JULY 2018

MRx CLINICAL ALERT

YOUR MONTHLY SOURCE FOR DRUG INFORMATION HIGHLIGHTS

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HOT TOPIC: FIRST BIOSIMILAR FOR NEULASTA® IS APPROVED

On June 4, 2018, the United States (US) Food and Drug Administration (FDA) approved pegfilgrastim-jmdb (Fulphila™), by Mylan GmbH/Biocon. It is the first biosimilar to Amgen's leukocyte growth factor pegfilgrastim (Neulasta). There are no clinically meaningful differences between pegfilgrastim-jmdb and its reference product regarding potency, safety, and purity as determined by structural and functional description, study data in animals, pharmacokinetic and pharmacodynamic data in humans, and other safety and efficacy data; however, no biosimilar approved in the US is deemed interchangeable with its reference product by the FDA.

Pegfilgrastim-jmdb was approved for the *eligible* indication to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy. It was not, however, approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation (hematopoietic subsyndrome of acute radiation syndrome), which is held by the reference product. Pegfilgrastim-jmdb is given via intravenous (IV) or subcutaneous (SC) injection by a healthcare professional (HCP) or patient/caregiver. With an expected July 2018 launch date, pegfilgrastim-jmdb will be the fifth biosimilar available in the US and may offer improved access to this important biologic medication.

HCV GUIDELINE UPDATE

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) updated their living guidelines for the treatment of hepatitis C virus (HCV) infection. It includes revisions on HCV testing and management in pregnant women and new sections regarding key populations of people who inject drugs (PWID), men who have sex with men (MSM), and incarcerated individuals.

To reduce the risk of HCV transmission to future offspring, AASLD/IDSA advise starting antiviral therapy in HCV-infected women of reproductive age before pregnancy is considered. Treatment during pregnancy is not recommended due to a lack of safety and efficacy data. HCV RNA and routine liver function tests are recommended during pregnancy.

In PWID and MSM, HCV testing should be performed at least yearly and counseling on reducing HCV transmission should be offered. Connection to programs for needle and syringe services and substance use disorder treatment should also be offered to PWID. AASLD/IDSA emphasize recent drug use is not a contraindication to HCV treatment.

Incarcerated persons should be offered HCV testing. HCV treatment should be provided to those chronically infected, if sentence is long enough to complete a course of antiviral therapy. Links to community healthcare services for treatment and/or surveillance of HCV complications should be provided upon release from jail/prison.

SPOTLIGHT: ICER REPORT ON MIGRAINE TREATMENT

In May 2018, erenumab (Aimovig™), a first-in-class injectable calcitonin gene-related peptide (CGRP) inhibitor, received approval for the preventive treatment of migraines. Two additional agents in the class, fremanezumab and galcanezumab, are expected to be approved this year in September. Clinical data report that these agents reduce the number of migraine days by 1 to 3 days per month.

On May 31, 2018, following an announcement of a wholesale acquisition cost (WAC) for erenumab, the Institute for Clinical and Economic Review (ICER) released an updated Evidence Report assessing the comparative clinical effectiveness and value of CGRP inhibitors. Amgen revealed a yearly WAC price for erenumab of $6,900 (decreased from the initially anticipated $8,500/year). Based on an estimated annual net price of $5,000 (assuming a 27% discount), ICER determined erenumab and fremanezumab would be cost-effective in patients who failed at least 1 other migraine preventive treatment (e.g., select antidepressants, antiseizure agents, beta-blockers). ICER estimated of patients affected by chronic or episodic migraine, treatment of 16% with erenumab and 22% with fremanezumab, annually, could maintain affordability.

NEW GUIDELINES FOR MS THERAPY

The American Academy of Neurology (AAN) published new guidelines on disease modifying therapies (DMT) for adults with multiple sclerosis (MS). DMT selection should be based on efficacy, safety, route of administration, lifestyle, and cost. Yearly serial imaging for the first 5 years may be considered in patients who are not on DMT with clinically isolated syndrome (CIS) or relapsing forms of MS with no relapses in the preceding 2 years, and with no new MRI lesion activity. DMT initiation is recommended in patients with a single clinical demyelinating event and ≥ 2 brain lesions typical of MS. The AAN recommends alemtuzumab (Lemtrada®), fingolimod (Gilenya®), or natalizumab (Tysabri®) to treat highly active MS. Natalizumab may be prescribed only when there is a reasonable chance of benefit in patients with a positive anti-John Cunningham virus (JCV) antibody index > 0.9. Ocrelizumab (Ocrevus®) should be offered to patients with primary progressive MS who are likely to benefit.

