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New Drugs 2018: PART 3

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Abstract: This article discusses eight drugs recently approved by the FDA, including their indications and contraindications, precautions, dosage, and nursing considerations. The article also includes summary charts on 14 recently approved antineoplastic drugs and four drugs approved for rare disorders.

Keywords: abaloparatide, abemaciclib, acalabrutinib, avelumab, axicabtagene, benznidazole, brigatinib, cerliponase alfa, copanlisib dihydrochloride, deflazacort, delafloxacin meglumine, durvalumab, emicizumab-kxwh, enasidenib mesylate, etelcalcetide hydrochloride, latanoprostene bunod, letermovir, meropenem trihydrate, midostaurin, neratinib maleate, niraparib tosylate monohydrate, ribociclib succinate, secnidazole, telotristat ethyl, tisagenlecleucel, vestronidase alfa-vjbk

THIS ARTICLE REVIEWS select drugs recently approved by the FDA, including:

- three antibacterial drugs.
- a new treatment for secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis.
- 14 antineoplastic drugs.
- four new approvals for certain rare disorders.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the prescribing information, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions for all these drugs.

SELECTED REFERENCES

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ANTIBACTERIAL DRUGS

Delafloxacin meglumine

First fluoroquinolone effective against MRSA infections

A fluoroquinolone antibacterial agent, delafloxacin meglumine (*Baxdela*, Melinta) has properties similar to other members of this class such as levofloxacin, moxifloxacin, and ciprofloxacin. Available in formulations for oral and I.V. administration, it is indicated to treat 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 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*.[1]

Delafloxacin is the first fluoroquinolone demonstrated to be effective against infections caused by MRSA. Its spectrum of antibacterial action, which also includes problem pathogens such as *P. aeruginosa,* is broader than that of other antimicrobial drugs indicated to treat ABSSSI.

The effectiveness of delafloxacin was demonstrated in two noninferiority studies in approximately 1,500 patients, in which it was compared with I.V. vancomycin and aztreonam. Aztreonam was discontinued if no Gram-negative bacteria were identified in the baseline cultures. An objective clinical response at 48 to 72 hours following initiation of treatment was defined as a 20% or greater decrease in infected lesion size. This response was achieved in approximately 80% of the patients with both treatment regimens in both studies. The success of treatment at about 14 days exceeded 95% for both treatment regimens.

Delafloxacin was well tolerated in the clinical studies. Treatment was discontinued because of adverse reactions in less than 1% of patients, compared with discontinuation in approximately 3% of patients treated with vancomycin and aztreonam. Phototoxicity and QT interval prolongation have been reported with the use of other fluoroquinolones, but were not experienced with delafloxacin in the clinical studies.

Because fluoroquinolones have been reported to cause degenerative changes in articular cartilage and arthropathy in skeletally immature animals, the use of delafloxacin in children is not recommended. Use of any systemic fluoroquinolone in children is limited to treating serious infections such as inhalational anthrax or plague for which very few antimicrobial treatment options are available.

Precautions: (1) Monitor patients for signs and symptoms of *Clostridium difficile*-associated diarrhea, which has been reported with the use of almost all systemic antibacterial agents. (2) Immediately discontinue the drug if the patient experiences signs and symptoms of a hypersensitivity reaction, such as rash, which may occur after the first dose or after subsequent doses. (3) Avoid use of delafloxacin and other fluoroquinolones in patients with a history of tendon disorders, peripheral neuropathy, or myasthenia gravis. As with other fluoroquinolones, the labeling for delafloxacin includes boxed warnings regarding the risks of tendonitis; tendon rupture; peripheral neuropathy; central nervous system effects such as dizziness, confusion, and tremors; and exacerbation of myasthenia gravis. Because these disorders are associated with serious and potentially irreversible complications, treatment with a fluoroquinolone should be immediately discontinued in patients who experience these adverse reactions. (4) In patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) in whom delafloxacin is to be administered I.V., the dosage should be reduced because of potential accumulation of the I.V. vehicle, sulfobutylether-beta-cyclodextrin. Serum creatinine concentrations should be closely monitored in these patients. If serum creatinine concentrations increase, consideration should be given to changing to oral administration of the drug. If eGFR decreases to less than 15 mL/min/1.73 m^2, delafloxacin should be discontinued. Delafloxacin is not recommended in patients with end-stage renal disease. (5) Fluoroquinolones may form chelates with multivalent metal cations (such as those in antacids and vitamin/mineral formulations) that may reduce absorption of the drug following oral administration. Delafloxacin should be administered at least 2 hours before or 6 hours after products containing metal cations. When administered I.V., delafloxacin should not be coadministered with any solution containing multivalent cations (such as magnesium) through the same I.V. line.

