

## New Drug Update 2018\*

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### Objectives:

After attending this program, the participant will be able to:

1. Identify the indications and routes of administration of the new therapeutic agents.
2. Identify the important pharmacokinetic properties and the unique characteristics of the new drugs.
3. Identify the most important adverse events and precautions of the new drugs.
4. Compare the new drugs to the older therapeutic agents to which they are most similar in activity.
5. Identify information regarding the new drugs that should be communicated to patients.

### New Drug Comparison Rating (NDCR) system

- 5 = important advance
- 4 = significant advantage(s) (e.g., with respect to use/effectiveness, safety, administration)
- 3 = no or minor advantage(s)/disadvantage(s)
- 2 = significant disadvantage(s) (e.g., with respect to use/effectiveness, safety, administration)
- 1 = important disadvantage(s)

### Additional information

The Pharmacist Activist monthly newsletter: [www.pharmacistactivist.com](http://www.pharmacistactivist.com)

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**Delafloxacin meglumine** (Baxdela – Melinta)

Antibacterial Agent

2017 New Drug Comparison Rating =

Indication: Administered orally or intravenously for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the Gram-positive bacteria *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Staphylococcus haemolyticus*, *Staphylococcus lugdunensis*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Streptococcus pyogenes*, and *Enterococcus faecalis*, and the Gram-negative bacteria *Escherichia coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*

Comparable drugs: Levofloxacin, moxifloxacin

Advantages:

- Has been demonstrated to be effective in ABSSSI caused by MRSA
- Spectrum of antibacterial action includes a larger number of Gram-positive and Gram-negative bacteria
- May be less likely to cause QT interval prolongation and phototoxicity
- May be less likely to interact with other medications

Disadvantages:

- Labeled indications are more limited (whereas comparable drugs are also indicated for respiratory and certain other infections)
- Is administered every 12 hours (whereas comparable drugs are administered every 24 hours)

Most important risks/adverse events: Risk of tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects (e.g., dizziness, confusion, tremors), and exacerbation of myasthenia gravis (boxed warnings; should be avoided in patients with a history of tendon disorders, peripheral neuropathy, or with a history of myasthenia gravis; treatment should be immediately discontinued in patients in whom such adverse events occur; patients should be advised to not drive or engage in other activities that require mental alertness and coordination until they know how the drug affects them); risk of *Clostridium difficile*-associated diarrhea; use in children is not recommended; dosage for intravenous administration should be reduced in patients with severe renal impairment (serum creatinine concentrations should be monitored); may form chelates with multivalent metal cations (should be administered at least 2 hours before or 6 hours after products such as antacids and vitamin/mineral supplements that contain multivalent cations)

Most common adverse events: Nausea (8%), diarrhea (8%), headache (3%), transaminase elevations (3%)

Usual dosage: Bioavailability of a single oral dose of 450 mg is comparable to that of a single intravenous dose of 300 mg: 300 mg every 12 hours over 60 minutes by intravenous infusion, or 450 mg every 12 hours orally; treatment may be initiated intravenously and then switched to oral administration as appropriate; duration of treatment is 5 to 14 days; in patients with severe renal impairment, the dosage for intravenous administration should be reduced to 200 mg every 12 hours because of the potential accumulation of the intravenous vehicle

Products: Tablets – 450 mg; vials for injection – 300 mg as a lyophilized powder (should be reconstituted and diluted with 5% Dextrose Injection or 0.9% Sodium Chloride Injection)

Comments: Delafloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of action, and is the first fluoroquinolone to be demonstrated to be effective in the treatment of infections caused by MRSA. Its effectiveness was evaluated in two studies in which it was compared with and demonstrated to be noninferior to the use of vancomycin and aztreonam in combination. An objective clinical response (a 20% or greater decrease in lesion size) at 48 to 72 hours was achieved in approximately 80% of the patients with both treatment regimens in both studies. The success of treatment as assessed on follow-up at about 14 days exceeded 95% for both treatment

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regimens. Its effectiveness as a single agent that may be administered orally provides an advantage over the concurrent intravenous use of vancomycin and aztreonam.

**Ozenoxacin** (Xepi – Medimetrix)

Antibacterial Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Topical treatment of impetigo due to *Staphylococcus aureus* or *Streptococcus pyogenes* in adults and pediatric patients 2 months of age and older

Comparable drugs: Mupirocin (e.g., Bactroban), retapamulin (Altabax)

Advantages:

--Is active against methicillin-resistant *S. aureus* (MRSA)(compared with retapamulin that is indicated for methicillin-susceptible isolates only)

--Is indicated for pediatric patients as young as 2 months of age (compared with retapamulin that is not indicated for patients younger than 9 months)

--Is less likely to cause adverse events

--Is applied less frequently (twice a day compared with mupirocin that is applied three times a day)

Disadvantages:

--Has not been directly compared with comparable drugs in clinical studies

--May be less effective

--Labeled indications and formulations are more limited (compared with mupirocin that is also indicated for the treatment of secondarily infected traumatic skin lesions, and is also available in a nasal ointment formulation for the eradication of nasal colonization with MRSA in adult patients and health care workers as part of an infection control program during institutional outbreaks of MRSA infection)

Most important risks/adverse events: Potential for microbial overgrowth of nonsusceptible bacteria and fungi (if such infections occur, use should be discontinued and alternative therapy instituted)

Most common adverse events: Rare reports of rosacea and seborrheic dermatitis

Usual dosage: A thin layer of cream is applied to the affected area twice a day for 5 days; affected area may be up to 100 cm<sup>2</sup> in adult and pediatric patients 12 years of age and older, or 2% of the total body surface area and not exceeding 100 cm<sup>2</sup> in pediatric patients less than 12 years of age; treated area may be covered with a sterile bandage or gauze dressing to protect the area and avoid accidental transfer of the cream to the eyes or other areas

Product: Cream – 1% (10 mg/gram)

Comments: Impetigo is a highly contagious bacterial skin infection that is usually caused by *S. aureus* or *S. pyogenes*. It occurs most often in infants and young children, and spreads easily in child care settings and schools. Impetigo that is localized and involves limited areas of skin is usually treated with a topically-applied antibacterial agent (i.e., mupirocin, retapamulin), and more extensive lesions are usually treated with an oral antibiotic.

Ozenoxacin is a quinolone antibacterial agent that is applied topically and exhibits a bactericidal action. Its action against *S. aureus* includes both methicillin-susceptible and methicillin-resistant isolates. Its effectiveness was evaluated in two placebo-controlled clinical trials in which overall success was defined as no need for additional antimicrobial therapy of the baseline affected area(s) and absence/reduction in clinical signs and symptoms assessed at the end of therapy (Day 6-7). Clinical success was demonstrated in 35% and 54% of the patients treated with ozenoxacin, compared with 19% and 38%, respectively, of those on placebo. Ozenoxacin has not been directly compared with mupirocin or retapamulin, but a comparison of the results of the studies of the individual drugs suggests that the new drug is less effective. For the treatment of impetigo, ozenoxacin is used in a cream formulation, whereas mupirocin and retapamulin are used in ointment formulations.