Patient status should be monitored annually or as directed by the product-specific risk evaluation and mitigation strategy (REMS). DMT effectiveness, tolerability, and adherence, as well as patient reproductive plans should be reviewed. Consider changing to another DMT if nonadherence, intolerable injection discomfort, injection fatigue, persistent laboratory abnormalities, or natalizumab antibodies are present. Discontinue DMT during pregnancy, unless the risk of MS activity outweighs the benefit of therapy. Continue current DMT in patients with stable MS; however, the patient and physician may decide a trial off therapy is warranted. The AAN supports stopping therapy in nonambulatory (≥ 2 years) patients with secondary progressive MS and no ongoing relapses or evidence of gadolinium-enhanced lesions.

RISK OF BIRTH DEFECTS WITH HIV TREATMENT DOLUTEGRAVIR

The FDA issued an alert regarding the risk of neural tube birth defects involving the brain, spine, and spinal cord with dolutegravir, an antiretroviral to treat human immunodeficiency virus-1 (HIV-1). Preliminary data from an ongoing observational study in Botswana reported cases of these birth defects in babies born to women treated with dolutegravir at the time of conception or early in the first trimester. So far, no cases have been reported in women starting dolutegravir later in pregnancy. A pregnancy test should be performed before starting dolutegravir in women of childbearing age. The Agency advises patients to not stop taking dolutegravir without talking to their HCP. Clinicians should inform women of childbearing age on a regimen containing dolutegravir (Juluca®, Tivicay®, Triumeq®) of these serious risks.

FDA ALERT ON MONOTHERAPY WITH KEYTRUDA® OR TECENTRIQ®

The FDA published a warning based on early clinical trial data (KEYNOTE-361 and IMVIGOR-130) of decreased survival associated with monotherapy with atezolizumab (Tecentriq) or pembrolizumab (Keytruda) as compared to platinum-based chemotherapy in treatment-naïve patients with metastatic urothelial carcinoma whose tumors express low levels of the programmed death-ligand 1 (PD-L1) protein. As a result, the indications of the respective PD-L1 and PD-1 inhibitors to treat platinum-ineligible patients were revised. The agents are now indicated to treat locally advanced or metastatic urothelial carcinoma in patients who are ineligible for cisplatin-based chemotherapy whose tumors express PD-L1 (≥ 5% and ≥ 10%, respectively) or in patients who are ineligible for any platinum-based chemotherapy regardless of expression level. The FDA advises selection of platinum-ineligible patients for treatment should be directed by the clinical trial criteria described in the product label. Patients should not stop taking their prescribed medication unless directed by their HCP.