Adverse reactions: nausea, vomiting, diarrhea, headache, serum transaminase elevations

Supplied as: oral tablets or a lyophilized powder for injection in quantities equivalent to 450 mg delafloxacin (tablets) and 300 mg for injection

Dosage: 300 mg every 12 hours over 60 minutes by I.V. infusion, or 450 mg every 12 hours orally for 5 to 14 days. The bioavailability of a single 450 mg oral dose is comparable to that of a single 300 mg I.V. dose. Treatment may be initiated I.V. and then switched to oral administration as appropriate. In patients with severe renal impairment, the I.V. dosage should be reduced to 200 mg every 12 hours.

Nursing considerations: (1) The contents of a vial for I.V. use must be reconstituted with 10.5 mL of 5% Dextrose Injection or 0.9% Sodium Chloride Injection. Shake the vial vigorously until the contents are dissolved, then dilute the reconstituted solution with the same vehicle to a total volume of 250 mL to achieve a concentration of 1.2 mg/mL. (2) Tell patients prescribed the oral formulation that they may take tablets without regard to food. (3) Instruct patients not to drive or engage in other activities that require mental alertness and coordination until they know how the drug affects them. (4) Teach patients to recognize signs and symptoms of tendonitis or tendon rupture, such as pain, edema, or inflammation of a tendon or weakness or inability to use one of their joints. Tell them to discontinue the drug and contact the healthcare provider immediately if these occur.

REFERENCE

1. Baxdela (delafloxacin) tablets, for oral use; Baxdela (delafloxacin) for injection, for intravenous use. Prescribing information. www.baxdela.com.

Meropenem trihydrate/ vaborbactam

Teaming up to defeat drug resistance

Beta-lactam antibacterial drugs such as the penicillins, cephalosporins, and carbapenems are highly effective treatments for many bacterial infections. However, an increasing number of bacteria can produce beta-lactamases (penicillinases, cephalosporinases, and carbapenemases) that break the beta-lactam ring and inactivate the antibacterial drug. To address this common mechanism of resistance, pharmaceutical companies have developed beta-lactamase inhibitors that preserve and extend the activity of the beta-lactam antibacterial drugs with which they are combined.

Carbapenem antibacterial drugs marketed in the US include imipenem (used in combination with cilastatin), ertapenem, doripenem, and meropenem. Indications for meropenem include complicated skin and skin structure infections, complicated intra-abdominal infections, and bacterial meningitis.

Meropenem trihydrate/vaborbactam (*Vabomere*, The Medicines Company) combines meropenem with the new beta-lactamase inhibitor vaborbactam. Although vaborbactam has no antibacterial activity, it protects meropenem from degradation by certain beta-lactamases such as *Klebsiella pneumoniae carbapenemase*. Administered I.V., the new product is indicated for patients age 18 and older with complicated urinary tract infections including pyelonephritis caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex.[1]

The effectiveness of meropenem/vaborbactam was demonstrated in a multicenter trial in which it was compared with piperacillin/tazobactam. At the end of I.V. treatment with meropenem/vaborbactam, 98% of patients had cure or improvement of symptoms and a negative urine culture, compared with 94% of patients treated with piperacillin/tazobactam. Approximately 7 days after completing treatment, 77% of patients treated with meropenem/vaborbactam had resolved symptoms and a negative urine culture, compared with 73% of patients treated with piperacillin/tazobactam. Treatment was discontinued because of adverse reactions in 3% of patients treated with meropenem/vaborbactam and in 5% of patients treated with piperacillin/tazobactam.

