Magellan Rx MANAGEMENT

Clinical Alert

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Hot Topic:

FDA Final Guidance: Nonproprietary Naming of Biologic Products

The Food and Drug Administration (FDA) has released the much-awaited final guidance on nonproprietary naming of biologics. This Guidance for Industry details the agency's stance on naming newly-approved and previously-licensed biologics under the Public Health Service (PHS) Act. This current thinking applies to biological products, related biological agents, and biosimilars. Under the final naming convention, the biological products must bear a core name, followed by a distinguishing suffix. The suffix must be devoid of meaning, composed of 4 lowercase letters, without numerals or symbols, and be unique. The core name is attached to the suffix by a hyphen. Although manufacturers can submit 10 suffixes for the agency's consideration, the suffix will be designated by the FDA.

Applying suffixes is thought to minimize inadvertent or inappropriate substitution and improve the safety of patients receiving biologics. Furthermore, it can increase prescriber and patient confidence, improve biosimilar adoption, and ensure pharmacovigilance.

The FDA is still considering how to implement the naming nomenclature for previously-approved products. The agency intends to change the nonproprietary name of the first U.S. biosimilar, Zarxio™ by Sandoz, from filgrastim-sndz to filgrastim-bflm. The nonproprietary name of Amgen's reference product filgrastim (Neupogen®) will likely be changed to filgrastim-jcwp.

A biosimilar product will continue to be approved based on evidence that it is "highly similar" to the reference product, demonstrating that it has no clinically meaningful differences in safety and effectiveness from the originator agent. However, there are not any interchangeable biosimilars on the market. The FDA, which recently released draft guidance for interchangeability, is considering the appropriate suffix format for interchangeable products.

The full report on the FDA final guidance is available at http://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf.

Updates in Type 2 Diabetes Mellitus (T2DM) Therapy

The American Association of Endocrinologists (AACE) and the American College of Endocrinology (ACE) announced an update to their Comprehensive Type 2 Diabetes Management Algorithm. The 2017 algorithm continues to recommend individualized hemoglobin A1c (HbA1c) targets with therapy selection stratified by initial HbA1c level. Although a general target HbA1c is ≤ 6.5%, therapy should aim to minimize the risk of hypoglycemia, weight gain, and other adverse effects. AACE/ACE emphasizes the impact of obesity on the development of T2DM and the resulting microvascular complications. Weight-loss medications, in addition to lifestyle management, should be considered if needed to achieve therapeutic goals in diabetic and prediabetic patients. Additional lifestyle recommendations include sleep hygiene education and, when appropriate, nicotine replacement and alcohol or substance abuse treatment.

In regard to specific antidiabetic products, AACE/ACE notes recent labeling changes for metformin and states metformin use may be maintained as long as the estimated glomerular filtration rate (eGFR) exceeds 30 mL/min/1.73m^2 and the dose is adjusted, if needed; however, metformin should not be initiated in those with an eGFR

Drug Information Highlights

- Flu Season Update (2016-2017): During the week ending January 21, 2017, influenza activity increased in the U.S. The most frequently reported subtype was influenza A (H3). The proportion of outpatient visits for influenza-like illness (3.4%) exceeded the national baseline (2.2%). New York City and 10 states reported high activity and 10 states experienced moderate activity. The remaining states and Puerto Rico experienced low or minimal activity while data were insufficient in the District of Columbia. No current drug shortages of antiviral agents for the treatment of influenza have been reported.
- Kaléo announced that Auvi-Q®, an epinephrine auto-injector with audio and visual cues, will return to the U.S. market beginning February 14, 2017. Auvi-Q is indicated for the emergency treatment of allergic reactions (Type I) including anaphylaxis, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. It is intended for immediate administration, including self-administration, in patients at increased risk for anaphylaxis. Auvi-Q will be available in 2 doses, 0.3 mg and 0.15 mg; each will be available in a package containing 2 auto-injectors and 1 trainer auto-injector. Auvi-Q was removed from the market in October 2015 due to potentially inaccurate dosing. Auvi-Q is not interchangeable for brand Epipen® epinephrine auto-injector or Mylan's authorized generic for Epipen. It is also not interchangeable for Lineage's authorized generic to Adrenaclick®.
- Nurse Assist issued a voluntary Class I recall of all unexpired lots of IV Flush Syringes (0.9% sodium chloride) due to a potential link to *Burkholderia cepacia* bloodstream infections. The effects of *B. cepacia* infections vary from no symptoms to serious respiratory infections, particularly in patients with cystic fibrosis. Recalled lots were distributed from February 16, 2016 to September 30, 2016.
- The FDA issued a Safety Communication regarding surgically-implanted infusion pumps due to reports of serious adverse events, including patient injury and death, when used in the magnetic resonance (MR) environment. Reports include dosing inaccuracies and other mechanical pump problems. The FDA advises that providers should discuss this risk with patients. If magnetic resonance imaging (MRI) is required, patients should bring their pump identification to the MRI exam, and MRI