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### **Meropenem trihydrate/vaborbactam (Vabomere – Medicines Company) Antibacterial Agent**

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered by intravenous infusion for the treatment of adults with complicated urinary tract infections (cUTI) including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex

Comparable drugs: Ceftazidime/avibactam (Avycaz)

Advantages:

--May be effective in certain infections that do not respond to other antibacterial agents

Disadvantages:

--Indication for urinary tract infections is more limited (does not include infections caused by *Citrobacter freundii* complex, *Proteus mirabilis*, or *Pseudomonas aeruginosa*)

--Labeled indications are more limited (ceftazidime/avibactam is also indicated for the treatment of complicated intra-abdominal infections)

--Is infused intravenously over 3 hours (whereas ceftazidime/avibactam is infused over 2 hours)

Most important risks/adverse events: Contraindicated in patients with known hypersensitivity to any component of the product, or to other drugs in the same class, as well as in patients who have demonstrated anaphylactic reactions to any beta-lactam antibacterial agent; possibility of *Clostridium difficile*-associated diarrhea; seizures and other central nervous system adverse events (risk is increased in patients with underlying CNS disorders; patients treated on an outpatient basis should not operate machinery or motorized vehicles until they know how treatment is tolerated); may reduce the concentration of valproic acid or divalproex sodium and concurrent use is not recommended; dosage should be reduced in patients with impaired renal function; concentration of meropenem may be increased by probenecid and concurrent use is not recommended

Most common adverse events: Headache (9%), phlebitis/infusion site reactions (4%), diarrhea (3%)

Usual dosage: Administered by intravenous infusion over 3 hours; 2 grams of meropenem and 2 grams of vaborbactam every 8 hours for up to 14 days; the dosage should be reduced to 1 gram/1 gram every 8 hours in patients with an estimated glomerular filtration rate of 30 to 49 mL/min/1.73m<sup>2</sup>; the product labeling should be consulted for the recommended dosage in patients with more severely impaired renal function

Product: Single-use vials – 1 gram meropenem/1 gram vaborbactam; contents of a vial should be constituted with 0.9% Sodium Chloride Injection, and subsequently diluted with 0.9% Sodium Chloride Injection

Comments: The beta-lactam antibacterial agents (e.g., penicillins, cephalosporins, carbapenems) are highly effective in the treatment of many bacterial infections. However, an increasing number of bacteria are able to produce beta-lactamase enzymes that break the beta-lactam ring and inactivate the antibacterial agent. Beta-lactamase inhibitors have been developed that preserve and extend the activity of the beta-lactam antibiotics with which they are used in combination. In 2015, ceftazidime/avibactam was approved and is the first such combination considered to have activity against some carbapenem-resistant Enterobacteriaceae, including those that produce *Klebsiella pneumoniae* carbapenemase (KPC).

The carbapenem antibacterial agents marketed in the United States include imipenem (used in combination with cilastatin [e.g., Primaxin], meropenem (e.g., Merrem IV), ertapenem (Invanz), and doripenem (Doribax). The indications for meropenem include complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis. Meropenem/vaborbactam represents a combination of meropenem with the new beta-lactamase inhibitor, vaborbactam. Vaborbactam protects meropenem from degradation by certain beta-

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lactamases such as KPC. The new combination was evaluated in clinical trials in which it was compared with piperacillin/tazobactam (e.g., Zosyn). At the end of IV treatment 98% of the patients treated with the new product had cure/improvement of symptoms and a negative urine culture, compared with 94% of those treated with piperacillin/tazobactam.

**Secnidazole** (Solosec – Symbiomix)

Antibacterial Agent

2017 New Drug Comparison Rating (NDCR) =

Indication: Treatment of bacterial vaginosis in adult women

Comparable drugs: Metronidazole (e.g., Flagyl), tinidazole (Tindamax)

Advantages:

- Is administered as a single-dose treatment (whereas tinidazole is used in 2-dose or 5-dose regimens and metronidazole in more frequent treatment regimens)
- May be safer for use during pregnancy (metronidazole and tinidazole are contraindicated during the first trimester)
- Is less likely to interact with other medications/beverages (e.g., disulfiram-like reactions have been experienced following the consumption of alcoholic beverages in patients treated with metronidazole and tinidazole)

Disadvantages:

- Has not been directly compared with comparable drugs in clinical studies
- Labeled indications are more limited (metronidazole is also approved for numerous types of systemic anaerobic bacterial infections, amebiasis, and trichomoniasis, and tinidazole is also approved for amebiasis, giardiasis, and trichomoniasis)
- Route of administration/formulation options are more limited (compared with metronidazole that is also administered intravaginally for the treatment of bacterial vaginosis)
- Administration requires sprinkling granules onto applesauce, yogurt, or pudding

Most important risks/adverse events: Contraindicated in patients with a history of hypersensitivity to any of the nitroimidazole antimicrobial agents; vulvovaginal candidiasis (may require treatment with an antifungal agent); risk of carcinogenicity (has been reported in animal studies with other nitroimidazoles, but is not known whether there is risk with a single-dose in humans); breastfeeding is not recommended and should be discontinued for 96 hours after administration

Most common adverse events: Vulvovaginal candidiasis (10%), headache (4%), nausea (4%), dysgeusia (4%), vomiting (3%), diarrhea (3%), abdominal pain (2%), vulvovaginal pruritus (2%)

Usual dosage: A single dose of 2 grams as oral granules that are sprinkled onto applesauce, yogurt, or pudding; mixture should be consumed within 30 minutes without chewing or crushing the granules; a glass of water may be taken after the administration of the drug to aid in swallowing

Product: Oral granules – 2 grams in unit-of-use foil packets; granules are not intended to be dissolved in any liquid

Comments: Bacterial vaginosis is typically associated with the occurrence of vaginal itching, burning during urination, a thin vaginal discharge, and an abnormal “fishy” odor. It is thought to result from an overgrowth of certain bacteria (primarily anaerobic bacteria) that are normally present in the vagina, with the result that the normal flora/balance of bacteria is disrupted. The treatment options for bacterial vaginosis have included oral or intravaginal administration of metronidazole or clindamycin, or oral use of tinidazole.

Secnidazole is a nitroimidazole antimicrobial agent with properties that are most similar to those of metronidazole and tinidazole. It is active *in vitro* against most isolates of the following organisms that are associated with bacterial vaginosis: *Gardnerella vaginalis*, *Mobiluncus* spp., *Bacteroides* spp., *Prevotella* spp., and *Megasphaera*-like type I/II. Its effectiveness as a single-dose treatment of bacterial vaginosis was demonstrated in two placebo-controlled clinical trials. The percentage of patients experiencing a clinical response was significantly greater with the medication (68%; 53%) than in those receiving placebo (18%; 19%).

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### **Voxilaprevir/Sofosbuvir/Velpatasvir (Vosevi – Gilead)**

Antiviral Agents

2017 New Drug Comparison Rating (NDCR) =

Indications: Treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis who have 1) genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor, and 2) genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor

Comparable drugs: Sofosbuvir/velpatasvir (Epclusa)

Advantages:

--Is effective in patients who have failed certain previous HCV regimens

Disadvantages:

--Interacts with more medications

--Is not recommended in patients with moderate or severe hepatic impairment

Most important risks/adverse events: Risk of hepatitis B virus (HBV) infection reactivation in patients coinfecting with HCV and HBV who are not receiving HBV antiviral therapy (boxed warning; patients should be tested for evidence of current or prior HBV infection before initiating treatment); bradycardia in patients also being treated with amiodarone (concurrent use is not recommended; risk is greater in patients also receiving beta-blockers or those with underlying cardiac comorbidities and/or advanced liver disease); use in patients with moderate or severe hepatic impairment is not recommended because of significantly higher exposures of voxilaprevir; concentrations and activity are reduced by CYP450 and drug transporter (e.g., P-glycoprotein) inducers (concurrent use of rifampin is contraindicated and the use of other inducers such as rifabutin, carbamazepine, efavirenz, phenytoin, and St. John's wort is not recommended); activity is also reduced by tipranavir/ritonavir and concurrent use is not recommended; action of voxilaprevir may be increased by cyclosporine, atazanavir, and lopinavir, and concurrent use is not recommended; action of velpatasvir may be reduced by gastric acid-reducing agents (e.g., antacids, proton pump inhibitors) and recommended dosages and dosing intervals should be observed); may increase the action of digoxin, tenofovir disoproxil fumarate, dabigatran (Pradaxa), and the statins, and concurrent use should be closely monitored (concomitant use of rosuvastatin or pitavastatin is not recommended; pravastatin may be used in a daily dosage that does not exceed 40 mg; atorvastatin, fluvastatin, lovastatin, and simvastatin should be used in the lowest approved dosages)