Precautions: (1) Contraindicated in patients with known hypersensitivity to any component of the product or to other drugs in the same class, and in patients who have experienced anaphylactic reactions to any beta-lactam antibacterial agent. Hypersensitivity reactions were experienced by 2% of the patients who received meropenem/vaborbactam in the clinical studies. (2) Monitor patients for diarrhea during and after treatment. Almost all systemic antibacterial drugs, including meropenem, have been reported to cause *Clostridium difficile*-associated diarrhea; this possibility should be considered in all patients who experience diarrhea following use of an antibacterial drug. (3) Meropenem has been infrequently associated with seizures and other adverse central nervous system (CNS) reactions such as delirium or headache that could interfere with mental alertness and/or cause motor impairment. The risk of serious CNS adverse reactions is greater in patients with underlying CNS disorders, such as a seizure disorder. (4) In patients whose seizures are well controlled with the antiepileptic drugs (AEDs) valproic acid or divalproex sodium, concurrent use of meropenem/vaborbactam is generally not recommended. Meropenem and other carbapenems may reduce the concentration of these AEDs, increasing the risk of breakthrough seizures. (5) Concurrent use of probenecid is not recommended because probenecid competes with meropenem for active renal tubular secretion, increasing plasma concentrations of meropenem. (6) The dosage of meropenem/vaborbactam should be reduced in patients with impaired renal function. For patients

with changing renal function, serum creatinine concentrations and the eGFR should be monitored at least daily and the drug dosage adjusted as indicated.

Adverse reactions: headache, phlebitis/infusion site reactions, diarrhea

Supplied as: a sterile powder for constitution in single-dose vials containing meropenem trihydrate in an amount equivalent to 1 g of meropenem and 1 g of vaborbactam

Dosage: In adult patients with an eGFR of 50 mL/min/1.73 m^2 or more: 4 g (meropenem 2 g and vaborbactam 2 g) every 8 hours by I.V. infusion over 3 hours for up to 14 days. Consult the Prescribing Information for recommended dosage reductions for patients with an eGFR less than 50 mL/min/1.73 m^2.

Nursing considerations: (1) Before drug administration, assess patients for any previous hypersensitivity reactions to meropenem and vaborbactam, penicillins, cephalosporins, other beta-lactams, or other allergens. Discontinue the infusion if signs and symptoms of a hypersensitivity reaction develop during treatment. Teach patients to recognize and immediately report signs and symptoms of a hypersensitivity reaction they experience during or after the infusion. (2) Reconstitute the sterile powder with 0.9% Sodium Chloride Injection and dilute with the same vehicle as directed in the Prescribing Information. Complete the I.V. infusion of the diluted solution within 4 hours if stored at room temperature or 22 hours if stored in a refrigerator. (3) Warn patients being treated as outpatients not to drive, operate machinery, or engage in any other activity requiring alertness until they determine how the drug affects them. (4) Warn patients about the risk of *C. difficile*-associated diarrhea, characterized by watery and bloody stools (with or without abdominal cramps and fever), and inform them that this adverse reaction can develop days or even months after treatment. Tell them to report such signs and symptoms to the healthcare provider immediately.

REFERENCE

1. Vabomere (meropenem and vaborbactam) for injection, for intravenous use. Prescribing Information. www.vabomere.com/media/pdf/vabomere-us-prescribing-information.pdf.

Secnidazole

Offering relief from bacterial vaginosis

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in women of childbearing age. Symptomatic women typically present with vaginal discharge and/or vaginal odor. The discharge is off-white, thin, and homogeneous; the odor is an unpleasant "fishy smell" that may be more noticeable after sexual intercourse and during menses. BV is thought to result from a shift in vaginal flora away from Lactobacillus species toward more diverse bacterial species, including facultative anaerobes. The altered microbiome causes a rise in vaginal pH and symptoms.[1]

Risk factors for BV include sexual activity and douching. The treatment options for nonpregnant women with BV include oral or intravaginal metronidazole and oral or intravaginal clindamycin.[1,2]

