Pharmacy therapeutic update

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New drugs[a]

Product name[b]	Indication	Dose	Adverse reactions	Comments
Avatrombopag (Doptelet®) tablet for oral use – Dova Pharmaceuticals	Thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure.	Initiate avatrombopag 10 to 13 days prior to a scheduled procedure. The recommended dose of avatrombopag is based on a patient's platelet count prior to a scheduled procedure and should be taken orally with food once daily for 5 consecutive days. For recommended dose, please consult the prescribing information.	The most common adverse reactions are pyrexia, abdominal pain, nausea, headache, fatigue and peripheral edema.	Avatrombopag is the first TPO receptor agonist approved to treat low platelet counts in CLD. Other approved TPO receptor agonists (eltrombopag and romiplostim) are indicated for the treatment of chronic immune thrombocytopenia and/or idiopathic thrombocytopenic purpura. In the ADAPT-1 and ADAPT-2 trials, avatrombopag was superior to placebo for the proportion of patients that did not require a platelet transfusion at both the 40 mg dose (ADAPT-1, 88% vs. 38%; ADAPT-2, 88% vs. 33%) and the 60 mg dose (ADAPT-1, 66% vs. 23%; ADAPT-2, 69% vs. 35%).
Baricitinib (Olumiant®) tablet for oral use – Eli Lilly and Company	Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.	The recommended dose is 2 mg once daily. Baricitinib can be used as monotherapy or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDs).	Black box warning – serious infections, malignancy and thrombosis. The most common adverse reactions include upper respiratory tract infections, nausea, herpes simplex and herpes zoster.	Baricitinib joins tofacitinib (Xeljanz®) as the second FDA-approved JAK inhibitor for the treatment of adult patients with RA. Because Lilly originally proposed that the recommended dose should be 4 mg, the approved 2 mg dose was only evaluated in 2 of the 4 phase 3 trials and reduction in radiologic progression was not assessed with the 2 mg dose. The 4 mg dose was not approved due to uncertainty about dose-related toxicity. The FDA has asked Lilly to conduct a long-term safety study to evaluate benefit versus risk.
Epoetin alfa-epbx (Retacrit™) injection for intravenous or subcutaneous use – Hospira Inc, a Pfizer company	Erythropoiesis-stimulating agent (ESA) indicated for treatment of anemia due to chronic kidney disease in patients on dialysis and not on dialysis, zidovudine in patients with HIV-infection and the effects of concomitant myelosuppressive chemotherapy. Also indicated for reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery.	Please consult the prescribing information for dosage recommendations.	Black box warning – increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access and tumor progression or recurrence. For common adverse reactions, please consult the prescribing information.	Epoetin alfa-epbx is the first FDA-approved biosimilar of Procrit® and Epogen®. It was approved for all the same indications as the reference products, but did not receive interchangeable status. As there are no pending patents to prevent biosimilar competition, it is expected that Pfizer will launch epoetin alfa-epbx in the 3rd or 4th quarter. Biosimilarity was demonstrated based on the results of comparative structural and physicochemical analyses, functional and biological analyses and nonclinical and clinical analyses. There are no other ESA biosimilars close to approval.

New drugs (continued)[a]