Most common adverse events: Headache (21%), fatigue (17%), diarrhea (13%), nausea (13%)

Usual dosage: One tablet once a day with food for 12 weeks

Product: Tablets – 100 mg voxilaprevir, 400 mg sofosbuvir, and 100 mg velpatasvir (should be dispensed in the original container)

Comments: The development of direct-acting antiviral agents has resulted in cure rates of chronic HCV infection exceeding 90%. These agents inhibit enzymes/proteins that are essential for HCV replication: daclatasvir, elbasvir, ledipasvir, ombitasvir, and velpatasvir are HCV NS5A inhibitors; grazoprevir, paritaprevir, simeprevir, and voxilaprevir are HCV NS3/4A protease inhibitors; sofosbuvir is a nucleotide analog NS5B inhibitor and dasabuvir is a nonnucleoside NS5B polymerase inhibitor. A sofosbuvir/velpatasvir combination formulation was marketed in 2016 as the first product to be approved for treating all 6 major HCV genotype infections. The new antiviral agent voxilaprevir has been added to these agents and the 3-drug combination formulation is the first to be approved for patients whose previous treatment with certain other antiviral regimens has not been successful. The new

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combination was evaluated in two studies in which the primary endpoint was sustained virologic response 12 weeks following completion of treatment (SVR12). The first study was placebo-controlled and a SVR12 response was experienced by 96% of the patients across all 6 HCV genotypes, and no placebo patients achieved SVR12. In the second study patients were treated with the new combination or sofosbuvir/velpatasvir. Treatment with the new product resulted in higher SVR12 rates in patients with genotypes 1a (97% vs. 82%) and 3 (96% vs. 85%) infection.

**Glecaprevir/pibrentasvir** (Mavyret – Abbvie)

Antiviral Agents

2017 New Drug Comparison Rating (NDCR) =

Indication: Treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; is also indicated for the treatment of adult patients with HCV genotype 1 infection, who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both.

Comparable drugs: Sofosbuvir/velpatasvir (Epclusa)

Advantages:

- Has been demonstrated to be effective in an 8-week course of treatment (whereas the recommended duration of treatment for sofosbuvir/velpatasvir is 12 weeks)
- Is effective in patients who have failed certain previous HCV regimens (although the combination of voxilaprevir, sofosbuvir, and velpatasvir [Vosevi] is also effective in patients who have failed certain previous HCV regimens)
- Is not likely to interact with amiodarone and cause bradycardia (a risk that is associated with sofosbuvir)
- Effectiveness has been demonstrated in patients with severe renal impairment

Disadvantages:

- Is contraindicated in patients with severe hepatic impairment and use is not recommended in patients with moderate hepatic impairment (whereas sofosbuvir/velpatasvir is used with ribavirin in patients with moderate and severe hepatic impairment)

Most important risks/adverse events: Risk of hepatitis B virus (HBV) infection reactivation in patients coinfecter with HCV and HBV who are not receiving HBV antiviral therapy (boxed warning; patients should be tested for evidence of current or prior HBV infection before initiating treatment); contraindicated in patients with severe hepatic impairment and is not recommended in patients with moderate hepatic impairment; concentrations are increased by atazanavir and concurrent use is contraindicated because of the increased risk of ALT elevations; concurrent use of ethinyl estradiol-containing products (e.g., combination oral contraceptives) is not recommended because of increased risk of ALT elevations; concentrations may be increased by darunavir, lopinavir, or ritonavir, and concurrent use is not recommended; concentrations may be increased by cyclosporine and use is not recommended in patients requiring stable cyclosporine doses higher than 100 mg per day; concentrations and effectiveness may be reduced by drugs that induce P-glycoprotein/CYP3A (concurrent use with rifampin is contraindicated, and use with carbamazepine, efavirenz, or St. John's wort is not recommended); may increase the concentration and activity of digoxin, dabigatran, and the statins (concurrent use with atorvastatin, lovastatin, or simvastatin is not recommended, and the other statins, as well as digoxin, should be used in lower dosages)

Most common adverse events (incidence in treatment-naïve patients without cirrhosis treated for 8 weeks): Headache (16%), fatigue (11%), nausea (9%), diarrhea (7%), elevations of total bilirubin (4%)

Usual dosage: Three tablets once a day with food for 8 weeks in treatment-naïve patients without cirrhosis, and for 12 weeks in patients with compensated cirrhosis; product labeling should be consulted for the recommended duration of treatment for patients previously treated with other HCV regimens

Product: Tablets – 100 mg glecaprevir and 40 mg pibrentasvir

Comments: Glecaprevir is an HCV NS3/4A protease inhibitor and pibrentasvir is an HCV NS5A inhibitor and is the first antiviral combination that is used in an 8-week course of treatment for all HCV genotypes 1-6 infections in

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patients without cirrhosis who have not been previously treated. The effectiveness of the combination was evaluated in multiple studies in patients with HCV infection without cirrhosis or with compensated (mild) cirrhosis. The primary endpoint was sustained virologic response 12 weeks following completion of treatment (SVR12). A SVR12 response was experienced by 95% - 100% of the patients in most of the studies. Effectiveness was also demonstrated in patients who had failed certain previous HCV regimens although longer courses of treatment (12-16 weeks) are recommended for most of these patients, as well as treatment-naïve patients with mild cirrhosis.

**Semaglutide** (Ozempic – Novo Nordisk)

Antidiabetic Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drugs: Exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza), lixisenatide (Adlyxin), dulaglutide (Trulicity); (albiglutide [Tanzeum] has also been available but marketing has been discontinued)

Advantages:

- Is administered less frequently (once a week compared with liraglutide and lixisenatide that are administered once a day and the Byetta formulation of exenatide that is administered twice a day)
- Is more effective in reducing hemoglobin A1C concentrations (compared with exenatide extended-release)
- May be associated with a greater loss of weight

Disadvantages:

- Labeled indications are more limited (compared with liraglutide for which indications also include use to reduce the risk of major adverse cardiovascular events in patients with diabetes and established cardiovascular disease)
- Dosage titration requires an additional step (compared with dulaglutide)

Most important risks/adverse events: Thyroid C-cell tumors (reported in studies in rodents but risk in humans is not known; boxed warning; contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2); pancreatitis (other antidiabetic agents should be considered in patients with a history of pancreatitis; treatment should be discontinued if pancreatitis is suspected); hypersensitivity reactions; acute kidney injury and worsening of chronic renal failure (risk is increased in patients who have experienced gastrointestinal adverse events [e.g., diarrhea, dehydration]); diabetic retinopathy complications (patients with a history of diabetic retinopathy should be monitored); hypoglycemia (when used concurrently with insulin or an insulin secretagogue (e.g., sulfonylureas); women should discontinue treatment at least 2 months before a planned pregnancy; delays gastric emptying and may alter the absorption of oral medications

Most common adverse events: Nausea (20%), vomiting (9%), diarrhea (9%), abdominal pain (6%)

Usual dosage: Administered subcutaneously in the abdomen, thigh, or upper arm; initially, 0.25 mg once a week for 4 weeks (this dosage is subtherapeutic and is used only for treatment initiation); after 4 weeks, the dosage is increased to 0.5 mg once a week; if additional glycemic control is needed after at least 4 weeks on the 0.5 mg dose, dosage may be increased to 1 mg once a week

Products: Injection supplied in prefilled single-patient-use pens containing 2 mg/1.5 mL; pens deliver 0.25 mg, 0.5 mg, or 1 mg of the drug per injection (should be stored in a refrigerator prior to first use)

Comments: Semaglutide is the sixth glucagon-like peptide-1 (GLP-1) receptor agonist to be approved in the United States. These agents have multiple actions that include suppression of glucagon secretion, stimulation of glucose-dependent insulin secretion, slowing gastric emptying, and promoting satiety. The effectiveness of semaglutide was demonstrated in studies in which it was used as monotherapy and in combination with metformin, metformin and sulfonylureas, metformin and/or a thiazolidinedione, and basal insulin. It reduced hemoglobin A1C and fasting plasma glucose concentrations, and the mean changes in weight from baseline were a weight loss of 4 to 5 kg.