< 45 mL/min/1.73m^2. AACE/ACE also added insulin glargine U-300 (Toujeo®) and insulin degludec (Tresiba®), newer basal insulin formulations with prolonged and stable pharmacokinetics and pharmacodynamics, as treatment options. In addition, the algorithm suggests that the oral sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin (Jardiance®) and the injectable glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide (Victoza®) may offer renal and cardiovascular (CV) benefits. Empagliflozin recently gained approval for CV risk reduction in patients with T2DM, and Novo Nordisk is currently seeking this indication for liraglutide.

AACE/ACE also recommends treating other atherosclerotic cardiovascular disease (ASCVD) risk factors in those with comorbidities, such as dyslipidemia and hypertension. They include new treatment goals for patients at 'extreme risk' for ASCVD, defined as T2DM plus established clinical CV disease or chronic kidney disease (CKD) stage 3 or 4. Goals for those at extreme risk include low-density lipoprotein cholesterol (LDL-C) < 55 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) < 80 mg/dL, triglycerides < 150 mg/dL, and apolipoprotein B < 70 mg/dL. AACE/ACE emphasizes close glucose monitoring in diabetic and pre-diabetic patients on niacin, as it may increase serum glucose levels.

Similarly, the American College of Physicians (ACP) updated their 2012 guidelines on oral pharmacologic treatment for T2DM. They recommend metformin for all patients when pharmacologic treatment is needed (strong recommendation). They also recommend that clinicians consider adding an agent from 1 of the following classes when a second oral treatment is considered: sulfonylureas, thiazolidinediones, SGLT2 inhibitors, or dipeptidyl peptidase-4 (DPP-4) inhibitors (weak recommendation). ACP encourages providers to discuss treatment benefits, adverse effects, and costs with the patient prior to initiating therapy.

Furthermore, an article recently published in the *Annals of Internal Medicine* and funded primarily by the U.S. Department of Veterans Affairs reviewed data from 17 published observational studies on the use of metformin in patients with T2DM with moderate to severe CKD, congestive heart failure (CHF), or chronic liver disease (CLD) with hepatic impairment. The authors reported reduced all-cause mortality in diabetic patients with CKD, CHD, or CLD with hepatic impairment. A reduced rate of readmissions due to heart failure in patients with CKD or CHF was also reported.

Detailed information on the guidelines presented may be accessed at www.aace.com and www.acponline.org.