DRUG INFORMATION **HIGHLIGHTS**

- The shortage of epinephrine auto-injectors indicated for the emergency treatment of allergic reactions, including anaphylaxis, continues nationwide. This has resulted in intermittent shortages for Mylan's Epipen® 0.3 mg, Epipen Jr® 0.15 mg, and the authorized generic (AG) versions. While Impax is now shipping its AG version of the discontinued Adrenaclick®, there is not enough product to fill all backorders. No shortages are reported for Kaleo's Auvi-Q® 0.3 mg, 0.15 mg, and 0.1 mg. Adamis' Symjepi® 0.3 mg was FDA-approved in June 2017, but has not entered the US market.
- As a follow-up to an April 2017 Health Advisory Notification (HAN), the Centers for Disease Control and Prevention (CDC) published a Health Update regarding possible clinical treatment failure of *Shigella* infections. The CDC continues to identify an increasing number of ciprofloxacin-resistant *Shigella* isolates and has identified strains resistant to azithromycin. It is unclear if fluoroquinolone (FQ) treatment of a *Shigella* infection with ciprofloxacin (MIC of 0.12–1 µg/mL) will worsen clinical outcome or increase the risk of transmission. The CDC recommends careful monitoring of antibiotic treatment and consulting an infectious disease specialist for *Shigella* infection with possible FQ or azithromycin failure. Stool samples should be cultured and positive cases reported to local/state health departments.
- Apotex voluntarily recalled 1 lot (NDC 60505-0829-01, lot# NJ4501, expiry July 2020) of fluticasone propionate nasal spray (50 mcg/spray, 120 metered sprays) due to reports of small glass particles in the product. This could cause nasal irritation and/or reduced functionality of the pump.
- During the 2017–2018 influenza season, 174 pediatric deaths were reported. About 80% occurred in children who were not vaccinated against the flu. The American Academy of Pediatrics (AAP) stated, in advance of a formal policy statement in September 2018, they will recommend children be vaccinated with the injectable inactivated influenza vaccine in the 2018–2019 influenza season. The recommendation is based on data demonstrating effectiveness of the flu shot over the quadrivalent live attenuated influenza vaccine nasal spray. The AAP, however, does state that the nasal spray vaccine can be given as a last resort, but could leave the child at higher risk for the flu compared to the flu shot. The nasal spray vaccination is not recommended in children < 2 years of age or those with chronic medical conditions, such as asthma.
- The FDA issued a Drug Safety Communication warning that oral drug products containing benzocaine should not be used to treat infants and children < 2 years old, and should only be used in adults and children ≥ 2 years of age if they contain certain warnings on the drug label. The FDA advises that benzocaine products carry serious risks of methemoglobinemia and provide little to no benefits for teething. The Agency is instructing manufacturers to stop marketing over-the-counter (OTC) oral benzocaine products for treating teething pain in infants and children < 2 years of age. The FDA is prepared to remove the product from the market if manufacturers do not comply. Labeling will also require addition of a warning about methemoglobinemia and contraindications of use in infants and children < 2 years, including use for teething.

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

- **July 2018:** insulin glargine, follow-on to Lantus®; SC insulin analogue; types 1 and 2 diabetes mellitus (T1DM, T2DM); Mylan/Biocon.
- **July 10, 2018:** Opdivo®; nivolumab; IV PD-1 inhibitor; metastatic colorectal cancer, in combination with ipilimumab; Bristol-Myers Squibb.
- **July 27, 2018:** buprenorphine sublingual spray; opioid partial agonist-antagonist; acute pain; Insys.
- **July 27, 2018:** buprenorphine SC depot; opioid partial agonist-antagonist; substance use disorder; Braeburn.
- **July 27, 2018:** risperidone monthly SC depot; atypical antipsychotic; schizophrenia; Indivior.
- **July 27, 2018:** tafenoquine; oral antimalarial; malaria prevention; GlaxoSmithKline.
- **August 2, 2018:** Invokana® and Invokamet® XR; canagliflozin and canagliflozin/metformin-ER; oral sodium-glucose linked transporter 2 (SGLT2) inhibitor and oral SGLT2 inhibitor/biguanide; cardiovascular disease (CVD) risk reduction with T2DM; Janssen.
- **August 6, 2018:** elagolix; oral luteinizing hormone releasing hormone (LHRH) antagonist; endometriosis; Abbvie.
- **Quarter 3, 2018:** damoctocog alfa pegol; IV pegylated recombinant coagulation factor VIII; hemophilia A; Bayer.
- **Quarter 3, 2018:** darunavir/cobicistat/emtricitabine/tenofovir alafenamide; oral antiretroviral; HIV-1 infection; Janssen.