Secnidazole (*Solosec*, Symbiomix) is a nitroimidazole antimicrobial with properties similar to those of metronidazole and tinidazole. It is active *in vitro* against most isolates of the following organisms with BV: *Gardnerella vaginalis*, *Mobiluncus* spp., *Bacteroides* spp., *Prevotella* spp., and *Megasphaera*-like type I/II.[3]

Administered orally, secnidazole is indicated to treat BV in adult women. Its effectiveness as a single-dose treatment was demonstrated in two placebo-controlled clinical trials in which the percentage of patients experiencing a clinical response was significantly greater in those treated with the medication than in those receiving placebo.

Other nitroimidazole antimicrobial agents have been reported to be carcinogenic in animal studies, but whether a single dose of secnidazole is associated with a cancer risk in humans is unknown.

Metronidazole and tinidazole are contraindicated during the first trimester of pregnancy, but no adverse developmental outcomes were found with secnidazole in animal reproduction studies and the labeling for the new drug does not include a restriction for use in pregnancy. However, because nitroimidazole derivatives are present in human milk, breastfeeding is not recommended during treatment with secnidazole or for 96 hours following administration.

Disulfiram-like reactions following the consumption of alcoholic beverages have been reported with use of metronidazole and tinidazole; these may include flushing, tachycardia, palpitations, nausea, vomiting, and acidosis.[4] But because in vitro studies showed that secnidazole has no effect on aldehyde dehydrogenase activity, its labeling does not include a precaution regarding the use of alcoholic beverages.

Precaution: Contraindicated in patients with a history of hypersensitivity to any nitroimidazole derivative.

Adverse reactions: vulvovaginal candidiasis, headache, nausea, dysgeusia, vomiting, diarrhea, abdominal pain, vulvovaginal pruritus

Supplied as: oral granules in a unit-of-use foil packet, with each packet containing 2 g of the drug

Dosage: a single dose of 2 g sprinkled on applesauce, yogurt, or pudding

Nursing considerations: (1) Tell patients to sprinkle the contents of the foil packet onto applesauce, yogurt, or pudding, and to consume the mixture within 30 minutes without chewing or crushing the granules.

Patients may drink a glass of water after administration of the drug to aid in swallowing, but warn them not to mix the medication with any liquid because the granules will not dissolve. The dose may be taken without regard to meals. (2) Teach patients to recognize and report signs and symptoms of vulvovaginal candidiasis, the most common adverse reaction to secnidazole. These may include vulvar pruritus, burning, and irritation, with or without discharge, possibly leading to dysuria and dyspareunia.[1] Symptomatic vulvovaginal candidiasis may require treatment with antifungal medication.

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3. Solosec (secnidazole) oral granules. Prescribing Information. www.solosechcp.com.

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ANTIPARASITIC DRUG

Benznidazole

First FDA-approved treatment for Chagas disease

Also known as American trypanosomiasis, Chagas disease is a parasitic infection caused by the protozoal organism *Trypanosoma cruzi*. Although Chagas disease primarily affects people in South and Central America, an estimated 300,000 people in the US may have the infection.[1]

An infected triatomine insect vector (or "kissing" bug) takes a blood meal and releases trypomastigotes in its feces near the site of the bite wound. Trypomastigotes enter the host through the bite wound or through intact mucosal membranes, such as the conjunctiva. Transmission can also occur congenitally from mother to infant, via transfusion of blood components, via transplantation of an organ from an infected donor, and via consumption of contaminated food or drink. After years of infection, patients may experience serious heart disease, such as cardiomyopathy, and gastrointestinal complications.[2]

Indicated for pediatric patients ages 2 to 12 years, benznidazole is a nitroimidazole antimicrobial with properties similar to those of metronidazole and tinidazole. It is the first medication to be approved in the US for treatment of Chagas disease. It was approved under the provisions of the accelerated approval program based on patients who became immunoglobulin G antibody-negative against the recombinant antigens of *T. cruzi*. Studies to determine the clinical benefit of treatment are continuing.[1,3]

The effectiveness of benznidazole was evaluated in two placebo-controlled clinical trials in children ages 6 to 12 years. The percentage of patients who seroconverted from positive to negative was significantly greater in the patients treated with benznidazole compared with patients who received placebo. An additional study of the safety and pharmacokinetics of the drug in patients ages 2 to 12 years was the basis for dosage recommendations for children as young as age 2 years. The effectiveness and safety of benznidazole have not been established in patients below age 2 years and above age 12 years.

