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MRx CLINICAL ALERT

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SCOTUS RULES ON BIOSIMILARS

On June 12, 2017, the Supreme Court of the United States (SCOTUS) issued a unanimous decision in a case involving Sandoz (the manufacturer of biosimilar filgrastim-sndz [Zarxio®]) versus Amgen (the manufacturer of the originator product filgrastim [Neupogen®]). The decision affects 2 specific provisions impacting biosimilars within the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which provides a pathway for biosimilar approval. SCOTUS voted that a biosimilar manufacturer does not need to wait until after Food and Drug Administration (FDA) approval of the biosimilar product to give launch notice ("Notice of Commercial Marketing") to the originator manufacturer. Rather, the notice can be provided before or after FDA approval of the biosimilar product. On the "Requirement for Disclosure" or "patent dance," SCOTUS voted that there is not a federal requirement to provide this information. Therefore, the "patent dance" is not mandatory under federal law; however, it may be required under state law. The SCOTUS decision reverses any prior lower court rulings.

KEY DIABETES OUTCOMES TRIALS PUBLISHED: CANVAS AND DEVOTE

Patients with type 2 diabetes mellitus (T2DM) are at increased risk of cardiovascular (CV) complications compared to those without diabetes. The FDA requires that post-marketing CV outcomes studies be performed to assess the CV risks and benefits of novel antidiabetic agents. CV outcomes data have been published in the *New England Journal of Medicine* for canagliflozin (Invokana®) and insulin degludec (Tresiba®).

The *Canagliflozin Cardiovascular Assessment Study (CANVAS)* Program combined data from 2 clinical trials, CANVAS and CANVAS-Renal (CANVAS-R), to assess CV, renal, and safety outcomes in patients (n=10,142) with T2DM and at a high risk for major CV events (MACE). Analysis revealed that, after a mean follow-up of 188 weeks, the primary outcome of MACE (composite of death from CV causes, nonfatal myocardial infarction [MI], or nonfatal stroke) was 14% lower (hazard ratio [HR], 0.86) with canagliflozin compared to placebo. While a statistically significant difference was found in the composite outcome, this was not found for the individual components of CV death, nonfatal MI, or nonfatal stroke. Regarding renal function, canagliflozin led to a delay in progression of albuminuria (HR, 0.73) and a 40% reduction in composite renal outcomes (HR, 0.6), such as renal replacement therapy, sustained 40% reduction in estimated glomerular filtration rate (eGFR), or death from renal causes; however, these findings were not considered statistically significant based on the prespecified hypothesis testing sequence. Notably, there was nearly a 2-fold higher risk of amputation, primarily of the toe or metatarsal, with canagliflozin

compared to placebo, which led to the May 2017 FDA requirement that canagliflozin-containing products carry a boxed warning regarding amputations.

In the event-driven CV outcomes study entitled *Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE),* patients with T2DM (n=7,637) were randomized to receive insulin degludec (Tresiba®) or insulin glargine U-100 (Lantus®) once daily between dinner and bedtime. The primary outcome of MACE occurred in 8.5% of patients in the degludec group compared to 9.3% in the insulin glargine group (HR, 0.91), meeting the prespecified non-inferiority criteria. Other parameters assessed revealed similar mean hemoglobin A1c levels in each group, but a lower mean fasting plasma glucose level was reported in the insulin degludec arm (128 mg/dL versus 136 mg/dL). In addition, severe hypoglycemia occurred less often with insulin degludec compared to insulin glargine (4.9% versus 6.6%).

ACP UPDATES OSTEOPOROSIS GUIDELINES

Based on a systematic review of literature and evidence for specific pharmacotherapy treatments, the American College of Physicians (ACP) published an update to the 2008 guidelines for the treatment of low bone density and osteoporosis to prevent fractures in men and women. The guideline is also endorsed by the American Academy of Family Physicians (AAFP). ACP recommends that pharmacologic therapy to reduce the risk for hip and vertebral fractures be offered to women with osteoporosis. They advise that treatment occur for 5 years, although bone mineral density (BMD) monitoring is not needed during the 5-year treatment period. ACP recommends the use of alendronate (Fosamax®), risedronate (Actonel®), zoledronic acid (Reclast®), and denosumab (Prolia®); however, they recommend against using menopausal estrogen or estrogen with progesterone or raloxifene (Evista®) in women with osteoporosis. They further state that treatment decisions in older osteopenic women (≥ 65 years old) who are at a high risk of fracture should be based on a discussion with the patient regarding her preference, fracture risk, treatment benefits and harms, and cost. Regarding therapy in men, ACP recommends that clinicians offer treatment with bisphosphonates to reduce the risk of vertebral fractures in those with clinical osteoporosis.