RECENT FDA APPROVALS

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
fluticasone furoate	Arnuity® Ellipta®	The indication for the inhaled corticosteroid, fluticasone furoate (Arnuity Ellipta), was expanded to include maintenance treatment of asthma in patients ages 5 to 11 years. A new 50 mcg blister pack was approved to accommodate the 50 mcg daily dose in this population.	GlaxoSmithKline	sNDA approval 05/17/2018
denosumab	Prolia®	Denosumab (Prolia) received a new indication for the treatment of osteoporosis associated with newly initiated or sustained systemic glucocorticoid therapy in men and women at high fracture risk. The medication is administered by an HCP as 60 mg SC every 6 months.	Amgen	sBLA approval 05/18/2018
sodium zirconium cyclosilicate	Lokelma™	The potassium binder, sodium zirconium cyclosilicate (Lokelma), was approved to treat hyperkalemia in adults. It should not be used as emergency treatment for life-threatening hyperkalemia due to a delayed onset of action. The initial dose is 10 mg orally 3 times daily for up to 48 hours. The maintenance dose is 10 mg once daily and can be adjusted to a target potassium range. The oral powder, approved as 5 g and 10 g packets, is mixed in ≥ 15 mL of water and consumed immediately.	AstraZeneca	NDA approval 05/18/2018
avatrombopag	Doptelet™	The thrombopoietin receptor agonist, avatrombopag (Doptelet), was approved to treat thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure. Available as a 20 mg oral tablet, the recommended dose is 2 to 3 tablets, depending on the serum platelet level, taken daily for 5 days. Avatrombopag should be started 10 to 13 days before a scheduled procedure, which should be performed 5 to 8 days after the last dose.	Akarx/Dova	NDA Priority approval 05/21/2018
abiraterone acetate	Yonsa®	Abiraterone (Yonsa), a 17 α-hydroxylase/C17, 20-lyase (CYP17) inhibitor, was approved in combination with methylprednisolone to treat metastatic castration-resistant prostate cancer (CRPC). Available as 125 mg micronized tablets, the dosage is 500 mg (4 tablets) orally once daily. Patients should receive concurrent gonadotropin-releasing hormone (GnRH) analogue therapy or should have undergone a bilateral orchiectomy. Yonsa should be used cautiously as dosing can vary from other abiraterone formulations.	Sun	505(b)(2) NDA approval 05/22/2018
halobetasol propionate	No trade name	A new formulation of topical halobetasol propionate, a 0.05% foam in 50 g aluminum cans, received approval. The corticosteroid is indicated for the topical treatment of plaque psoriasis (PSO) in patients ≥ 18 years of age. The foam should be applied as a thin film to the affected skin as directed twice daily for up to 2 weeks. No more than 50 g should be applied per week. Avoid use on the face, groin, or axillae. Halobetasol propionate foam is not for ophthalmic, oral, or intravaginal use.	ABM	NDA approval 05/24/2018

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
pegvaliase-pqpz	Palynziq™	The FDA approved the Orphan drug pegvaliase-pqpz (Palynziq) to reduce blood phenylalanine levels in adults with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations > 600 micromol/L on existing management. The initial dose of the phenylalanine-metabolizing enzyme is 2.5 mg SC once weekly for 4 weeks. The dose is then titrated over ≥ 5 weeks, as tolerated, to a target of 20 mg once daily; 40 mg/day may be considered in select patients. Discontinue if targeted results are not achieved after 16 weeks with 40 mg/day. The first dose should be given under HCP supervision, but may be self-administered, thereafter. Anaphylaxis can occur; thus, patients should carry an auto-injectable epinephrine at all times while on therapy. Pegvaliase-pqpz is available as 2.5 mg/0.5 mL, 10 mg/0.5 mL, or 20 mg/mL in single-dose prefilled (SDF) syringes only through a restricted REMS program.	Biomarin	BLA approval 05/24/2018
certolizumab pegol	Cimzia®	The tumor necrosis factor (TNF) inhibitor, certolizumab pegol (Cimzia), gained a new indication for adults with moderate to severe PSO who are candidates for systemic therapy or phototherapy. The PSO dose is 400 mg (two 200 mg injections) SC every other week. In some patients weighing ≤ 90 kg, an initial dose of 400 mg and at weeks 2 and 4, then 200 mg every other week may be considered.	UCB	sBLA approval 05/25/18
estradiol	Imvexxy™	Estradiol vaginal inserts (Imvexxy) were approved to treat moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy due to menopause. Vaginal inserts containing 4 mcg or 10 mcg of estradiol are administered once daily for 2 weeks, then twice weekly thereafter.	TherapeuticsMD	505(b)(2) NDA approval 05/29/2018
tofacitinib	Xeljanz®	The Janus kinase (JAK) inhibitor, tofacitinib (Xeljanz), gained a new indication for use in adults with moderately to severely active ulcerative colitis (UC). The UC dosage is 10 mg orally twice daily for ≥ 8 weeks, then 5 mg or 10 mg twice daily. Discontinue if adequate benefit is not found after 16 weeks of treatment using 10 mg twice daily. The extended-release tablet (Xeljanz XR) is not indicated for UC.	Pfizer	sNDA approval 05/30/2018
amlodipine besylate/ celecoxib	Consensi®	Consensi, a combination of amlodipine besylate, a calcium channel blocker, and celecoxib, a nonsteroidal anti-inflammatory drug (NSAID), was approved in patients for whom treatment with amlodipine for hypertension and celecoxib for osteoarthritis are appropriate. Consensi fixed-dose tablets are approved in the following combinations: 2.5 mg/200 mg, 5 mg/200 mg, and 10 mg/200 mg. The initial dose is one 5 mg/200 mg tablet orally once daily; it may be titrated to 10 mg/200 mg once daily for blood pressure control. Select patients may be started with 2.5 mg/200 mg. If analgesic therapy is no longer indicated, discontinue Consensi and initiate an alternative antihypertensive therapy.	Kitov	505(b)(2) NDA approval 05/31/2018