Precautions: (1) Contraindicated in patients with a history of hypersensitivity to any of the nitroimidazoles. (2) If the patient experiences serious cutaneous reactions such as erythema multiforme, treatment should be immediately discontinued. If less serious skin reactions occur and additional signs or symptoms of systemic involvement such as fever or purpura are experienced, discontinuing treatment is recommended. (3) If the patient experiences neurologic signs and symptoms, immediate discontinuation of treatment is recommended. Benznidazole may cause paresthesia or symptoms of peripheral neuropathy that may take several months to resolve; central nervous system effects such as dizziness have also been reported. (4) Monitor complete blood cell counts for signs of bone marrow depression, such as neutropenia, thrombocytopenia, anemia, and leukopenia. Total and differential leukocyte counts are recommended before, during, and after therapy. (5) Benznidazole is contraindicated in patients who have taken disulfiram within the previous 2 weeks because of the potential for psychotic reactions. Alcohol consumption is also contraindicated. These beverages and any products containing propylene glycol should be avoided during treatment and for at least 3 days following treatment to prevent disulfiram-like reactions such as flushing, abdominal cramping, headache, nausea, and vomiting.

Adverse reactions: abdominal pain, rash, weight loss, headache, nausea, vomiting, neutropenia, urticaria, pruritus, eosinophilia, anorexia

Supplied as: 12.5 mg and 100 mg oral tablets

Dosage: 5 mg/kg to 8 mg/kg/day administered in two divided doses separated by approximately 12 hours for 60 days

Nursing considerations: (1) The drug may be administered without regard to food. (2) Tablets containing 100 mg of the drug are functionally scored twice and can be administered whole or broken at the scored lines to provide smaller doses (25 mg, 50 mg, and 75 mg). Consult the Prescribing Information for details about preparing a slurry of the tablets in water as an alternative for children who cannot swallow tablets.

REFERENCES

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2. Bern C. Chagas disease: acute and congenital Trypanosoma cruzi infection. UpToDate. 2017. www,uptodate.com.

3. Benznidazole tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209570lbl.pdf.

Antineoplastic drugs marketed in 2017[1-14]

Drug *(trade name,* manufacturer, description)	**Route**	**Indications**
Abemaciclib (*Verzenio*, Lilly) An inhibitor of cyclin-dependent kinases 4 and 6, enzymes that promote cell proliferation in estrogen receptor-positive breast cancer cell lines	Oral	• In combination with fulvestrant for women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy • As monotherapy for adults with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
Acalabrutinib (*Calquence*, AstraZeneca) An inhibitor of Bruton tyrosine kinase, an enzyme involved in activation of pathways necessary for B-cell proliferation	Oral	Adults with mantle cell lymphoma who have received at least one prior therapy
Avelumab (*Bavencio*, EMD Serono) A programmed death ligand-1 (PD-L1) blocking antibody that blocks the interaction between PD-L1 and its receptors, resulting in the restoration of immune responses, including antitumor immune responses	I.V. infusion	• Patients age 12 years and older with Merkel cell carcinoma, a rare, aggressive form of skin cancer • Patients with locally advanced or metastatic urothelial carcinoma (UC) who: – have disease progression during or following platinum-containing chemotherapy – have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
Axicabtagene ciloleucel (*Yescarta*, Kite; Gilead) A chimeric antigen receptor (CAR) T-cell therapy. This CD19-directed genetically modified autologous T-cell immunotherapy binds to CD19-expressing cancer cells and normal B cells. A patient's own T cells are harvested and genetically modified to express a CAR. The anti-CD19 CAR T cells are infused back into the patient, where they can recognize and eliminate CD19-expressing cancer cells.	I.V. infusion	Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
Brigatinib (*Alunbrig*, Ariad) A tyrosine kinase inhibitor with activity against multiple kinases including anaplastic lymphoma kinase (ALK)	Oral	Patients with ALK-positive metastatic non–small cell lung cancer who have progressed on or are intolerant to crizotinib
Copanlisib dihydrochloride (*Aliqopa*, Bayer) Inhibitor of phosphatidylinositol-3-kinase isoforms expressed in malignant B cells	I.V. infusion	Adults with relapsed follicular lymphoma (a slow-growing type of non-Hodgkin lymphoma) who have received at least two prior systemic therapies
Durvalumab (*Imfinzi*, AstraZeneca) A programmed death-ligand 1 (PD-L1) blocking antibody that blocks the interaction between PD-L1 and its receptors, restoring immune responses	I.V. infusion	Patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy, or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

