi™, for adults with chronic HCV infection who have failed prior direct-acting antiviral (DAA) treatment. It is indicated in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have genotypes (GT) 1, 2, 3, 4, 5, or 6 and had prior treatment with an NS5A inhibitor-containing HCV regimen or adults with GT 1a or 3 and prior treatment with a sofosbuvir-containing regimen that did not include an NS5A inhibitor. Vosevi is an oral fixed-dose, combination of the NS5B nucleotide polymerase inhibitor, sofosbuvir (400 mg), the HCV NS5A inhibitor, velpatasvir (100 mg), and the HCV NS3/4A protease inhibitor, voxilaprevir (100 mg). It is dosed as 1 tablet daily for 12 weeks.

Its approval was supported by 2 key clinical trials that evaluated 12 weeks of Vosevi in patients with HCV GT 1-6 without cirrhosis or with compensated cirrhosis who had failed prior DAA therapy. In POLARIS-1, Vosevi demonstrated an overall sustained viral response 12 weeks after completing therapy (SVR12) of 96% in patients with GT 1-6 who were previously treated with a regimen containing an NS5A inhibitor. In POLARIS-4, Vosevi was compared to Gilead's pangenotypic dual-combination DAA, Epclusa® (sofosbuvir/velpatasvir). This trial reported an overall SVR12 of 97% with Vosevi versus 88% with Epclusa in patients with GT 1, 2, or 3 who had failed a DAA-containing regimen that did not include an NS5A inhibitor; no benefit over Epclusa was seen in patients with GT 1b or 2. Vosevi was generally well tolerated. Common Vosevi adverse effects include headache, fatigue, diarrhea, and nausea.

Vosevi is the second pangenotypic agent to be approved in the United States (U.S.) and fills the unmet need as the first salvage therapy in DAA-experienced patients, including regimens that contain an NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir).

Abbvie is also seeking approval for its pangenotypic, once-daily, fixed-dose, combination of glecaprevir and pibrentasvir, including as an 8-week regimen in select patients. The expected date of FDA approval is August 18, 2017.

GUIDELINES ON THE PERI-OPERATIVE USE OF ANTIRHEUMATIC AGENTS

The American College of Rheumatology (ACR) and the American Association of Hip and Knee Surgeons published collaborative guidelines on the perioperative use of antirheumatic medications in adults undergoing select elective total hip or knee arthroplasty. The guidelines attempt to mitigate risk of infection and rheumatic disease flare before and after surgery in adults with rheumatoid arthritis (RA),

spondyloarthritis (SpA), juvenile idiopathic arthritis (JIA), or systemic lupus erythematosus (SLE).

Key recommendations include continuation of the traditional disease modifying antirheumatic drugs (DMARDs), methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. Surgery should be planned at the end of the specific dosing cycle for tumor necrosis factor (TNF) inhibitors and other biologics (e.g., abatacept, anakinra, belimumab, rituximab, tocilizumab, secukinumab, and ustekinumab). The exception to this is tofacitinib therapy, which should be interrupted 7 days pre-operatively. Further, medications to treat SLE (e.g., azathioprine, cyclosporine, mycophenolate mofetil, and tacrolimus) should be continued at the current dose throughout the peri-operative period in patients with severe disease and withheld at least 7 days prior to surgery in patients with less severe SLE. In general, biologic agents may be restarted approximately 14 days post-surgery, after the surgical wound has healed and suture/staples have been removed. In patients with RA, SpA, or SLE, continuation of the current daily dose of glucocorticoids is preferred over the use of supra-physiologic doses ("stress-dosing").

