MARCH 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

Download at:
magellanrx.com

AMERICAN COLLEGE OF RHEUMATOLOGY (ACR) PUBLISHES REVIEW OF BIOSIMILARS

Biosimilars are defined by the FDA as biologic products that are "highly similar" to a reference/originator product with "no clinically meaningful differences" in safety or effectiveness. Biosimilars are not generics. Generics are small molecule drugs that are equivalent to the reference brand product; biosimilars are biologic products that are not identical to their reference biologic.

ACR reviewed the approval pathway for biosimilars, their manufacturing, indication extrapolation, interchangeability and substitution, transition and change, and pharmacoeconomics. ACR states, while clinicians continue to be uneasy with the extrapolation of indications for biosimilar products, the limited data support extrapolation by providing reassuring evidence in "real-world" studies. They further state they expect that transitioning to biosimilars will become as commonplace here in the United States (US) as it is in Europe.

ACR states they initially supported a cautious pursuit of biosimilars. Given that a handful of biosimilars have come to fruition and several more are on the horizon, ACR has reevaluated their position. Encouraged by a rigorous biosimilar evaluation by the FDA and agencies abroad, ACR concluded that healthcare providers (HCPs) should incorporate biosimilars, where appropriate, into rheumatic disease treatment regimens. ACR emphasizes that providers need to maintain knowledge of biosimilars and monitor evolving policies and guidelines regarding their development and use.

AMERICAN HEART ASSOCIATION (AHA) PROVIDES GUIDANCE ON THE INTERSECTION OF CARDIOVASCULAR DISEASE (CVD) AND BREAST CANCER

Although many may consider breast cancer to be the biggest health threat to women, CVD is actually the leading cause of mortality in women. However, they have several risk factors in common. The AHA published a Scientific Statement on the juncture of these two disease states, providing a review of their prevalence, shared risk factors, cardiotoxic effects of breast cancer treatments, and prevention and treatment of CVD in patients with breast cancer.

Shared risk factors discussed include dietary patterns (e.g., dietary fat, alcohol use, red and processed meat consumption), physical inactivity, above recommended body mass index (BMI), tobacco use, age, family history, and postmenopausal hormone replacement therapy (HRT). Several treatments for breast cancer may also increase the risk of CVD. Chemotherapeutic agents, including anthracyclines, alkylating agents, taxanes, and antimetabolites, as well as endocrine therapy, such as tamoxifen, aromatase inhibitors,

and ovarian suppression therapy can increase the risk of CVD. Newer treatments for breast cancer that may also increase the risk of CVD in women include human epidermal growth factor receptor 2 (HER2)-targeted therapies, select tyrosine kinase and cyclin-dependent kinase (CDK) 4/6 inhibitors, and radiation therapy. The statement presents literature evaluating the mitigation of these treatment-related risk factors, including the use of chelating agents, various administration options, and radiation techniques.

The Scientific Statement also addresses monitoring options for CVD in women treated for breast cancer. These include early identification of risk using myocardial strain imaging/echocardiography, cardiac biomarkers (e.g., troponin I, brain natriuretic peptide), or a combination of both. In addition, the statement examined the role of exercise and pharmacologic therapies (e.g, beta blockers, renin-angiotensin-aldosterone system blockade) for the prevention of breast cancer therapy-related CVD. Based on the available literature, AHA states it is reasonable to treat anthracycline- or trastuzumab-induced cardiomyopathy with a beta blocker, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and/or spironolactone in accordance with AHA heart failure guidelines. Data on the benefit of aspirin in breast cancer prevention continue to be mixed, with ongoing trials aimed to provide additional insight. Likewise, data on the protective effects of statins in this population are limited.

AMERICAN ACADEMY OF NEUROLOGY (AAN) GUIDELINE UPDATE ON MILD COGNITIVE IMPAIRMENT (MCI)

The AAN updated their 2001 guideline on MCI using a systematic method and review. Prevalence of MCI increases with age, ranging from 6.7% in patients 60 to 64 years of age to 25.2% for those 80 to 84 years of age. Persons with MCI are at increased risk of progressing to dementia.

AAN recommends that clinicians assess MCI with validated tools; evaluate patients for modifiable risk factors, functional impairment, and behavioral and/or neuropsychiatric symptoms; and monitor cognitive status over time (all Level B recommendations). Regarding pharmacologic treatment, medications that can impair cognition should be discontinued when possible and patients should be treated for behavioral symptoms (Level B). While there is no high-quality evidence to support pharmacotherapy for MCI, AAN concedes that prescribers may choose to offer cholinesterase inhibitors (Level B) following a collaborative discussion with the patient on their lack of clinical evidence (Level A). In addition to diagnosis, prognosis, and long-term planning, HCPs should discuss with patients the lack of effective medicine options and recommend regular (twice weekly) exercise (Level B). Notably, AAN does state that clinicians may recommend cognitive training (Level C) to improve cognitive measures.