(continued)

Antineoplastic drugs marketed in 2017[1-14] *(continued)*

Drug *(trade name,* manufacturer, description)	Route	Indications
Enasidenib mesylate (*Idhifa,* Celgene) An isocitrate dehydrogenase-2 (IDH2) inhibitor	Oral	Adults with relapsed or refractory acute myeloid leukemia with an IDH2 mutation as detected by an FDA-approved test
Midostaurin (*Rydapt*, Novartis) A tyrosine kinase inhibitor with activity against multiple kinases including FLT3	Oral	Indicated in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation chemotherapy for treatment of adults with newly diagnosed acute myeloid leukemia who are FLT3 mutation positive, as detected by an FDA-approved test. Also indicated for adults with aggressive systemic mastocytosis, systemic mastocytosis with associated hematologic neoplasm, or mast cell leukemia.
Neratinib maleate (*Nerlynx*, Puma) A kinase inhibitor that irreversibly binds to epidermal growth factor receptor, HER2, and HER4	Oral	Indicated for the extended adjuvant treatment of adults with early-stage HER2-overexpressed/amplified breast cancer, to follow trastuzumab-based therapy
Niraparib tosylate monohydrate (*Zejula*, Tesaro) A poly (ADP-ribose) polymerase inhibitor; this action may result in a reduction in the repair of DNA inside cancer cells resulting in cell death and possibly a delay or inhibition of tumor growth	Oral	Maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
Ribociclib succinate (*Kisqali*, Novartis) An inhibitor of cyclin-dependent kinases 4 and 6, enzymes that promote cell proliferation in breast cancer cell lines	Oral	Indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer
Telotristat ethyl (*Xermelo*, Lexicon) Metabolized to telotristat, which inhibits tryptophan hydroxylase, the enzyme that mediates the rate-limiting step in serotonin biosynthesis. Serotonin is overproduced in patients with carcinoid syndrome, which may result in uncontrolled diarrhea; this drug reduces the production of peripheral serotonin.	Oral	Indicated in combination with a somatostatin analogue (SSA), such as octreotide or lanreotide, to treat carcinoid syndrome diarrhea in adults whose symptoms are inadequately controlled by SSA therapy
Tisagenlecleucel (*Kymriah*, Novartis) A CAR T-cell therapy. This CD19-directed genetically modified autologous T-cell immunotherapy eliminates CD19-expressing malignant and normal cells. A patient's T cells are harvested and genetically modified to express a CAR. The anti-CD19 CAR T cells are infused back into the patient, where they can recognize and eliminate CD19-expressing cancer cells.	I.V. infusion	• Children and adults up to age 25 with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse • Adults with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

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3. Bavencio (avelumab) injection, for intravenous use. Prescribing Information. www.emdserono.com/content/dam/web/corporate/non-images/country-specifics/us/pi/bavencio-pi.pdf.
4. Yescarta (axicabtagene ciloleucel) suspension, for intravenous infusion. www.fda.gov/downloads/UCM581226.pdf.
5. Alunbrig (brigatinib) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208772lbl.pdf.
6. Aliqopa (copanlisib dihydrochloride) for injection, for intravenous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf.
7. Imfinzi (durvalumab) injection, for intravenous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf.
8. Idhifa (enasidenib mesylate) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209606s000lbl.pdf.
9. Rydapt (midostaurin) capsules, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/207997s000lbl.pdf.
10. Nerlynx (neratinib maleate) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf.
11. Zejula (niraparib tosylate monohydrate) capsules, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208447lbl.pdf.
12. Kisqali (ribociclib succinate) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209092s000lbl.pdf.
13. Xermelo (telotristat ethyl) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208794s000lbl.pdf.
14. Kymriah (tisagenlecleucel) suspension for intravenous infusion. Prescribing Information. www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kymriah.pdf.