JOINT POSITION STATEMENT ON AROMATASE INHIBITOR-ASSOCIATED BONE LOSS (AIBL) ISSUED

Aromatase inhibitors (AIs) suppress estrogen levels beyond that attained from natural menopause, thereby leading to accelerated bone loss and an increased risk of fracture. A joint position statement by the International Osteoporosis Foundation and multiple other organizations recommends that all post-menopausal women with hormone-sensitive breast cancer who are initiating AI treatment be assessed for fracture risk and advised on the need for exercise and calcium and/or vitamin D supplementation. Bone-directed therapy is recommended throughout AI treatment for patients meeting the following criteria: T-score < -2 standard deviations (SD), T-score < -1.5 SD with 1 additional risk factor, or ≥ 2 risk factors. Examples of fracture risk factors include age > 65 years, low body mass index, family or personal fracture history, smoking, and long-term oral corticosteroid use. Patients with a T-score > -1.5 and no risk factors should be managed based on bone mineral density (BMD) loss within the first year and local osteoporosis guidelines. Subcutaneous (SC) denosumab (Prolia®) and intravenous (IV) zoledronic acid (Reclast®) are the preferred agents for the prevention and treatment of AIBL. Denosumab is preferred when fracture risk is the main concern, while zoledronic acid is favored when disease recurrence is a priority. They further state that emerging anti-cancer benefits from bisphosphonates offer additional rationale for their proactive use during adjuvant AI therapy. Finally, the consensus group recommends routinely assessing compliance and measuring BMD after 12 to 24 months of treatment.

BEHAVIORAL HEALTH CORNER

VAST-D: ANTIDEPRESSANT SWITCHING VERSUS AUGMENTATION IN MDD

Major depressive disorder (MDD) is a chronic, debilitating disorder affecting millions of adults annually in the U.S. Research shows that less than one-third of patients achieve remission with their first course of therapy.

The VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study was a multisite, single-blind trial including 1,522, primarily male (86.7%), U.S. Veterans Health Administration (VHA) patients with MDD that were unresponsive to at least 1 course of antidepressant treatment. Its primary objective was to compare the effectiveness and safety of switching to the norepinephrine-dopamine reuptake inhibitor, sustained-release (SR) bupropion (300 mg to 400 mg); or augmenting current treatment with either SR bupropion or the second-generation antipsychotic, aripiprazole (5 mg to 15 mg). The primary endpoint of remission was defined as a 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C_{16}) score ≤ 5 at 2 consecutively scheduled follow-up visits.

During the 12-week acute phase, aripiprazole augmentation led to a significantly higher rate of remission (28.9%) compared with switching to bupropion monotherapy (22.3%; relative risk [RR], 1.3; p=0.02); however, the difference was only modest. The differences in other remission comparisons were not significant. Response, as measured by ≥ 50% reduction in QIDS-C_{16} and by the Clinical Global Impression Improvement, was also significantly higher with aripiprazole augmentation than with bupropion monotherapy or augmentation. During the 24-week continuation phase, relapse rates were similar among all groups. Aripiprazole was associated with less anxiety and more weight gain compared to either bupropion regimen.

Notable limitations of VAST-D were a lack of generalizability due to the predominantly older male population and the limited medications studied.

DRUG INFORMATION **HIGHLIGHTS**

- Endo Pharmaceuticals has announced that they will voluntarily discontinue marketing of reformulated oxymorphone hydrochloride extended-release tablet (Opana® ER). The decision comes after a request by the FDA to remove the product from the market based on post-marketing data that demonstrated a significant shift in the route of abuse of Opana ER from nasal to injection following the product's reformulation. The shift in abuse has been associated with a serious outbreak of human immunodeficiency virus (HIV) and HCV, as well as cases of thrombotic microangiopathy.
- GlaxoSmithKline has made a business decision to stop the manufacture of the anticonvulsant medication, ezogabine (Potiga®). Discontinuation of the product is not related to its safety or efficacy.
- Novo Nordisk initiated a recall of 6 lots of NovoPen Echo® insulin cartridge holders after reports of cracking or breaking of the device if exposed to chemicals, such as cleaning agents. Use of a damaged device can result in delivery of a reduced dose of insulin; adverse events have been reported. Affected batches were distributed between 8/1/2016 and 6/22/2017. Novo Nordisk is alerting distributors, pharmacies, healthcare professionals, and patients of the recall and will replace affected product. Patients using an affected pen are advised to check their blood glucose level more frequently until they receive a new cartridge holder.
- Blinatumomab (Blincyto®) has received full FDA approval for the treatment of adults and children with relapsed or refractory B cell precursor acute lymphocytic leukemia (ALL), including Philadelphia chromosome-positive (Ph+) and -negative (Ph-) types. Previously, it was only given accelerated approval for Ph+ ALL.
- Abatacept (Orencia®) was granted a new indication for the treatment of adults with psoriatic arthritis (PsA). For PsA, it is dosed as a once-weekly 125 mg SC injection, without the need of an IV loading dose. Abatacept can be used with or without non-biologic DMARDs, but should not be used with TNF antagonists. Abatacept is also approved for adults with RA or JIA.
- 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 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 greater than 6 months in controlled trials.