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Semaglutide (in a dosage of 1 mg once a week) provided a greater reduction in A1C concentrations than sitagliptin (-1.5% vs. -0.7% at week 56), exenatide extended-release (-1.4% vs. -0.9% at week 56), and insulin glargine (-1.5% vs. -0.9% at week 30). Semaglutide has also been evaluated in a cardiovascular outcomes trial in patients with diabetes and a high risk of cardiovascular events. The primary composite endpoint was the time to first occurrence of a major adverse cardiovascular event. The number of these experiences was lower in patients treated with semaglutide compared with placebo (6.6% vs. 8.9%), suggesting an advantage for the medication. However, the design of the trial limits the conclusion to semaglutide being noninferior to placebo.

### **Ertugliflozin L-pyroglyutamic acid (Steglatro – Merck)**

Antidiabetic Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparable drugs: Canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance)

Advantages:

--Warning in labeling regarding risk of lower limb amputation is not as definitive (compared with canagliflozin that has a boxed warning in its labeling regarding this risk)

--Has not been associated with reports of patients experiencing bladder cancer (compared with dapagliflozin)

Disadvantages:

--Labeled indications are more limited (compared with empagliflozin that is also indicated to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease)

Most important risks/adverse events: Renal function impairment (contraindicated in patients with severe renal impairment); hypersensitivity reactions (contraindicated in patients with a history of a serious reaction); hypotension (risk is increased in patients with impaired renal function or low systolic blood pressure, the elderly, and in patients treated with a diuretic); lower limb amputation (patients should be monitored for infections or ulcers of lower limbs); ketoacidosis; urinary tract infections; hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); pregnancy (use is not recommended during the second and third trimesters); nursing mothers (use is not recommended); positive urine glucose test results (alternative methods to monitor glycemic control should be used)

Most common adverse events: Female genital mycotic infection (12%), male genital mycotic infection (4%), urinary tract infection (4%), headache (3%), back pain (3%), increased LDL-C concentrations (5%)

Usual dosage: Initially - 5 mg once a day in the morning; in patients who tolerate treatment and require additional glycemic control, dosage may be increased to 15 mg once a day; treatment should not be initiated in patients with an estimated glomerular filtration rate (eGFR) of 30 to <60 mL/minute/1.73m<sup>2</sup>); in patients in whom the eGFR falls to and persists within this range during treatment, continued use of the drug is not recommended

Products: Film-coated tablets – 5 mg, 15 mg; combination formulations with metformin (Segluromet: 2.5 mg/500 mg, 2.5 mg/1,000 mg, 7.5 mg/500 mg, 7.5 mg/1,000 mg); combination formulations with sitagliptin (Steglujan; 5 mg/100 mg, 15 mg/100 mg)

Comments: Sodium-glucose cotransporter 2 (SGLT2) is expressed in the proximal renal tubules and is responsible for the reabsorption of the majority of glucose filtered by the kidneys. Ertugliflozin is the fourth SGLT2 inhibitor, joining canagliflozin, dapagliflozin, and empagliflozin, and these agents reduce the reabsorption of filtered glucose, thereby increasing urinary glucose excretion and lowering blood glucose and glycosylated hemoglobin (A1C) concentrations. Its effectiveness has been demonstrated in studies in which it was used as monotherapy, or in combination with regimens with metformin and/or other antidiabetic agents. In the placebo-controlled study of ertugliflozin monotherapy (in doses of 5 mg and 15 mg once a day), the reduction in A1C at week 26 was -0.7% and -0.8%, respectively, compared with -0.2% in the patients receiving placebo. The percentage of patients achieving an A1C of less than 7% was 30% and 39%, respectively, for the two doses of ertugliflozin, compared with 17% of

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those receiving placebo. Similar reductions in A1C attributed to ertugliflozin were also reported in studies in which it was used in combination with metformin and/or sitagliptin (Januvia). In patients with type 2 diabetes and moderate renal impairment (eGFR 30 to <60 mL/minute/1.73m<sup>2</sup>), reductions of A1C were not significantly different between the drug and placebo, and efficacy of the drug was not demonstrated in these patients. None of the SGLT2 inhibitors should be used in the treatment of patients with type 1 diabetes or diabetic ketoacidosis..

The labeled indications for empagliflozin have been expanded to include use to reduce the risk of cardiovascular death in patients with type 2 diabetes and established cardiovascular disease. However, this is not a labeled indication for ertugliflozin, canagliflozin, or dapagliflozin.

**Betrixaban** (Bevyxxa – Portola)

Anticoagulant

2017 New Drug Comparison Rating (NDCR) =

Indication: Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE

Comparable drugs: Apixaban (Eliquis), edoxaban (Savaysa), rivaroxaban (Xarelto)

Advantages:

--Is the first orally-administered anticoagulant to be demonstrated to be effective for VTE prophylaxis for in-hospital and extended-duration use in acutely ill medical patients

--Is as effective or more effective than enoxaparin for VTE prophylaxis in acutely ill medical patients

--Is administered once a day (compared with apixaban that is administered twice a day)

Disadvantages:

--Labeled indications are more limited (comparable drugs are indicated for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, and for the treatment of deep vein thrombosis [DVT] and pulmonary embolism [PE]; apixaban and rivaroxaban are also indicated for reducing the risk of recurrence of DVT and PE, and for the prophylaxis of DVT in patients undergoing hip or knee replacement surgery)

Most important risks/adverse events: Contraindicated in patients with active pathological bleeding; risk of epidural or spinal hematomas in patients receiving neuraxial anesthesia or undergoing spinal puncture (boxed warning); risk of bleeding (risk factors include the concomitant use of other medications that may be associated with bleeding events [e.g., aspirin and other antiplatelet agents, other anticoagulants, nonsteroidal anti-inflammatory drugs]; concurrent use of another anticoagulant should be avoided); risk of bleeding events is increased in patients with severe renal impairment, and patients being treated with a P-glycoprotein (P-gp) inhibitor (e.g., amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil); use should be avoided in patients with hepatic impairment

Most common adverse events: Clinically relevant non-major bleeding events (2.45%), urinary tract infection (3%), constipation (3%), hypokalemia (3%)

Usual dosage: Initial single dose of 160 mg, followed by 80 mg once a day, with doses administered at the same time of day with food; recommended duration of treatment is 35 to 42 days; in patients with severe renal impairment, or who are being treated with a P-gp inhibitor, the dosage should be reduced to an initial single dose of 80 mg, followed by 40 mg once a day with food

Products: Capsules – 40 mg, 80 mg

Comments: Betrixaban is the fourth orally-administered anticoagulant that acts by inhibiting Factor Xa activity, joining rivaroxaban, apixaban, and edoxaban. However, its labeled indication is different than those of the comparable drugs and it is the first orally-administered anticoagulant demonstrated to be effective for in-hospital and extended-duration prophylaxis of VTE in patients with acute medical illnesses whose mobility is significantly restricted. Its effectiveness was demonstrated in a study of approximately 7,500 patients that compared extended duration betrixaban (35 to 42 days) with short duration enoxaparin (administered subcutaneously for 6 to 14 days).