Detailed guidelines are available at annals.org.

ACR UPDATES GUIDELINES FOR GLUCOCORTICOID-INDUCED OSTEOPOROSIS

The American College of Rheumatology (ACR) updated guidance on managing glucocorticoid-induced osteoporosis in adults and children. Fracture risk should be assessed within 6 months after starting long-term glucocorticoid treatment and every 12 months during treatment. Assessment should include the use of the FRAX® tool in patients 40 years of age and older. In those younger than 40 years with a high risk of fracture, BMD testing should occur within 6 months of the initiation of glucocorticoid treatment.

Treatment should include optimal calcium and vitamin D intake and lifestyle changes consistent with good bone health, such as smoking cessation, weight management, balanced diet, and exercise. ACR's further recommendations on antiresorptive treatment are based on individual patient characteristics, including fracture risk, age, and special populations (e.g., childbearing age, children, transplant recipients). No further treatment is needed beyond the lifestyle recommendations listed above in patients with a low risk of fracture, but these patients should receive yearly fracture risk reassessments, including BMD testing every 2 to 3 years. In those with moderate to high risk of fracture, oral bisphosphonates are generally recommended. Subsequent treatments are based on individual characteristics and include intravenous (IV) bisphosphonates, teriparatide (Forteo®), denosumab (Prolia), and raloxifene (Evista®).

The full guidance may be found at rheumatology.org.

CDC ADVISORY FOR *SHIGELLA*

The Centers for Disease Control and Prevention (CDC) issued a Health Advisory for diagnosing and managing *Shigella* strains with possible reduced susceptibility to ciprofloxacin (e.g., minimum inhibitory concentration [MIC] of 0.12-1 µg). They recommend obtaining isolates for susceptibility testing and reserving antibiotic therapy for patients for whom this treatment is clinically indicated or when public health officials advise treatment in an outbreak setting. If antibiotic therapy is needed, it should be tailored based on susceptibility results. Counseling patients on proper infection control measures and seeking additional guidance from the local health department are also recommended.

DRUG INFORMATION **HIGHLIGHTS**

- On June 8, 2017, the FDA requested that Endo Pharmaceuticals remove reformulated oxymorphone hydrochloride extended-release tablet (Opana® ER) from the market due to concerns that its benefits may no longer outweigh its risks. The FDA's decision is based on a review of post-market data that demonstrates a significant shift in the route of abuse of Opana ER from nasal to injection following the product's reformulation. This shift has been associated with a serious outbreak of HIV and hepatitis C virus (HCV), as well as cases of thrombotic microangiopathy.
- Novartis introduced a new 150 mg/mL solution of canakinumab (Ilaris®) for subcutaneous (SC) injection that will eliminate the need for reconstitution. Novartis subsequently announced their business decision to permanently discontinue manufacture of the lyophilized powder formulation.
- The agency approved a new formulation of daclizumab (Zinbryta®), as a single-dose, prefilled autoinjector containing a 150 mg/mL solution. It serves as an alternative to the prefilled syringe for the treatment of relapsing forms of multiple sclerosis.
- Bristol-Myers Squibb voluntarily recalled 1 lot of apixaban (Eliquis®) 5 mg tablets due to a finding of an incorrect tablet strength of 2.5 mg in a 60-count bottle (Lot HN0063, expired 9/19). The 2 tablet strengths are different in appearance. To date, there have been no reports of harm.
- The FDA approved a 1,064 mg aripiprazole lauroxil (Aristada®) suspension for injection in a single-use prefilled syringe for intramuscular (IM) administration every 2 months for the treatment of schizophrenia. Other approved dosages (441 mg, 662 mg, 882 mg) are administered IM every 4 or 6 weeks, depending on the strength.
- An expanded indication for the kinase inhibitor, ceritinib (Zykadia®), was approved to treat patients with metastatic NSCLC whose tumors are anaplastic lymphoma kinase (ALK)-positive, as a fulfillment of its post-marketing requirements. The medication was previously approved under accelerated approval status for the same indication only after progression or intolerance to crizotinib.
- Merck's pembrolizumab (Keytruda®), a human programmed death receptor-1 (PD-1)-blocking antibody, has received approval for unresectable or metastatic solid tumors with a biomarker for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and as first-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) under accelerated approval. An additional supplemental approval includes locally advanced or metastatic urothelial carcinoma. The medication is also indicated for the treatment of melanoma, head and neck squamous cell carcinoma, and classical Hodgkin lymphoma (cHL).
- The FDA approved a new formulation of ritonavir (Norvir®), a 100 mg/packet oral powder indicated for the treatment of pediatric patients with HIV-1 infection. It can be prepared to make doses in 100 mg increments. It should be mixed with soft food or liquid and administered within 2 hours of preparation. It can also be administered via a feeding tube after mixing with water.
- Lupin announced a voluntary recall of 1 lot of norethindrone acetate/ethinyl estradiol/ferrous fumarate (Mibelas™ 24 FE) (Lot: L600518; expiration: 5/18) due to a packaging error that replaced the first 4 days of active tablets with 4 non-hormonal placebo tablets. Also, the lot number and expiration date are not visible. No adverse effects have been reported to date.