BEHAVIORAL HEALTH CORNER

ALCOHOL USE DISORDER (AUD) - UPDATED TREATMENT GUIDELINES

The American Psychiatric Association (APA) published a revised Practice Guideline for the Pharmacologic Treatment of Patients with AUD. The APA provided several statements on the assessment and determination of treatment goals. Recommendations propose the initial assessment includes review of current and historical use of alcohol, tobacco, and other substances of abuse, along with co-occurring conditions (Level 1C recommendations). APA suggests the use of physiological biomarkers as part of the initial evaluation and ongoing monitoring (Level 2C). The APA also suggests initial goals (e.g., alcohol abstinence, reduction or moderation of use) be agreed on between the provider and patient. The patient should be aware of the risks of alcohol use on self and others (both Level 2C).

Pharmacotherapy recommendations include a statement on the FDA-approved or off-label use of products in patients with moderate to severe AUD who have a goal of reducing alcohol consumption or achieving abstinence, unless contraindications exist. APA recommends that naltrexone or acamprosate be offered to patients who prefer pharmacotherapy or have not responded to nonpharmacological treatments alone (Level 1B). Disulfiram may be offered to patients who prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate, and who understand the risks of alcohol consumption while using disulfiram (Level 2C). APA also suggests off-label use of medications, specifically topiramate or gabapentin, be offered to patients who prefer these medications or are intolerant to non-disulfiram FDA-approved treatments (Level 2C). The APA recommends against the use of antidepressants (Level 1B) and benzodiazepines (Level 1C). Furthermore, the APA provides guidance for the treatment of pregnant or breastfeeding women, patients with renal or hepatic impairment, and those with concomitant opioid use.

DRUG INFORMATION **HIGHLIGHTS**

- Flu Season Update (2017-2018): During the week ending 02/24/18, the Centers for Disease Control and Prevention (CDC) reported continued widespread flu activity in 45 states, with 32 states reporting high activity. A season total of 114 pediatric deaths have occurred. Influenza A(H3N2) continued to dominate, but H1N1 is increasing. Despite confirmed oseltamivir availability from brand and generic manufacturers (except Avkare), temporary shortages at the pharmacy level have been experienced. There have also been spot shortages of the rapid influenza diagnostic tests (RIDT). CDC reports 50% to 70% sensitivity of the RIDTs; false negative results can occur at times of high flu activity. CDC estimates an interim overall vaccine effectiveness (VE) of 36% for the 2017-2018 flu vaccine. CDC continues to recommend flu vaccination for people ≥ 6 months of age as influenza viruses are expected to be prevalent for several weeks. The FDA is investigating ways to improve the VE against H3N2 for future flu vaccines.
- Effective immediately, Mylan Specialty announced its plans to discontinue any future shipments of the inhaled corticosteroid, flunisolide aerosol (Aerospan®), indicated to treat bronchospasm. This market withdrawal is not due to concerns of safety or efficacy.
- Due to business reasons, Roche announced that they will stop shipping saquinavir mesylate (Invirase®) 200 mg capsules on March 31, 2018 with product availability continuing until the September 2018 expiry date. Saquinavir mesylate (Invirase) 500 mg tablets will remain on the market. Generic saquinavir is not available in the US.
- On March 2, 2018, Abbvie/Biogen announced a voluntary global withdrawal of daclizumab (Zinbryta®), an interleukin-2 inhibitor indicated to treat relapsing forms of multiple sclerosis (MS). Daclizumab was approved in 2016 with a boxed warning of risks of hepatic injury, including auto-immune hepatitis and other immune-mediated disorders. The market discontinuation follows 7 European reports of serious inflammatory encephalitis and meningoenephalitis.
- The CDC Advisory Committee on Immunization Practices endorsed the use of the live attenuated influenza vaccine nasal spray FluMist® Quadrivalent for the 2018-2019 flu season. Its use was not recommended during the 2015-2016 and 2017-2018 seasons due to lack of effectiveness against influenza A(H1N1); however, AstraZeneca has reformulated the H1N1 component and expects FluMist to be more effective. Moreover, similar efficacy against H3N2 and influenza B was found between FluMist and the injectable inactivated influenza vaccine. The committee also recommended to add FluMist back to the Vaccines for Children program. The committee's recommendations are advisory in nature and do not bind the FDA to a decision.
- The FDA approved a 250 mcg formulation of roflumilast (Daliresp®) based on the OPTIMIZE study, which supported a lower starting dose of the phosphodiesterase 4 inhibitor and up-titration to improve tolerability. Indicated to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD, the recommended dosage regimen is 250 mcg once daily for 4 weeks followed by a maintenance dose of 500 mcg once daily.