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Efficacy was based on the composite outcome up to the Day 35 visit of the occurrence of asymptomatic proximal DVT, symptomatic proximal or distal DVT, non-fatal PE, or VTE-related death. Betrixaban reduced the composite outcome compared with those taking enoxaparin plus placebo (4.4% vs. 6.0%). Symptomatic events were reported in 0.9% and 1.5%, respectively, in patients treated with betrixaban and enoxaparin, and VTE-related death occurred in 0.3% and 0.5% of patients, respectively. The incidence of major bleeding (e.g., intracranial bleeding) was 0.67% in patients treated with betrixaban and 0.57% in patients treated with enoxaparin.

As with apixaban, edoxaban, and rivaroxaban, there is currently no specific antidote that reverses an excessive anticoagulant action of betrixaban.

### **Safinamide mesylate** (Xadago – Newron)

Antiparkinson Agent

2017 New Drug Comparison Rating (NDCR) =

Indication: Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes

Comparable drugs: Rasagiline (Azilect), selegilene (e.g., Eldepryl, Zelapar)

Advantages:

--May be used in patients with renal impairment (compared with selegilene that is not recommended in patients with severe renal impairment)

Disadvantages:

--Has not been directly compared in clinical trials with comparable drugs

--Labeled indications are more limited (compared with rasagiline for which the labeled indications also include monotherapy and adjunctive treatment without levodopa)

--Is contraindicated in patients with severe hepatic impairment

Most important risks/adverse events: Hypertension (may cause or exacerbate hypertension; because of risk of severe hypertension/hypertensive crisis, concurrent use with another monoamine oxidase [MAO] inhibitor including linezolid is contraindicated; concurrent use with isoniazid should be closely monitored; concurrent use with amphetamine, methylphenidate, and derivatives is contraindicated; caution must be observed when used concurrently with other prescription or nonprescription sympathomimetic medications, including oral, nasal, or ophthalmic decongestants and cold remedies, and patients should be monitored for hypertension; patients should be advised to avoid foods containing a large amount of tyramine [e.g., aged cheeses]); serotonin syndrome (concurrent use with serotonin-norepinephrine reuptake inhibitors [e.g., duloxetine, venlafaxine], tricyclic, tetracyclic, or triazolopyridine antidepressants, cyclobenzaprine, or St. John's wort is contraindicated; concurrent use with a selective serotonin reuptake inhibitor [e.g., fluoxetine] is best avoided); concurrent use with an opioid analgesic or dextromethorphan is contraindicated; at least 14 days should elapse between discontinuation of safinamide and initiation of treatment with another MAO inhibitor, serotonergic drug, or opioid analgesic; may cause sleep attacks/sudden onset of sleep (patients should be advised of risk); may cause or exacerbate dyskinesia; may cause hallucinations, psychotic behaviors, and problems of impulse control/compulsive behaviors (e.g., intense urges to gamble, spend money, or binge eat; increased sexual urges); if used during pregnancy, may cause harm to the unborn child; use is contraindicated in patients with severe hepatic impairment; may increase action of breast cancer resistance protein substrates (e.g., methotrexate, rosuvastatin)

Most common adverse events: Dyskinesia (17%), fall (6%), nausea (6%), insomnia (4%)

Usual dosage: Initially, 50 mg once a day at the same time each day; after 2 weeks, the dosage may be increased to 100 mg once a day; in patients with moderate hepatic impairment the maximum recommended dosage is 50 mg once a day; if treatment is to be discontinued the dosage should be reduced to 50 mg daily for one week before stopping therapy to reduce the risk of hyperpyrexia and confusion

Products: Tablets – 50 mg, 100 mg

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Comments: Safinamide is the third MAO type B inhibitor to be marketed for the treatment of patients with Parkinson's disease, joining rasagiline and selegiline. By inhibiting MAO-B activity, these agents reduce the catabolism of dopamine, resulting in increased dopamine concentrations and dopaminergic activity in the brain. The inhibition of MAO-B activity by safinamide is considered to be reversible, whereas selegiline and rasagiline irreversibly inhibit MAO-B activity. However, whether this distinction is of clinical importance is not known. The effectiveness of safinamide was demonstrated in two placebo-controlled studies. In both studies, safinamide significantly increased "on" time without troublesome dyskinesia compared to placebo, and this was accompanied by a similar significant reduction in "off" time, as well as a reduction in the United Parkinson's Disease Rating Scale Part III scores that were assessed during "on" time.

**Edaravone** (Radicava – Mitsubishi Tanabe)

Agent for Amyotrophic Lateral Sclerosis

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered intravenously for the treatment of amyotrophic lateral sclerosis (ALS)

Comparable drug: Riluzole (Rilutek)

Advantages:

--Slows the worsening of symptoms of ALS

Disadvantages:

--Prolongation of survival has not been demonstrated

--Is administered intravenously (whereas riluzole is administered orally)

Most important risks/adverse events: Hypersensitivity reactions; sulfite allergic reactions (formulation contains sodium bisulfite that may cause allergic or asthmatic reactions in susceptible individuals [e.g., patients with asthma]; contraindicated in patients with a history of hypersensitivity to edaravone or any of the inactive ingredients)

Most common adverse events: Contusion (15%), gait disturbance (13%), headache (10%), dermatitis (8%), eczema (7%), and respiratory failure, respiratory disorder, and/or hypoxia (6%)

Usual dosage: An intravenous infusion of 60 mg as two consecutive 30 mg intravenous infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]); initial treatment cycle is 60 mg once a day for 14 days, followed by a 14-day drug-free period; in subsequent treatment cycles, a 60 mg dose is administered once a day for 10 days out of 14-day periods, followed by 14-day drug-free periods

Product: Injection – single-dose polypropylene bags containing 30 mg/100 mL; product should be protected from light and stored in an overwrapped package to protect from oxygen degradation until time of use; oxygen indicator will turn blue or purple if the oxygen has exceeded acceptable levels; once the overwrap package is opened, the medication should be used within 24 hours

Comments: ALS, commonly known as Lou Gehrig's disease, is a rare, progressive, neurodegenerative disease that affects 12,000 to 15,000 Americans. It is characterized by the destruction of nerve cells that control voluntary muscles that are involved in functions such as chewing, walking, breathing, and talking. As the activity of the nerve cells declines, the muscles become weaker and paralysis results. Most patients with ALS die from respiratory failure, usually within three to five years from when symptoms first appear. Riluzole was approved by the FDA in 1995 and has been the only drug available that is indicated for the treatment of ALS. It has been demonstrated to prolong survival (on average by about 3 months) and/or time to tracheostomy.

Edaravone was evaluated in a placebo-controlled trial that was conducted in Japan in 137 patients, of which 69 patients were in the edaravone arm of the study and 68 were in the placebo arm. More than 90% of the patients in each group were being treated with riluzole. The ALS Functional Rating Scale – Revised (ALSFRS-R) was used in assessing the patients, and consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food,

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dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24. The decline in these scores from baseline was significantly less in the edaravone-treated patients as compared to placebo. The mechanism of action through which the drug provides its benefit, and whether it prolongs survival, are not known.