Product name[b]	Indication	Dose	Adverse reactions	Comments
Erenumab-aooe (Aimovig™) injection for subcutaneous use – Amgen	Calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults.	The recommended dosage is 70 mg once monthly; some patients may benefit from a dosage of 140 mg once monthly (administered as 2 consecutive injections of 70 mg each). The subcutaneous injection should be administered in the abdomen, thigh or upper arm.	The most common adverse reactions are injection site reactions and constipation.	Erenumab is the first and only FDA-approved calcitonin gene-related peptide antagonist. Three clinical trials support its approval. In the STRIVE and ARISE trials, treatment with erenumab 70 mg reduced the mean number of migraine days per month by 1.0 to 1.4 compared with placebo in patients with episodic migraines. In the STRIVE trial, the 140 mg dose was associated with a mean reduction of almost 2 days per month. In a third trial, patients with chronic migraine had, on average, a reduction of 2.5 fewer monthly migraine days than placebo-treated patients.
Lofexidine (Lucemyra™) tablet for oral use – US WorldMeds	Central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults.	The usual dosage is 0.54 mg (3 tablets) taken orally 4 times daily at 5- to 6-hour intervals. Treatment may be continued for up to 14 days with dosing guided by symptoms. Discontinue lofexidine with a gradual dose reduction over 2 to 4 days.	The most common adverse reactions are orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation and dry mouth.	Lofexidine is the first nonopioid drug approved to mitigate opioid withdrawal symptoms. It is not intended as a treatment for opioid use disorder, but rather as a component of a long-term treatment plan. Two placebo-controlled clinical trials support its approval. In both trials, lofexidine reduced opioid withdrawal symptom severity and increased treatment retention rates. In a 2016 Cochrane review, both clonidine and lofexidine were more effective than placebo for the management of withdrawal from heroin or methadone, but were not significantly different from a strategy of reducing doses of methadone over a period of 10 days. Clonidine appears to be associated with a greater degree of hypotension than lofexidine.
Pegfilgrastim-jmdb (Fulphila™) injection for subcutaneous use – Mylan	Leukocyte growth factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.	The recommended dose is 6 mg administered subcutaneously once per chemotherapy cycle. In pediatric patients weighing less than 45 kg, use weight based dosing.	The most common adverse reactions are bone pain and pain in extremity.	Pegfilgrastim-jmdb is the first FDA-approved biosimilar of Amgen's pegfilgrastim (Neulasta®). It is approved for all of the same indications as reference pegfilgrastim except for the hematopoietic subsyndrome of acute radiation syndrome indication, which is protected by Orphan Drug Exclusivity until November 2022. It is likely that pegfilgrastim-jmdb will not face any successful patent challenge by Amgen and will be launched within the next several weeks. The FDA's goal date to review Coherus's pegfilgrastim biosimilar application is November 3.

New drugs (continued)[a]

Product name[b]	Indication	Dose	Adverse reactions	Comments
Pegvaliase-pqpz (Palynziq™) injection for subcutaneous use – BioMarin Pharmaceutical Inc	Phenylalanine-metabolizing enzyme indicated to reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management.	The recommended initial dosage is 2.5 mg subcutaneously once weekly for 4 weeks. Titrate the dosage in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20 mg once daily. The maximum dose is 40 mg once daily.	Black box warning – risk of anaphylaxis. The most common adverse reactions are injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea and fatigue.	Pegvaliase is the first approved enzyme substitution therapy that targets the underlying cause of PKU. The current mainstay of therapy for PKU is dietary manipulation; however, a trial of sapropterin dihydrochloride (Kuvan®) is also recommended. Unlike sapropterin dihydrochloride, pegvaliase does not require patients to adhere to a restrictive diet, but it has unique safety concerns. In clinical trials, approximately 9% of patients had an anaphylactic reaction. Due to safety concerns, pegvaliase is only available through a restricted program that requires prescribers and pharmacists to be certified and patients to be enrolled in an education program.
Sodium zirconium cyclosilicate (Lokelma™) for oral suspension – AstraZeneca	Potassium binder indicated for the treatment of hyperkalemia in adults.	The recommended initial dosage is 10 g administered 3 times a day for up to 48 hours. For maintenance treatment, the recommended dose is 10 g once daily. The dose may be adjusted at weekly intervals as needed (by 5 g daily) to obtain desired serum potassium target range.	The most common adverse reaction is mild to moderate edema.	Sodium zirconium cyclosilicate (ZS-9) is expected to compete with patiromer (Veltassa®). Although sodium polystyrene sulfonate is also indicated for the treatment of hyperkalemia, its slow onset of action, low efficacy, and adverse event profile makes it a less desirable option. ZS-9 and patiromer have not been compared head-to-head, but based on the results of a meta-analysis, ZS-9 may have a faster onset of action and improved tolerability.