American College of Cardiology (ACC) Guidance for Periprocedural Anticoagulation in Patients with Nonvalvular Atrial Fibrillation (NVAF)

The ACC published an expert consensus decision pathway intended to assist providers with periprocedural anticoagulation management in patients with NVAF. When deciding if an interruption in anticoagulation is needed, providers should consider the type and half-life of the oral anticoagulant, the patient's bleeding risk, the bleeding risk of the procedure, and other patient-specific clinical information. For example, some procedures have demonstrated a lower bleeding risk when vitamin K antagonist (VKA) therapy is uninterrupted and heparin bridging is given. The HAS-BLED score should be used to assess the patient's bleeding risk; HAS-BLED assesses the following: blood pressure, liver or renal function, history of stroke, major bleeding or anemia, labile international normalized ratio (INR) in patients using VKAs (e.g., warfarin), patient age, concomitant medications, and alcohol consumption. In addition, recent bleeding events, platelet abnormalities, efficacy of current anticoagulant, and any prior procedural bleeding should be considered. For all patients on a VKA, INR should be measured 5 to 7 days prior to the procedure. ACC does not recommend interrupting VKA therapy in patients undergoing procedures with a low risk or no risk of bleeding who do not have additional patient-related risk factors for bleeding. If VKA therapy is interrupted, it should be stopped 3 to 4 days prior to the procedure if the INR is 1.5 to 1.9, 5 days prior if the INR is 2 to 3, and at least 5 days prior if the INR exceeds 3. The INR should be re-checked within 24 hours before the procedure, as well. The duration of anticoagulation interruption for patients using direct oral anticoagulants (DOAC), such as apixaban (Eliquis®), dabigatran etexilate (Pradaxa®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®), should be based on estimated renal function and procedural bleeding risk; however, DOACs should not be used in patients undergoing mechanical valve replacement. Bridging with intravenous (IV) heparin should only be considered in select VKA-treated patients. Prior to restarting an oral anticoagulant, the provider should ensure complete hemostasis. Generally, VKA therapy may be restarted within 24 hours, IV heparin bridging (if required) within 24 to 72 hours, and DOAC within 24 to 72 hours.

The full decision pathway is available at www.acc.org.

technologists should verify safe use based on pump type.