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

- **August, 2017:** Besponsa; inotuzumab ozogamicin; IV anti-CD-22 antibody-cytotoxin conjugate; ALL; Pfizer.
- **August 10, 2017:** Heplisav-B; hepatitis B virus (HBV) vaccine; HBV infection prevention; Dynavax.
- **August 18, 2017:** Maviret; glecaprevir/pibrentasvir; oral DAA; chronic HCV genotypes 1-6; Abbvie.
- **August 24, 2017:** Nurelin; amantadine ER; oral N-methyl-D-aspartate (NMDA) receptor antagonist; drug-induced dyskinesia; Adamas.
- **August 24, 2017:** Vyzulta; latanoprostene bunod 0.024%; ophthalmic nitric oxide-releasing prostaglandin F2 alpha (PGF2α) analogue; glaucoma, ocular hypertension; Bausch & Lomb/Nicox.
- **August 25, 2017:** Victoza®; liraglutide; SC glucagon-like peptide-1 (GLP-1) agonist; cardiovascular risk reduction with type 2 diabetes; Novo Nordisk.
- **August 29, 2017:** KamRAB; rabies immune globulin (human); intramuscular (IM) post-exposure rabies treatment; Kamada.
- **August 30, 2017:** Austedo™; deutetrabenazine; oral vesicular monoamine transporter 2 (VMAT2) inhibitor; tardive dyskinesia; Teva.
- **August-September, 2017:** Vabomere; meropenem/vaborbactam; IV carbapenem beta-lactamase inhibitor; complicated urinary tract infection; The Medicines Company.
- **August-November, 2017:** QVAR® BAI; beclomethasone dipropionate; inhaled corticosteroid; asthma; Teva.
- **September 3, 2017:** trastuzumab (biosimilar to Genentech's Herceptin®); IV anti-HER2 antibody; breast cancer (HER+); Biocon/Mylan.
- **Quarter 3, 2017:** Lynparza®; olaparib; oral poly ADP-ribose polymerase (PARP) inhibitor; ovarian cancer (platinum-sensitive; maintenance); AstraZeneca.
- **Half 2, 2017:** allopurinol/lesinurad; oral xanthine oxidase inhibitor plus a uric acid reabsorption inhibitor; hyperuricemia; AstraZeneca/Ironwood.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
C1 esterase inhibitor (human)	Haegarda®	The FDA has approved a plasma-derived concentrate of C1 esterase inhibitor (human) (C1-INH), Haegarda, indicated for routine prophylaxis to prevent hereditary angioedema (HAE) attacks in adolescent and adult patients. It was granted Orphan Drug status by the FDA. It is made from human blood and carries a risk of infectious transmission, including viruses and, theoretically, Creutzfeldt-Jakob Disease (CJD) and its variant form (vCJD). After reconstitution, it is self-administered as 60 IU/kg SC twice weekly (every 3 or 4 days). Haegarda is available in single-use vials of 2,000 IU and 3,000 IU of C1-INH.	CSL Behring	FDA BLA approval 06/22/2017
rituximab and hyaluronidase (human)	Rituxan Hycela™	Rituximab/hyaluronidase (Rituxan Hycela) was approved for the treatment of the following conditions: previously untreated, relapsed/refractory, and non-progressing follicular lymphoma (FL); previously untreated diffuse large B cell lymphoma (DLBCL); and previously untreated and previously treated chronic lymphocytic leukemia (CLL). It provides a SC injection option to IV rituximab in combination with hyaluronidase after at least 1 full dose of IV rituximab has been administered. Boxed warnings include a potential risk of severe mucocutaneous reactions, HBV reactivation, and progressive multifocal leukoencephalopathy. It is approved as 1,400 mg/23,400 units per 11.7 mL and 1,600 mg/26,800 units per 13.4 mL (rituximab/hyaluronidase) solutions in ready-to-use, single-dose vials. Administered by a healthcare professional per the recommended dosing schedules, the dose is 1,400 mg/23,400 units SC over 5 minutes for FL and DLBCL and 1,600 mg/26,800 units over 7 minutes for CLL. It is given as a single agent or in combination with chemotherapy depending on the diagnosis and previous therapy.	Genentech	FDA BLA approval 06/22/2017
betrixaban	Bevyxxa®	Betrixaban (Bevyxxa), a factor Xa inhibitor, has been approved for the prophylaxis of venous thromboembolism (VTE) in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. Its safety and efficacy have not been established in patients with prosthetic heart valves. It carries a boxed warning for the risk of epidural or spinal hematomas in specific patients. The recommended dose is an initial single dose of 160 mg, followed by 80 mg once daily, taken orally at the same time each day with food. The recommended duration of treatment is 35 to 42 days. It is approved as 40 mg and 80 mg capsules.	Portola	FDA NDA priority approval 06/23/2017