New indications[a,c]

Product name[b]	Indication	Dose	Adverse reactions	Comments
Certolizumab pegol (Cimzia®) injection and for injection for subcutaneous use – UCB Inc	TNF blocker indicated for treatment of adults with moderate-to-severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.	The recommended dosage is 400 mg (given as 2 subcutaneous injections of 200 mg each) every other week. For some patients (with body weight ≤ 90 kg), a dose of 400 mg initially and at weeks 2 and 4, followed by 200 mg every other week may be considered.	Black box warning – serious infections and malignancy. The most common adverse reactions are upper respiratory tract infection, rash and urinary tract infection.	Certolizumab pegol is the first Fc-free, pegylated anti-TNF treatment for PsO. Several TNF blockers are approved for the treatment of PsO including adalimumab (Humira®), etanercept (Enbrel®) and infliximab (Remicade®). The approval of certolizumab pegol for the treatment of PsO was based on data from the phase 3 clinical development program that consisted of the CIMPASI-1, CIMPASI-2 and CIMPACT trials. In all 3 trials, certolizumab pegol demonstrated statistically significant improvement for all primary and co-primary endpoints compared with placebo and maintained the response through 48 weeks.

New indications (continued)[a,c]

Product name[b]	Indication	Dose	Adverse reactions	Comments
Denosumab (Prolia®) injection for subcutaneous use – Amgen Inc	RANK ligand inhibitor indicated for treatment of glucocorticoid-induced osteoporosis (GIOP) in men and women at high risk of fracture.	The recommended dosage is 60 mg every 6 months as a subcutaneous injection in the upper arm, upper thigh or abdomen.	The most common adverse reactions are back pain, hypertension, bronchitis and headache.	The approval of denosumab for GIOP was supported by the 12-month primary analysis of a 24-month phase 3 trial that compared denosumab with risedronate in glucocorticoid-initiating and glucocorticoid-continuing patients. In both subpopulations, denosumab was noninferior and superior to risedronate in terms of lumbar spine bone mineral density and total hip bone mineral density. The study was not powered to detect differences between the treatments in fracture risk. The American College of Rheumatology Guideline for the Prevention and Treatment of GIOP was published in August 2017.
Rituximab (Rituxan®) injection for intravenous use – Genentech	CD20-directed cytolytic antibody indicated for the treatment of adult patients with moderate to severe Pemphigus Vulgaris (PV) in adult patients.	The initial dose is 2 – 1000 mg IV infusions separated by 2 weeks in combination with a tapering course of glucocorticosteroids, then a 500 mg IV infusion at month 12 and every 6 months thereafter or based on clinical evaluation.	Black box warning – fatal infusion reactions, severe mucocutaneous reactions, hepatitis b virus reactivation and progressive multifocal leukoencephalopathy. The most common adverse reactions are infusion reactions, depression and infections.	Rituximab is the first biologic approved for treatment of moderate to severe PV. Its approval was supported by the Ritux 3 trial. Results of the trial demonstrated that significantly more patients assigned to rituximab plus short-term prednisone were in complete remission off-therapy at month 24 compared with patients assigned to prednisone alone (89% vs. 34%; *P*<.0001). Newly published expert consensus recommendations for the treatment of PV include a discussion about rituximab's potential place in therapy.
Venetoclax (Venclexta®) tablet for oral use – AbbVie Inc	BCL-2 inhibitor indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least 1 prior therapy.	Initiate therapy with venetoclax at 20 mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400 mg. If used in combination with rituximab, administer rituximab after the 5-week ramp-up schedule with venetoclax. Continue venetoclax for 24 months from day 1 of cycle 1 of rituximab.	The most common adverse reactions when used in combination with rituximab are neutropenia, diarrhea, upper respiratory tract infection, fatigue, cough and nausea.	With this approval, venetoclax plus rituximab is the first oral-based, chemotherapy-free combination with a fixed treatment duration for CLL. The approval of the combination of venetoclax and rituximab for the treatment of patients with relapsed/refractory (R/R) CLL or SLL is based on the results of the MURANO phase 3 trial. In the trial, patients with R/R CLL randomized to receive venetoclax for up to 2 years plus rituximab for 6 months had significantly higher investigator-assessed, 2-year progression-free survival than patients randomized to receive bendamustine plus rituximab for 6 months (84.9% vs. 36.6%; *P*<.001).