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

- **July 7, 2017:** Endari; pharmaceutical grade L-glutamine; oral amino acid supplement; sickle cell disease; Emmaus Life Sciences.
- **July 19, 2017:** Dextenza; dexamethasone; corticosteroid ocular implant; post-ophthalmic surgery pain; Ocular Therapeutix/Ora.
- **July 21, 2017:** Nerlynx; neratinib; oral tyrosine kinase inhibitor; HER2+ breast cancer; Puma Biotechnology.
- **July 28, 2017:** Abilify Maintena®; aripiprazole; IM atypical antipsychotic; maintenance bipolar I disorder; Bristol-Myers Squibb/Otsuka.
- **July 30, 2017:** Benjorna; methylphenidate delayed-release; oral central nervous system (CNS) stimulant; attention deficit hyperactivity disorder (ADHD); Highland.
- **August, 2017:** inotuzumab ozogamicin; IV anti-CD-22 antibody-cytotoxin conjugate; acute lymphocytic leukemia; Pfizer.
- **August 2, 2017:** Opdivo®; nivolumab; IV PD-1 inhibitor; colorectal cancer (MSI-H, dMMR); Bristol-Myers Squibb/Ono.
- **August 8, 2017:** sofosbuvir/velpatasvir/voxilaprevir; oral direct-acting antiviral (DAA); chronic hepatitis C virus infection (HCV) genotypes 1-6; Gilead.
- **August 10, 2017:** Heplisav-B; hepatitis B virus (HBV) vaccine; HBV infection prevention; Dynavax.
- **August 18, 2017:** glecaprevir/pibrentasvir; oral DAA; chronic HCV genotypes 1-6; Abbvie.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
edaravone	Radicava™	The FDA granted Orphan Drug designation and approval to edaravone (Radicava) to treat amyotrophic lateral sclerosis (ALS). The 60 mg IV dose is administered by a healthcare professional as two 30 mg (100 mL) polypropylene bags infused consecutively over 60 minutes. The initial treatment cycle is daily for 14 days followed by a 14-day drug-free period. Subsequent treatment cycles consist of dosing on 10 of 14 days, followed by a 14-day drug-free period. Edaravone is expected to be available in the U.S. in August, 2017.	Mitsubishi Tanabe	FDA NDA approval 05/05/2017
sarilumab	Kevzara®	Sarilumab (Kevzara), an interleukin-6 (IL-6) receptor antagonist, received approval for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to 1 or more disease-modifying antirheumatic drugs (DMARDs). The approved dose of 200 mg once every 2 weeks may be self-administered as a SC injection. Sarilumab may be prescribed as monotherapy or in combination with methotrexate or other conventional DMARDs. Sarilumab is available as 150 mg and 200 mg, each in a volume of 1.14 mL in a single-dose prefilled syringe.	Sanofi-Aventis	FDA BLA approval 05/22/2017
cetirizine	Zerviate™	The first topical preparation of cetirizine (Zerviate), a histamine-1 (H1) receptor antagonist, was approved for the treatment of ocular itching associated with allergic conjunctivitis in adults and children ≥ 2 years of age. The recommended dose is 1 drop in each affected eye twice daily. Zerviate is approved as a 0.24% (2.4 mg/mL) solution in 5 mL and 7.5 mL bottles. Launch is planned during 2017.	Nicox	FDA NDA priority approval 05/30/2017
glycopegylated coagulation factor IX (recombinant)	Rebinyn®	The FDA approved glycopegylated coagulation factor IX (Rebinyn) for use in adults and children with hemophilia B for on-demand treatment and control of bleeding episodes and perioperative management of bleeding. Rebinyn is not indicated for routine prophylaxis or immune tolerance induction in patients with hemophilia B. Dosing and duration of treatment is based on location and extent of bleeding and the patients' clinical condition. A single dose of 40 IU/kg may be sufficient for minor bleeds and prior to minor surgery; 80 IU/kg may be required for major bleeds and prior to major surgery. Patients may self-administer the IV dose. Rebinyn is approved as single-use vials containing 500 IU, 1,000 IU, and 2,000 IU. Availability is expected in the first half of 2018.	Novo Nordisk	FDA BLA approval 05/31/2017