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

- **March 2018:** Latuda®; lurasidone; oral antipsychotic; bipolar disorder (ages 10-17 years); Sumitomo Dainippon.
- **March 2018:** rituximab, biosimilar to Genentech's Rituxan®; intravenous (IV) CD20-directed cytolytic antibody; rheumatoid arthritis, chronic lymphocytic leukemia, non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies-associated vasculitis; Celltrion/Teva.
- **March 2018:** tildrakizumab; subcutaneous (SC) interleukin-23 inhibitor; plaque psoriasis; Sun.
- **Mar-Apr 2018:** trastuzumab, biosimilar to Genentech's Herceptin®; IV HER2/neu receptor antagonist; HER2+ breast, gastric, and gastroesophageal cancers; Celltrion/Teva.
- **Mar-May 2018:** Hizentra®; SC immune globulin 20%; chronic inflammatory demyelinating polyneuropathy; CSL.
- **Mar-May 2018:** ulipristal; oral progesterone receptor modulator; uterine fibroids; Allergan.
- **March 19, 2018:** Yonsa; abiraterone ultramicrosize tablet; oral androgen biosynthesis inhibitor; metastatic castration-resistant prostate cancer; Churchill.
- **March 26, 2018:** Jatenzo; testosterone undecanoate; oral androgenic steroid; hypogonadism; Clarus.
- **March 29, 2018:** Blincyto®; blinatumomab; IV CD19-directed CD3 T cell engager; acute lymphoblastic leukemia (minimal residual disease-positive B cell precursor); Amgen.
- **April 3, 2018:** ibalizumab; IV humanized anti-CD4 antibody; human immunodeficiency virus-1 (HIV-1) infection; Theratechnologies.
- **April 3, 2018:** Keytruda®; pembrolizumab; IV programmed death receptor-1 inhibitor; refractory primary mediastinal B cell lymphoma; Merck.
- **April 6, 2018:** Rubraca®; rucaparib; oral poly (ADP-ribose) polymerase inhibitor; recurrent ovarian cancer (platinum complete/partial response); Clovis.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
plecanatide	Trulance®	The FDA approved a new indication for the guanylate cyclase-C agonist, plecanatide (Trulance), to treat adults with irritable bowel syndrome with constipation (IBS-C). Plecanatide is also indicated for chronic idiopathic constipation in adults. Dosage for both conditions is 3 mg orally once daily.	Synergy	sNDA approval 01/24/2018
vancomycin	Firvanq™	Vancomycin oral solution (Firvanq) garnered approval for use in adults and pediatric patients < 18 years of age to treat *Clostridium difficile*-associated diarrhea (CDAD) and enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains). It is approved as a kit containing 3.75 g, 7.5 g, 10.5 g, or 15 g of vancomycin powder with a grape-flavored diluent to be reconstituted by a pharmacist to strengths of 25 or 50 mg/mL as directed. Market availability is expected on April 2, 2018.	Cutis	505(b)(2) NDA Priority approval 01/26/2018
somatropin	Zomacton®	The FDA approved a new indication for the recombinant growth hormone (GH), somatropin (Zomacton), for the replacement of endogenous GH in adults with GH deficiency. In adults, the initial non-weight based dose is approximately 0.2 mg/day and the starting weight-based dosing (not recommended for obese patients) is 0.006 mg/kg/day. Dosage can be increased according to individual patient requirements as outlined in the prescribing information.	Ferring	505(b)(2) sNDA approval 01/30/2018
avibactam/ ceftazidime	Avycaz®	Avycaz, a combination of the beta-lactamase inhibitor, avibactam, and the cephalosporin, ceftazidime, was awarded a new indication and a Qualified Infectious Disease Product designation for the treatment of adults with hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) caused by select susceptible Gram-negative microorganisms. For this indication, dosage is 2.5 grams every 8 hours administered IV over 2 hours for 7 to 14 days. Avycaz is also indicated for adults with complicated intra-abdominal or urinary tract infections.	Allergan	505(b)(2) sNDA Priority approval 02/01/2018
ferumoxytol	Feraheme®	The FDA expanded the indication of the iron replacement product, ferumoxytol injection, (Feraheme) for the treatment of iron deficiency anemia (IDA) in adults with an intolerance or unsatisfactory response to oral iron. It is also indicated for IDA in patients with chronic kidney disease. Recommended dose is 510 mg IV over at least 15 minutes, which is repeated once in 3 to 8 days.	AMAG	sNDA approval 02/02/2018