### **Naldemedine tosylate (Symproic – Purdue; Shionogi)**

Agent for Constipation

2017 New Drug Comparison Rating (NDCR) =

Indication: Treatment of opioid-induced constipation (OIC) in adults with chronic non-cancer pain

Comparable drugs: Methylnaltrexone (Relistor), naloxegol (Movantik)

#### Advantages:

- May be administered without regard to food (compared with naloxegol that should be taken on an empty stomach)
- Dosage does not have to be reduced in patients with renal impairment (compared with naloxegol)
- Concurrent use with a strong CYP3A4 inhibitor is not contraindicated (compared with naloxegol with which concurrent use is contraindicated)

#### Disadvantages:

- May interact with P-glycoprotein (P-gp) inhibitors (e.g., cyclosporine)
- Is more likely to interact with CYP3A inhibitors and inducers (compared with methylnaltrexone)
- Route of administration options are more limited (compared with methylnaltrexone that may also be administered subcutaneously)
- Use should be avoided in patients with severe hepatic impairment (compared with methylnaltrexone)

Most important risks/adverse events: Contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction; gastrointestinal perforation (patients should be monitored for severe, persistent, or worsening abdominal pain); opioid withdrawal symptoms; pregnancy (could precipitate opioid withdrawal in an unborn child if used during pregnancy; should only be used during pregnancy if the anticipated benefit justifies the risk); should not be used by a nursing mother; should not be used in patients with severe hepatic impairment; action is reduced by strong CYP3A inducers (e.g., carbamazepine, St. John's wort) and concurrent use should be avoided; action is increased by moderate (e.g., diltiazem) and strong (e.g., clarithromycin) CYP3A inhibitors, as well as by P-gp inhibitors (e.g., cyclosporine), and concurrent use should be closely monitored; concurrent use with another opioid antagonist should be avoided because of the increased risk of opioid withdrawal

Most common adverse events: Abdominal pain (8%), diarrhea (7%), nausea (4%), gastroenteritis (2%)

Usual dosage: 0.2 mg once a day

Product: Tablets – 0.2 mg

Comments: Naldemedine is the third drug with opioid antagonist activity to be approved for the treatment of adults with opioid-induced constipation, joining methylnaltrexone and naloxegol. Lubiprostone (Amitiza) is another option for the treatment of OIC, and it acts as a chloride channel activator in the gastrointestinal tract (GIT).

Naldemedine is a derivative of naltrexone, and is a peripherally-acting mu-opioid receptor antagonist in tissues such as the GIT. It differs structurally from naltrexone by the addition of a side chain that reduces the ability of the drug to cross the blood-brain barrier. It is also a substrate of the P-gp transporter and, based on these

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properties, the central nervous system penetration of the drug is expected to be negligible when it is used in the recommended dosage, which limits the potential for interference with centrally-mediated opioid analgesia.

The effectiveness of naldemedine was demonstrated in two placebo-controlled studies in patients with OIC and non-cancer related pain (e.g., back pain) who had been treated with an opioid for at least 4 weeks. A responder was defined as a patient who had at least 3 spontaneous bowel movements (SBMs) per week and a change from baseline of at least 1 SBM per week for at least 9 out of the 12 study weeks and 3 out of the last 4 weeks. In the two studies, 48% and 53% of the patients treated with naldemedine experienced an increase in the number of SBMs per week, compared with 35% and 34% of those receiving placebo.

### **Benralizumab (Fasenra – AstraZeneca)**

Antiasthmatic Agent

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype;

Is not indicated for the treatment of other eosinophilic conditions, or for the relief of acute bronchospasm or status asthmaticus

Comparable drugs: Mepolizumab (Nucala), reslizumab (Cinqair)

#### Advantages:

--Is administered less frequently (every 8 weeks for maintenance treatment, compared with every 4 weeks with comparable drugs)

--Formulation is more convenient to administer (is supplied in prefilled syringes whereas mepolizumab requires reconstitution and reslizumab is administered by intravenous infusion)

--Is indicated for patients as young as 12 years of age (compared with reslizumab that is indicated for patients 18 years and older)

--May be less likely to cause serious hypersensitivity reactions (compared with reslizumab that has a boxed warning regarding this risk in its labeling)

#### Disadvantages:

--Labeled indications are more limited (compared with mepolizumab that is also indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis)

Most important risks/adverse events: Hypersensitivity reactions; reduction in dosage or discontinuation of systemic or inhaled corticosteroids (to avoid systemic withdrawal symptoms and/or unmasking of conditions previously suppressed by systemic corticosteroid therapy; dosage should be reduced gradually); parasitic (helminth) infections (should be treated prior to starting benralizumab; if a helminth infection develops during treatment and does not respond to antihelminth treatment, benralizumab should be discontinued until the infection resolves)

Most common adverse events: Headache (8%), pharyngitis (5%)

Usual dosage: Administered subcutaneously – 30 mg once every 4 weeks for the first 3 doses, and then once every 8 weeks (labeling notes it should be administered by a healthcare professional)

Product: Single-dose prefilled syringes – 30 mg/1 ml (should be stored in a refrigerator)

Comments: Multiple cell types, including eosinophils, and mediators (e.g., cytokines) are involved in the inflammatory process that occurs in the airways of the lungs in patients with asthma. Interleukin-5 (IL-5) is the major cytokine that is responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Benralizumab is the third agent that reduces the activity of IL-5 to be approved. Whereas mepolizumab and reslizumab act on IL-5 itself, benralizumab directly binds to the alpha subunit of IL-5 receptors,

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thereby preventing the binding of IL-5 to its receptors, leading to apoptosis of eosinophils through antibody-dependent cell-mediated cytotoxicity.

The effectiveness of benralizumab was evaluated in two placebo-controlled studies in patients with severe asthma and high blood eosinophil counts who had a history of two or more asthma exacerbations in the past 12 months. The two studies were 48 and 56 weeks in duration, and the primary endpoint was the rate of asthma exacerbations. In these studies, 35% and 40% of the patients treated with benralizumab experienced an exacerbation compared with 51% of the patients in each study who received placebo. The effect of benralizumab on reducing the use of maintenance oral corticosteroids was evaluated in a third study for a period of 28 weeks. The median percent reduction in the daily oral corticosteroid dose from baseline was 75% in patients treated with benralizumab compared to 25% in patients receiving placebo. In all three studies, patients treated with the new drug experienced consistent improvements from baseline in the mean forced expiratory volume in 1 second (FEV<sub>1</sub>).

### **Guselkumab (Tremfya – Janssen)**

Agent for Psoriasis

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Comparable drug: Ustekinumab (Stelara)

#### Advantages:

- May be more effective in some patients
- One dosage regimen is appropriate for all adult patients (whereas ustekinumab is used in two dosage regimens based on patient weight)

#### Disadvantages:

- Labeled indications are more limited (ustekinumab is also indicated for patients with active psoriatic arthritis and patients with moderately to severely active Crohn's disease)
- Is administered more frequently (every 8 weeks for maintenance treatment compared with every 12 weeks)

Most important risks/adverse events: Infections (treatment should not be initiated in patients with a clinically important active infection until the infection is resolved or adequately treated; if a serious infection occurs during treatment or if an infection is not responding to standard therapy, guselkumab should be discontinued until the infection resolves); exacerbation of tuberculosis (patients should be evaluated for tuberculosis prior to initiating treatment); live vaccines should not be administered during treatment

Most common adverse events: Upper respiratory infections (14%), headache (5%), injection site reactions (5%), arthralgia (3%), diarrhea (2%)

Usual dosage: Administered subcutaneously – 100 mg at Weeks 0 and 4, and every 8 weeks thereafter

Product: Single-dose prefilled syringes – 100 mg (should be stored in a refrigerator)

Comments: Interleukin-23 (IL-23) is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab is a human monoclonal antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with IL-23 receptors, thereby inhibiting the release of proinflammatory cytokines and chemokines. It has also been reported to reduce serum concentrations of IL-17A, IL-17F, and IL-22 relative to pretreatment concentrations, but the relationship between these pharmacodynamic markers and the clinical response to the drug is not fully understood. Ustekinumab was the first IL-23 inhibitor to be approved for the treatment of plaque psoriasis, and it also inhibits IL-12.