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
triptorelin	Triptodur™ Kit	Triptorelin (Triptodur) was given Orphan Drug status and approved for the treatment of pediatric patients ≥ 2 years of age with central precocious puberty. It is a gonadotropin releasing hormone (GnRH) agonist administered as a single IM injection of 22.5 mg once every 24 weeks under the supervision of a physician. The kit contains 22.5 mg of triptorelin for reconstitution with 2 mL of diluent (sterile water for injection.)	Arbor	FDA NDA approval 06/29/2017
fibrinogen (human)	Fibryna®	Fibryna, a human fibrinogen concentrate, was granted FDA approval for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. It does not have approval for use for dysfibrinogenemia. The dose and frequency is individualized based on body weight to a target fibrinogen plasma level of 100 mg/dL for minor bleeds and 150 mg/dL for major bleeds. It is a lyophilized powder in single-use bottles containing approximately 1 g fibrinogen concentrate per container.	Octapharma	FDA BLA approval 07/03/2017
L-glutamine	Endari™	The FDA granted Orphan Drug status and approval to L-glutamine oral powder, Endari. A prescription amino acid indicated to reduce the acute complications of sickle cell disease (SCD) in adult and pediatric patients ≥ 5 years of age, it is the first FDA-approved SCD treatment in the pediatric population. Endari is administered orally as 5 g to 15 g twice daily based on body weight. It should be mixed in 8 ounces of a cold or room temperature beverage or 4 to 6 ounces of food before consuming. It is approved as 5 g of L-glutamine powder per packet.	Emmaus Medical	FDA NDA priority approval 07/07/2017
guselkumab	Tremfya™	Guselkumab (Tremfya) is an interleukin-23 blocker approved for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Approved as a 100 mg/mL single-dose prefilled syringe, it is self-administered SC at weeks 0 and 4, then every 8 weeks thereafter.	Janssen	FDA BLA priority approval 07/13/2017
neratinib	Nerlynx™	The FDA approved the tyrosine kinase inhibitor, neratinib (Nerlynx), for the extended adjuvant treatment of early stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy. Approved as a 40 mg oral tablet, the recommended dose is 6 tablets (240 mg) once daily with food, continuously for 1 year. The dose may be interrupted and/or reduced based on individual safety and tolerability.	Puma	FDA BLA approval 07/17/2017

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