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

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
efavirenz/ lamivudine/ tenofovir disoproxil fumarate	Symfi Lo™	The FDA approved the triple-combination antiretroviral, Symfi Lo (efavirenz 400 mg/ lamivudine 300 mg/ tenofovir disoproxil fumarate 300 mg), as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients weighing ≥ 35 kg. Recommended dose is 1 fixed-dose oral tablet once daily taken on an empty stomach, preferably at bedtime. Pregnancy should be avoided in women treated with Symfi Lo.	Mylan	505(b)(2) NDA approval 02/05/2018
abiraterone	Zytiga®	A new indication for use in combination with prednisone was granted to abiraterone (Zytiga) to treat patients with metastatic high-risk castration-sensitive prostate cancer. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog or have had prior bilateral orchiectomy. In the LATITUDE trial, abiraterone led to a 38% risk reduction of death compared to placebo. Dosage is 1,000 mg orally once daily. The CYP17 inhibitor is also indicated for metastatic castration-resistant prostate cancer.	Janssen	sNDA approval 02/07/2018
bictegravir/ emtricitabine/ tenofovir alafenamide	Biktarvy®	Orphan drug, triple-therapy Biktarvy (bictegravir 50 mg/ emtricitabine 200mg/ tenofovir alafenamide 25mg) was approved as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral (ARV)-naïve or who are virologically suppressed (HIV-1 RNA < 50 c/mL) on their current, stable ARV regimen for ≥ 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy. Recommended dosage is 1 fixed-dose oral tablet once daily, taken with or without food.	Gilead	NDA Priority approval 02/07/2018
dexamethasone	Dexycu™	Dexycu, a long-acting, injectable dexamethasone was approved for the treatment of post-operative inflammation associated with cataract surgery. It is administered by an HCP intraocularly into the posterior chamber of the eye after surgery. The Verisome® ER drug delivery technology allows for a single dose and eliminates the need for patient-administered corticosteroid drops. Dexycu is approved as a kit with an intraocular suspension of 9%, equivalent to dexamethasone 103.4 mg/mL, in a single-dose vial.	Icon	505(b)(2) NDA approval 02/09/2018
glatiramer acetate 40 mg/mL	Glatopa®	Generic glatiramer acetate (Glatopa) 40 mg/mL injection in 1 mL prefilled syringes was approved for the treatment of relapsing forms of multiple sclerosis. Glatopa 40 mg/mL, which is therapeutically equivalent to Copaxone® 40 mg/mL, is administered SC 3 times per week. Glatopa is also available as a daily 20 mg/mL SC injection.	Sandoz	ANDA approval 02/12/2018

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

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
tezacaftor/ ivacaftor + ivacaftor	Symdeko™	The Agency granted Orphan drug and Breakthrough therapy designations to Symdeko (tezacaftor/ ivacaftor + ivacaftor) to treat patients ≥ 12 years of age with cystic fibrosis (CF) who are homozygous for the *F508del* mutation or who have at least 1 mutation in the CF transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor. Symdeko is co-packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed-dose combination tablets with ivacaftor 150 mg tablets. The dosage in adults and pediatrics is 1 combination tablet in the morning and 1 ivacaftor tablet in the evening, consumed with fat-containing food, approximately 12 hours apart.	Vertex	NDA Priority approval 02/12/2018
apalutamide	Erleada™	The androgen receptor inhibitor apalutamide (Erleada), became the first agent FDA-approved for the treatment of non-metastatic castration-resistant prostate cancer. During treatment, patients should also receive a GnRH analog concurrently or should have had bilateral orchiectomy. Approved as 60 mg oral tablets, apalutamide is dosed as 240 mg (4 tablets) once daily, with or without food. Compared to placebo, apalutamide resulted in a 72% decrease in the risk of distant metastatic disease or death and ≥ 24 month increase in median metastasis-free survival. Launch is anticipated by early March 2018.	Janssen	NDA Priority approval 02/14/2018
hydroxyprogesterone caproate auto-injector	Makena®	FDA approved a new preservative-free (PF), single-use auto-injector for SC administration of the Orphan drug hydroxyprogesterone caproate (Makena). It is indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Makena is also available in single-dose (PF) and multi-dose vials for intramuscular administration.	AMAG	505(b)(2) sNDA approval 02/14/2018
durvalumab	Imfinzi®	Durvalumab (Imfinzi) garnered Breakthrough therapy designation and approval of a new indication for unresectable, stage III non-small cell lung cancer (NSCLC) in patients whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy. The dosage for NSCLC is 10 mg/kg via a 60 minute IV infusion every 2 weeks until disease progression or unacceptable toxicity. The programmed death-ligand 1 blocker is also indicated in select patients with urothelial carcinoma.	AstraZeneca	sBLA Priority approval 02/16/2018

ANDA=AbbreviatedNewDrugApplication;BLA=BiologicsLicenseApplication;NDA=NewDrugApplication;sBLA=SupplementalBiologicsLicenseApplication; 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.

References:
aan.com cdc.gov circ.ahajournals.org fda.gov rheumatology.org