The effectiveness of guselkumab was demonstrated in two studies in which it was compared with placebo and adalimumab (Humira). The primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 90% (PASI 90) and an Investigator's Global Assessment (IGA) of clear or minimal. These studies

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demonstrated superiority to adalimumab with assessments of patients demonstrated at Weeks 16, 24, and 48. For example, in the study in which patients were assessed at Week 48, 73% of the patients treated with guselkumab achieved a PASI 90 response, compared with 46% of those treated with adalimumab, and 47% of patients treated with the new drug achieved an IGA response of clear, compared with 24% of those treated with adalimumab. In a third study, the effectiveness of guselkumab was evaluated in patients who had not achieved an adequate response at Week 16 after initial treatment with ustekinumab. Patients were randomized to either continue with ustekinumab treatment or switch to guselkumab. Twelve weeks following randomization, 31% of the patients treated with guselkumab achieved an IGA response of clear or minimal, compared with 14% of the patients treated with ustekinumab.

### **Sarilumab** (Kevzara – Regeneron; Sanofi)

Antiarthritic Agent

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs)

Comparable drug: Tocilizumab (Actemra)

Advantages:

--May be administered less frequently in some patients (every two weeks compared with subcutaneous administration of tocilizumab once a week in some patients with rheumatoid arthritis)

Disadvantages:

--Labeled indications are more limited (tocilizumab is also indicated in the treatment of giant cell arteritis, and in patients 2 years and older with polyarticular juvenile idiopathic arthritis and systemic juvenile idiopathic arthritis)

--Has one route of administration (subcutaneous whereas tocilizumab may be administered subcutaneously or by intravenous infusion in patients with rheumatoid arthritis)

--Is administered more frequently in some patients (every 2 weeks whereas tocilizumab is administered every 4 weeks when administered intravenously for rheumatoid arthritis)

Most important risks/adverse events: Serious infections (boxed warning; e.g., tuberculosis [TB; patients should be evaluated for TB risk factors and tested for latent infection], invasive fungal infections and other opportunistic infections; treatment should not be initiated in patients with active infection, including localized infections; treatment should be interrupted if a patient develops a serious infection; should not be used concurrently with another biologic therapy); malignancies (possible increased risk because of immunosuppressive action); gastrointestinal perforation (primarily a complication of diverticulitis); serious hypersensitivity reactions; laboratory abnormalities including neutropenia, thrombocytopenia, and increased liver enzymes and blood lipids (neutrophils, platelets, ALT, and AST should be determined prior to starting treatment, and monitored 4 to 8 weeks after the start of therapy and every 3 months thereafter); use is not recommended in patients with active hepatic disease or hepatic impairment; live vaccines should not be given during treatment; should not be used by a nursing mother

Most common adverse events: Neutropenia (10%), increased ALT (5%), injection site erythema (4%), upper respiratory tract infection (3%), urinary tract infection (3%)

Usual dosage: Used as monotherapy or in combination with methotrexate or other conventional DMARDs; administered subcutaneously – 200 mg once every two weeks; dosage may be reduced to 150 mg once every 2 weeks if neutropenia, thrombocytopenia, or elevated liver enzymes occur; treatment should not be initiated in patients with an absolute neutrophil count less than 2,000/mm<sup>3</sup>, a platelet count less than 150,000/mm<sup>3</sup>, or who have ALT or AST values above 1.5 times the upper limit of normal

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Product: Injection – prefilled syringes – 150 mg/1.14mL and 200 mg/1.14 mL (should be stored in a refrigerator)

Comments: Interleukin-6 (IL-6) is a proinflammatory cytokine that is produced in a variety of cells including synovial and endothelial cells affected by inflammatory processes. Sarilumab is the second humanized monoclonal antibody that acts as an IL-6 inhibitor and has been approved for the treatment of patients with moderately to severely active rheumatoid arthritis, joining tocilizumab. The effectiveness of sarilumab was demonstrated in two placebo-controlled studies. Study 1 was conducted in patients who had an inadequate response to methotrexate, and Study 2 was conducted in patients who had an inadequate response or were intolerant to one or more tumor necrosis factor inhibitors (e.g., adalimumab [Humira]). Approximately 64% of the patients treated with sarilumab achieved an ACR20 response (representing a 20% improvement in criteria established by the American College of Rheumatology) at 12 weeks, compared with approximately 36% of patients receiving placebo. Patients treated with sarilumab also had higher ACR50 and ACR70 responses compared with placebo (35% vs. 13% and 16% vs. 3%, respectively). Other benefits include a reduction in signs and symptoms and improved physical function.

**Abaloparatide** (Tymlos – Radius)

Agent for Osteoporosis

2017 New Drug Comparison Rating (NDCR) =

Indication: Administered subcutaneously for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy

Comparable drug: Teriparatide (Forteo)

Advantages:

--Formulation does not require refrigeration after first use

Disadvantages:

--Has not been directly compared with teriparatide in clinical studies

--Labeled indications are more limited (teriparatide is also indicated for the treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture, and for increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture)

Most important risks/adverse events: Risk of osteosarcoma (boxed warning; has been reported in studies in rats but whether it is causative in humans is not known; is not recommended in patients at increased risk of osteosarcoma including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, bone metastases or skeletal malignancies, hereditary disorders predisposing to osteosarcoma, or prior external beam or implant radiation therapy involving the skeleton; cumulative use of abaloparatide and parathyroid hormone analogs [e.g., teriparatide] for more than 2 years of a patient's lifetime is not recommended); hypercalcemia (use should be avoided in patients with pre-existing hypercalcemia and those known to have an underlying hypercalcemic disorder, such as primary hyperparathyroidism); hypercalciuria and urolithiasis (urine calcium concentrations should be monitored if pre-existing hypercalciuria or active urolithiasis is suspected); orthostatic hypotension (first several doses should be administered where the patient can sit or lie down if necessary)

Most common adverse events: Hypercalciuria (11%), dizziness (10%), injection site pain (9%), nausea (8%), headache (8%), palpitations (5%)

Usual dosage: Administered subcutaneously into the periumbilical region of the abdomen: 80 mcg once a day at approximately the same time each day; supplemental calcium and vitamin D should be provided if dietary intake is inadequate

Product: Injection in single-patient-use prefilled pens that deliver 30 doses, each containing 80 mcg of the drug in 40 mL of sterile solution (should be stored in a refrigerator but, after first use, may be stored at room temperature for up to 30 days)

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Comments: Osteoporosis is characterized by a reduction in bone mineral density and bone strength, and is most commonly experienced in women following menopause when a reduction in estrogen concentrations results in a bone remodeling imbalance in which bone loss (resorption) exceeds bone formation. Abaloparatide is a synthetic 34-amino acid peptide that is an analog of human parathyroid hormone related peptide. Like teriparatide, it is a parathyroid hormone receptor agonist that stimulates bone formation, whereas other prescription medications used for postmenopausal osteoporosis (e.g., bisphosphonates) inhibit bone resorption.

The effectiveness of abaloparatide was demonstrated in a placebo-controlled clinical study in which most of the patients had experienced at least one prior fracture. The primary endpoint was the incidence of new vertebral fractures and, over an 18-month treatment period, there was a significant reduction in the incidence of these fractures in patients treated with the new drug (0.6%) compared with the patients receiving placebo (4.2%). There was also a significant reduction in the incidence of nonvertebral fractures. Although some patients in the study were treated with teriparatide, there are insufficient data to permit a comparison of the two drugs with respect to the incidence of fractures.