ANTIVIRAL DRUG

Letermovir

Protecting patients from CMV infection after hematopoietic stem cell transplantation

After a person is exposed to cytomegalovirus (CMV), a common herpesvirus, it remains in the body for life, usually in an inactive or latent form. Many adults have CMV antibodies in their blood and are CMV seropositive, indicating a previous exposure to or primary infection with CMV. People with normal immune function rarely develop signs and symptoms of CMV infection after an initial infection, which is typically mild in severity. However, patients with compromised immune function face a greater risk of viral reactivation, causing symptomatic infection or a secondary infection due to other pathogens. In these patients, CMV infection may cause serious complications such as retinitis and possibly blindness, pneumonia, and gastrointestinal disorders.[1]

Recipients of stem cell and organ transplants are particularly vulnerable to CMV infection and complications, including transplant failure and death. Hematopoietic stem cell transplantation (HSCT) is performed in some patients with certain blood or bone marrow cancers. Although HSCT offers many patients the best hope for a continuing remission, the procedure and associated immunosuppression increase the risk of CMV infection.[1]

Letermovir (*Prevymis*, Merck) is an antiviral agent with activity against CMV that inhibits the CMV DNA terminase complex required for viral DNA processing and packaging. Administered orally or as an I.V. infusion, it is indicated for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients (R+) of an allogeneic HSCT.[2]

The effectiveness of letermovir was evaluated in a placebo-controlled clinical trial in patients with disorders such as acute myeloid leukemia, myelodysplastic syndrome, and lymphoma who received an HSCT. The primary efficacy endpoint was the incidence of clinically significant CMV infection through Week 24 posttransplant (prophylaxis failure). Significantly fewer patients in the letermovir group (38%) failed prophylaxis, compared with 61% of those in the placebo group. All-cause mortality at Week 24 posttransplant was also lower in those treated with letermovir (12%) than in those receiving placebo (17%).

Letermovir appears less likely to cause serious adverse reactions than ganciclovir or valganciclovir, two antivirals currently available to treat CMV infection. Unlike the labeling for letermovir, the labeling for those drugs includes boxed warnings regarding the risks of hematologic toxicity, impairment of fertility, teratogenicity, and carcinogenicity.

Letermovir interacts with many other medications. It inhibits the CYP3A metabolic pathway and increases the action of medications that are substrates for this pathway, such as pimozide and ergot alkaloids. Consult the Prescribing Information for full details about drug interactions and recommended precautions.

Precautions: (1) Contraindicated for concurrent use with pimozide, ergot alkaloids, and pitavastatin and simvastatin when coadministered with cyclosporine. In patients in whom cyclosporine is not coadministered, the concurrent use of letermovir with pitavastatin or simvastatin is not recommended. (2) The concurrent use of letermovir and cyclosporine increases the activity of both drugs. In patients treated concurrently with both drugs, the dosage of letermovir should be reduced to 240 mg once a day and cyclosporine concentrations should be frequently monitored. The use of repaglinide is not recommended in these patients. (3) Concurrent use of letermovir and cyclosporin with atorvastatin or lovastatin is not recommended. In patients in whom cyclosporin is not co-administered, the dosage of atorvastatin should not exceed 20 mg daily. (4) Concurrent use of letermovir with rifampin is not recommended. (5) Concurrent use of letermovir may increase the action of sirolimus, tacrolimus, alfentanil, fentanyl, midazolam, quinidine, amiodarone, glyburide, rosiglitazone, and repaglinide. (6) Letermovir may decrease the action of warfarin, phenytoin, voriconazole, omeprazole, and pantoprazole; closely monitor patients for reduced effectiveness of these drugs. (7) Letermovir is not recommended for use in patients with severe hepatic impairment. (8) The vehicle for the parenteral formulation of letermovir includes hydroxypropyl betadex that may accumulate in patients with creatinine clearance less than 50 mL/min; closely monitor serum creatinine concentrations in these patients.