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
epinephrine	Symjepi™	A new formulation of epinephrine (Symjepi), a non-selective alpha and beta-adrenergic receptor agonist, was approved for the emergency treatment of allergic reactions (Type I) including anaphylaxis. The product is approved for use in patients weighing ≥ 30 kg and is injected IM or SC into the anterolateral aspect of the thigh. It can be injected through clothing, if necessary. The injection is approved as a single-dose, prefilled syringe for manual injection and contains 0.3 mg/0.3 mL in packages containing 1 or 2 syringes. Symjepi is anticipated to be available in the second half of 2017.	Adamis	FDA NDA approval 06/15/2017
delafloxacin	Baxdela™	Delafloxacin (Baxdela), a fluoroquinolone antibacterial, received FDA approval for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). Delafloxacin was given Qualified Infectious Disease Product designation by the FDA. The dose is administered every 12 hours either as 300 mg IV infused over 60 minutes or as 450 mg orally for 5 to 14 days. Delafloxacin is available as a 300 mg single-dose vial for reconstitution and subsequent injection and a 450 mg oral tablet.	Melinta	FDA NDA priority approval 06/19/2017
methylphenidate	Cotempla XR-ODT™	Cotempla XR-ODT, an extended-release, orally-disintegrating tablet form of methylphenidate, a CNS stimulant, was approved for the treatment of ADHD in pediatric patients aged 6 to 17 years. The Schedule II controlled substance is approved in 8.6 mg, 17.3 mg, and 25.9 mg strengths. Dosing is started at 17.3 mg once daily in the morning and can be increased by 8.6 mg to 17.3 mg weekly to a maximum of 51.8 mg per day. The product should be taken consistently with or without food. Cotempla XR-ODT is expected to be available in the fall of 2017.	Neos	FDA NDA approval 06/19/2017
amphetamine mixed salts	Mydayis™	The FDA approved mixed salts of a single-entity amphetamine (Mydayis), a CNS stimulant, indicated for the treatment of ADHD for patients 13 years and older. The recommended starting dose is 12.5 mg once-daily, taken upon awakening. Dosing can be titrated weekly by 12.5 mg up to a maximum of 25 mg and 50 mg, for pediatrics and adults, respectively. Boxed warnings and precautions of the potential risk of abuse and dependence are similar to other amphetamine salt formulations. Mydayis is a Schedule II controlled substance and is approved as 12.5 mg, 25 mg, 37.5 mg, and 50 mg extended-release capsules. Launch of Mydayis is planned for third quarter of 2017.	Shire	FDA NDA approval 06/20/2017

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References:

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