- The first generic for Abbvie's Kaletra® (lopinavir/ritonavir) oral solution has been approved by the FDA. Lopinavir/ritonavir is a fixed-dose combination of 2 protease inhibitors used with other antiretroviral agent for the treatment of human immunodeficiency virus (HIV)-1 infection in adult and pediatric patients 14 days and older. Generic versions of Kaletra 200/50 mg and 100/25 mg tablets have not been FDA-approved.
- The first generic version of the central nervous system (CNS) depressant Xyrem® (sodium oxybate oral solution; Jazz) was FDA approved. Sodium oxybate is a Schedule III controlled substance indicated for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. As with Xyrem, the generic will only be available through a Risk Evaluation Mitigation Strategy (REMS) program to ensure safe use and prevent inappropriate prescribing, misuse, abuse, and diversion. Neither Xyrem nor generic sodium oxybate are dispensed by retail pharmacies.
- The U.S. Preventive Services Task Force (USPSTF) reaffirmed their 2009 recommendation for the use of folic acid 400 to 800 mcg in all women who are planning or capable of pregnancy to reduce the risk of birth defects.
- The REMS for lomitapide (Juxtapid®; Aegerion) was updated to expand the number of certified pharmacies and to modify the safety labeling changes, notification letter, and REMS assessment.
- The REMS for idelalisib (Zydelig®; Gilead) was updated to align with safety labeling changes, including severe diarrhea and colitis, pneumonitis, and neutropenia.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **February 2017:** deflazacort; oral glucocorticoid; Duchenne muscular dystrophy; Marathon.
- **February 2017:** MK-8237; sublingual immunotherapy (house dust mite); allergic rhinitis; Merck/ALK-Abello.
- **February 28, 2017:** telotristat etiprate; oral peripheral serotonin inhibitor; carcinoid syndrome; Lexicon/Ipsen.
- **March 15, 2017:** Keytruda®; pembrolizumab; IV programmed cell death 1 (PD-1) inhibitor; refractory Hodgkin's lymphoma; Merck.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
magnesium sulfate/ potassium sulfate/ sodium sulfate	Colprep Kit	Colprep Kit for oral solution, an osmotic laxative indicated for cleansing of the colon as a preparation for colonoscopy in adults, has been approved by the FDA. Colprep Kit is comprised of 2 bottles of Colprep powder which must be reconstituted and diluted in water prior to ingestion. Recommended as a split-dose oral regimen, the first oral solution dosage is consumed in the evening before colonoscopy. The dose is repeated in 10 to 12 hours; the second dose must be administered at least 3½ hours before colonoscopy. The total volume of liquid required is approximately 2.8 L prior to the colonoscopy. Contraindications include gastrointestinal obstruction, bowel perforation, gastric retention, ileus, and toxic colitis or megacolon.	Gator	FDA NDA approval 12/27/2016
ranibizumab	Lucentis®	Ranibizumab (Lucentis), a vascular endothelial growth factor (VEGF) inhibitor, received a new indication for the treatment of myopic choroidal neovascularization (mCNV). Ranibizumab is the first FDA-approved therapy for mCNV, a complication of severe nearsightedness which may lead to blindness. Approved as single-use prefilled syringes and vials, the recommended dosage for mCNV is 0.5 mg (0.05 mL) administered by a healthcare professional intravitreally once a month for up to 3 months; patients may be retreated, if needed. Ranibizumab is also approved for the treatment of patients with neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, diabetic macular edema (DME), and diabetic retinopathy in patients with DME.	Genentech	FDA sBLA priority approval 01/05/2017
morphine sulfate extended-release (ER)	Arymo™ ER	An extended-release morphine sulfate Arymo ER was FDA-approved for the management of pain severe enough to require around-the-clock, long-term opioid management for which alternative treatments are inadequate. The product utilizes Egalet's proprietary Guardian™ abuse-deterrent technology which consists of both a physical and chemical barrier without the need for an opioid antagonist component. Arymo ER is a Schedule II controlled substance. It carries the same boxed warnings regarding addiction, abuse, and misuse and is subject to the same REMS requirements as other opioid products. Approved in 15 mg, 30 mg, and 60 mg tablet strengths, Arymo ER is dosed every 8 or 12 hours depending on pain levels and opioid tolerability. Tablets should be swallowed whole. Market launch is planned for the first quarter of 2017.	Egalet	FDA NDA approval 01/09/2017
hydrocodone bitartrate ER	Vantrela™ ER	Hydrocodone bitartrate ER (Vantrela ER) was granted approval for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. A Schedule II controlled substance, Vantrela ER is formulated with physicochemical abuse-deterrent properties. Vantrela ER is approved as 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg ER tablets. Administered every 12 hours, dosage is based on pain severity, patient tolerance, and prior opioid experience. It is subject to the same REMS and carries the same boxed warnings regarding addiction, abuse, and misuse as other opioids.	Teva	FDA NDA approval 01/17/2017
oxymetazoline hydrochloride	Rhofade™	Oxymetazoline HCl 1% cream (Rhofade) has been approved by the FDA for topical treatment of persistent facial erythema associated with rosacea in adults. The alpha$_{1A}$ adrenoceptor agonist cream is approved as a tube or pump and is to be applied once daily in a thin layer covering the entire face avoiding eyes and lips. Common adverse reactions include worsening inflammatory lesions of rosacea, application site dermatitis, pruritus, erythema, and pain. Rhofade is expected to be available in May 2017.	Allergan	FDA NDA approval 01/18/2017
plecanatide	Trulance™	Plecanatide (Trulance), a guanylate cyclase-C (GC-C) agonist, has been FDA-approved for the treatment of chronic idiopathic constipation (CIC) in adults. Safety and effectiveness have not been established in patients under 18 years of age. Plecanatide was approved as 3 mg tablets to be taken as 1 tablet orally once daily, with or without food. Contraindications include use in patients less than 6 years of age due to risk of serious dehydration and in patients with known or suspected mechanical gastrointestinal obstruction. The most common adverse effects experienced in clinical trials was diarrhea. Product launch is planned for the first quarter of 2017.	Synergy	FDA NDA approval 01/19/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

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https://www1.magellanrx.com/magellan-rx/publications/pharmacy-clinical-alerts.aspx

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