### **Latanoprostene bunod (Vyzulta – Valeant)**

Agent for Glaucoma

2017 New Drug Comparison Rating (NDCR) =

Indications: For ophthalmic administration for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Comparable drugs: Bimatoprost (Lumigan), latanoprost (e.g., Xalatan), tafluprost (Zioptan), travoprost (Travatan Z)

Advantages:

--None

Disadvantages:

--Has not been directly compared in clinical trials with comparable drugs

--Formulation contains benzalkonium chloride as a preservative (compared with tafluprost that is preservative-free and travoprost that includes an ionic-buffered preservative system)

--Unopened bottles should be refrigerated (compared with bimatoprost and travoprost that do not have to be stored in a refrigerator)

Most important risks/adverse events: Pigmentation (brownish) of the iris (is likely to be permanent) and eyelids; eyelash changes (e.g., increased length, color, thickness, shape, and number); use should generally be avoided in patients with active intraocular inflammation (e.g., iritis/uveitis); should be used with caution in patients with risk factors for macular edema; contact lenses should be removed prior to administration, and may be reinserted 15 minutes following administration

Most common adverse events: Conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), installation site pain (2%)

Usual dosage: One drop in the conjunctival sac in the affected eye(s) once a day in the evening; should not be administered more often than once a day; if more than one ophthalmic drug is being used, latanoprostene should be administered at least 5 minutes apart from another ophthalmic medication

Product: Ophthalmic solution – 0.024% (0.24 mg/mL); unopened bottles should be stored in a refrigerator; formulation contains benzalkonium chloride as a preservative that may damage contact lenses (contact lenses should be removed prior to administration)

Comments: Latanoprostene bunod is a prostaglandin analog that is used in an ophthalmic solution to reduce intraocular pressure, and has properties that are most similar to bimatoprost, latanoprost, tafluprost, and tavoprost. Unoprostone isopropyl was also marketed at one time, but is no longer available. Latanoprostene bunod increases

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the outflow of aqueous humor and is thought to act via both the uveoscleral and trabecular meshwork routes. Following ocular administration, it is rapidly metabolized in the eye to latanoprost acid and butanediol mononitrate. Its effectiveness was demonstrated in clinical studies of up to 12 months duration in patients with average baseline IOPs of approximately 27 mmHg. The IOP-lowering effect of latanoprostene was up to 7 to 9 mmHg, and its effectiveness appears to be similar to that of the comparable drugs.

### **Netarsudil dimesylate (Rhopressa – Aerie)**

Agent for Glaucoma

2018 New Drug Comparison Rating (NDCR) =

Indication: For ophthalmic administration for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Comparable drugs: Ophthalmic beta-adrenergic blocking agents (e.g., timolol)

#### Advantages:

- Is less likely to cause systemic adverse events
- Has a unique mechanism of action (is a rho kinase inhibitor)

#### Disadvantages:

- Is less effective in lowering IOP in some patients
- Is more likely to cause ocular adverse events

Most important risks/adverse events: Bacterial keratitis; contact lenses should be removed prior to administration, and may be reinserted 15 minutes following administration

Most common adverse events: Conjunctival hyperemia (53%); corneal verticillata (opacities), instillation site pain, conjunctival hemorrhage, each occurring in approximately 20% of patients; instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, reduced visual acuity, each occurring in 5-10% of patients

Usual dosage: One drop in the affected eye(s) once a day in the evening; if a dose is missed, treatment should continue with the next dose in the evening; twice a day dosing is not well tolerated and is not recommended; should be administered at least 5 minutes apart from another ophthalmic medication

Product: Ophthalmic solution – 0.02% (0.2 mg/mL); unopened bottles should be stored in a refrigerator; formulation contains benzalkonium chloride as a preservative, which may be absorbed by soft contact lenses (contact lenses should be removed prior to administration)

Comments: Netarsudil has a unique mechanism of action as a rho kinase inhibitor. It is thought to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork, but its exact mechanism of action is not known. Following ophthalmic administration, it is metabolized by esterases in the eye, and one of its metabolites is pharmacologically active. The effectiveness of netarsudil (0.02% once daily in the evening) was demonstrated in three controlled trials in which it was compared with timolol (0.5% twice a day). Patients treated with netarsudil experienced up to 5 mmHg reductions in IOP. In patients with a baseline IOP <25 mmHg, the IOP reductions were

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similar to those of timolol. However, in patients with baseline IOP 25 mmHg or greater, the mean IOP reductions were smaller with netarsudil than with timolol. Although timolol was administered twice a day in these clinical studies, some formulations of timolol (e.g., Timolol XE) may be administered once a day.

The ophthalmic use of beta-adrenergic blocking agents has been associated with the occurrence of systemic adverse events (e.g., pulmonary, cardiovascular, central nervous system) in some patients and their labeling includes contraindications, warnings, and precautions regarding certain of these risks. In contrast, netarsudil appears unlikely to cause systemic adverse events and its labeling does not identify such risks. However, the incidence of ocular adverse events with netarsudil is higher than that reported with ophthalmic beta-blockers or with the prostaglandin analogs such as latanoprost (e.g., Xalatan).

### **Voretigene neparvovec-rzyl (Luxturna – Spark)**

### **Agent for Retinal Dystrophy**

2018 New Drug Comparison Rating (NDCR) =

Indication: Administered by subretinal injection for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy; patients must have viable retinal cells

Comparable drug: None

#### Advantages:

- Is the first drug to be demonstrated to be effective in the treatment of biallelic RPE65 mutation-associated retinal dystrophy
- Is the first gene therapy that targets a disease caused by mutations in a specific gene

#### Limitations:

- Duration of treatment benefit has not yet been determined

Most important risks/adverse events: Endophthalmitis; decreased visual acuity; retinal abnormalities; cataract formation; increased intraocular pressure; expansion of intraocular air bubbles (patients should be instructed to avoid air travel, travel to high elevations, or scuba diving until the intraocular air bubble following administration has completely dissipated [may take one week or more]); treatment is not recommended in patients younger than 12 months of age because the drug would potentially be diluted or lost during cell proliferation

Most common adverse events: Conjunctival hyperemia (22%), cataract (20%), increased intraocular pressure (15%), retinal tear (10%), dellen (thinning of the corneal stroma; 7%), macular hole (7%), subretinal deposits (7%)

Usual dosage:  $1.5 \times 10^{11}$  vector genomes (vg) in each eye, administered by subretinal injection in a total volume of 0.3 mL; a single injection should be made in each eye on separate days within a close interval, but no fewer than 6 days apart; a systemic oral corticosteroid (equivalent to prednisone at 1 mg/kg/day [maximum of 40 mg/day]) should be given for a total of 7 days (starting 3 days before administration of the drug in the first eye), and followed by tapering the dose during the following 10 days; the same corticosteroid regimen should be used for treatment in the second eye

Product: Intraocular suspension for subretinal injection in a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye; vial and the two vials of diluents provided should be stored in the frozen state; drug is supplied in a concentration of  $5 \times 10^{12}$  vg/mL that requires a 1:10 dilution prior to administration; product labeling should be consulted for specific recommendations for diluting, preparing, and administration of injection; universal biohazard precautions should be observed during handling for up to 7 days following administration

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Comments: Hereditary retinal dystrophies are a group of genetic retinal disorders that are associated with worsening visual dysfunction. The human retinal pigment epithelial 65 kDa gene (RPE65) provides instructions for making an enzyme that is essential for normal vision. Mutations in the RPE65 gene lead to reduced or absent levels of RPE isomerohydrolase activity resulting in impairment of vision. The loss of vision often occurs during childhood or adolescence, and may eventually result in complete blindness. Biallelic RPE65 mutation-associated retinal dystrophy affects up to 2,000 individuals in the US. Biallelic mutation carriers have a mutation, but not necessarily the same mutation, in both copies of a particular gene.

Voretigene is provided in a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. It uses a naturally-occurring, live, non-replicating adeno-associated virus serotype 2, which has been genetically modified using recombinant techniques, to deliver the normal human RPE65 gene to the retinal cells. Its effectiveness was evaluated in a study of 31 patients, with almost two-thirds of the patients being less than 18 years of age. Significant improvements in functional vision, as assessed by the ability of a patient to navigate an obstacle course accurately and at a reasonable pace at different levels of environmental illumination, were demonstrated in the patients treated with voretigene, compared to those in the control group. The benefit was sustained over the two-year period of the study. Patients who were initially in the control group were treated with the drug after one year, following which they experienced similar improvement with the drug.