New formulations/combinations[a]

Product name[b]	Indication	Dose	Adverse reactions	Comments
$ **Abiraterone acetate** (Yonsa®) tablet for oral use – Sun Pharma	CYP17 inhibitor indicated in combination with methylprednisolone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).	The recommended dosage is 500 mg (4 tablets) administered orally once daily in combination with methylprednisolone 4 mg administered orally twice daily. The tablets can be taken with or without food. Patients should also receive a gonadotropin-releasing hormone analog concurrently or should have had bilateral orchiectomy.	The most common adverse reactions are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.	Yonsa is a new micronized formulation of abiraterone acetate that was approved via the 505(b)(2) regulatory pathway. Yonsa will be promoted as a branded drug and will compete against the non-micronized formulation of abiraterone acetate (Zytiga®). Zytiga differs from Yonsa in the following ways: 1. In addition to mCRPC, Zytiga is approved for treatment of patients with metastatic high-risk castration-sensitive prostate cancer; 2. Zytiga must be administered on an empty stomach; 3. Zytiga is approved in combination with prednisone; and 4. The dose of Zytiga is 1000 mg.
Amlodipine and celecoxib (Consensi™) tablet for oral use – Kitov Pharma	Combination of a calcium channel blocker (CCB) and a nonsteroidal anti-inflammatory (NSAID) drug indicated for patients for whom treatment with amlodipine for hypertension and celecoxib for osteoarthritis are appropriate.	Initiate at (amlodipine/celecoxib) 2.5/200 mg or 5 mg/200 mg orally once daily. Titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed for blood pressure control.	Black box warning – risk of serious cardiovascular and gastrointestinal events. The most common adverse reactions to celecoxib are abdominal pain, diarrhea, dyspepsia, flatulence, peripheral edema, accidental injury, dizziness, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection and rash. The most common adverse reactions to amlodipine are edema, fatigue, nausea, abdominal pain and somnolence.	This is the first FDA-approved, fixed-dose combination (FDC) of a CCB and an NSAID. A FDC may improve treatment adherence in patients. In the phase 3 trial that supported its approval, the combination of celecoxib and amlodipine was noninferior to amlodipine for the mean change in average daytime ambulatory systolic blood pressure (-10.6 mm Hg vs. -8.83 mm Hg, respectively) in subjects with newly diagnosed hypertension. Due to a trend toward superior blood pressure lowering effects with the combination, a follow-up study was conducted to quantify the renovascular effects of the combination. According to the company, results suggest that the combination led to a statistically significant reduction of serum creatinine.

[a]Product information regarding new medications, indications, and formulations is based on information retrieved from respective product prescribing information and the Food and Drug Administration website available at Drugs@FDA, accessed June 2018.

[b]$ Denotes a high-cost alert. High-cost is defined as a wholesale acquisition cost (WAC) of ≥ $1000.00 per dose for any medication or ≥ $20.00 per dose for an oral medication. WAC information was retrieved from Medi-Span, accessed June 2018. The high-cost alert only considers acquisition cost, not utilization-based spend.

P Denotes the drug is FDA-approved to treat pediatric patients.

[c]The following drugs were approved for treatment in expanded patient populations: 1. Emtricitabine and tenofovir disoproxil fumarate (Truvada®) – in combination with other antiretroviral agents for the treatment of HIV-1 infection in pediatric patients weighting at least 17 kg and in combination with safer sex practices for HIV-1 pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in at risk adolescent weighing at least 35 kg; 2. Methoxy polyethylene glycol-epoetin beta (Mircera®) – treatment of anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another erythropoiesis-stimulating (ESA) agent after their hemoglobin level was stabilized with an ESA.