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RECENT FDA APPROVALS continued

GENERIC NAME	TRADE NAME	DESCRIPTION	APPLICANT	FDA STATUS
baricitinib	Olumiant®	Baricitinib (Olumiant) is a JAK inhibitor indicated to treat adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to ≥ 1 TNF inhibitor. Baricitinib may be used alone or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs); however, it is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants, such as azathioprine and cyclosporine. Baricitinib is available as 2 mg tablets. The recommended dosage is 1 tablet once daily.	Eli Lilly	NDA approval 05/31/2018
pemetrexed disodium	Alimta®	The FDA granted Accelerated approval to the folate analogue metabolic inhibitor, pemetrexed disodium (Alimta), for use in combination with carboplatin and pembrolizumab for the initial treatment of patients with metastatic, non-squamous, non-small cell lung cancer (NSCLC); continued approval may depend on results of confirmatory trials. The dosage for this expanded indication in patients with an estimated creatine clearance ≥ 45 mL/minute is 500 mg/m^2 IV on the first day of each 21-day cycle. The labeling also provides details on use of folic acid, vitamin B_{12}, and dexamethasone.	Eli Lilly	sNDA approval 06/04/2018
methoxy polyethylene glycol-epoetin beta (PEG-EPO)	Mircera®	The Agency expanded the indication for methoxy polyethylene glycol-epoetin beta (Mircera), an erythropoiesis-stimulating agent (ESA), for the treatment of anemia associated with chronic kidney disease (CKD) to include patients ages 5 to 17 years on hemodialysis who are converting from another ESA after hemoglobin level stabilization. In this population, PEG-EPO is administered by IV injection once every 4 weeks. The dose is based on the total weekly ESA dosage at conversion. PEG-EPO is also indicated to treat adults with CKD-related anemia, on or not on dialysis. A 360 mcg/0.6 mL SDF syringe was approved to accommodate pediatric dosing.	Vifor	sBLA approval 06/07/2018
rituximab	Rituxan®	The CD20-directed cytolytic antibody, rituximab (Rituxan), received a new indication to treat adults with moderate to severe pemphigus vulgaris (PV). The dose for PV is two 1,000 mg IV infusions, separated by 2 weeks, combined with a tapering course of glucocorticoids, followed by a 500 mg IV infusion at month 12 and every 6 months thereafter, or based on clinical evaluation. Upon relapse, the dosage is 1,000 mg IV with consideration to resume or increase the glucocorticoid dose. Repeat rituximab infusions no sooner than 16 weeks after the previous infusion. Premedication with a glucocorticoid is recommended prior to each infusion. Rituximab received Breakthrough therapy and Orphan drug designations for PV.	Genentech	sBLA Priority approval 06/07/2018

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References:
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