Adverse reactions: nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, abdominal pain

Supplied as: *For oral use*: 240 mg and 480 mg tablets. *For I.V. injection:* single-dose vials containing 240 mg/12 mL (20 mg/mL) and 480 mg/24 mL (20 mg/mL).

Dosage: 480 mg once a day. Treatment should be initiated between Day 0 and Day 28 posttransplantation and continued through Day 100 posttransplantation.

Nursing considerations: (1) Letermovir tablets may be administered without regard to food. (2) Tell patients that if they miss a dose, they should take it as soon as they remember, unless it is nearly time for the next dose. In that case, they should skip the missed dose and take the next dose at the scheduled time. Warn them not to take two doses at the same time to make up for a missed dose. (3) Letermovir injection should be used only in

patients who cannot take oral therapy. Patients should be switched to the tablet formulation as soon as they can take oral medications; dosage adjustment is not necessary when switching formulations. (4) To prepare letermovir for I.V. infusion, add the contents of a vial into a 250 mL prefilled I.V. bag containing either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Consult the Prescribing Information for information regarding compatible I.V. bags and infusion set materials. (5) Administer the diluted formulation via a peripheral or central venous access device at a constant infusion rate over 1 hour. (6) Monitor patients for CMV reactivation following completion of therapy with letermovir.

REFERENCES

1. Merck receives FDA approval of Prevymis™ (letermovir) for prevention of cytomegalovirus (CMV) infection and disease in adult allogeneic stem cell transplant patients. Merck. News release. November 9, 2017.

2. Prevymis (letermovir) tablets, for oral use; Prevymis (letermovir) injection, for intravenous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939Orig1s000,209940Orig1s000lbl.pdf.

DRUG FOR OSTEOPOROSIS

Abaloparatide

Indicated for postmenopausal women with osteoporosis at high risk for fracture

Characterized by a reduction in bone mineral density and bone strength, osteoporosis is often asymptomatic until a fracture occurs. It is most commonly experienced in women following menopause when a reduction in estrogen concentrations causes a bone remodeling imbalance in which bone loss (resorption) exceeds bone formation. An estimated 8 million women in the US have osteoporosis, and two million osteoporotic fractures occur each year.[1]

Abaloparatide (*Tymlos*, Radius), a synthetic 34-amino acid peptide, is an analogue of human parathyroid hormone-related peptide. Like teriparatide, it is a parathyroid hormone receptor agonist that stimulates bone formation; the other prescription medications used for postmenopausal osteoporosis inhibit bone resorption. Administered subcutaneously, abaloparatide is specifically indicated for postmenopausal women with osteoporosis at high risk for fracture, defined as patients with a history of osteoporotic fracture, those with multiple risk factors for fracture, and those who have failed or are intolerant to other available osteoporosis therapy.[2]

The effectiveness of abaloparatide was demonstrated in a placebo-controlled clinical study in which most patients had experienced at least one prior fracture. The primary endpoint was the incidence of new vertebral fractures. Over an 18-month treatment period, a significant reduction in the incidence of these fractures was found in patients treated with the new drug (0.6%) compared with patients receiving placebo (4.2%). The incidence of nonvertebral fractures was also significantly reduced.

High dosages of abaloparatide caused an increased incidence of osteosarcoma in rats. Although whether the drug will cause osteosarcoma in humans is unknown, the labeling for abaloparatide includes a boxed warning regarding this risk.

Precautions: (1) Because of the potential risk of osteosarcoma, abaloparatide should not be used in patients at increased risk for osteosarcoma, including those with Paget disease of bone or unexplained elevations of serum 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. (2) Because abaloparatide may cause hypercalciuria, measurement of urinary calcium excretion should be considered in patients in whom preexisting hypercalciuria or active urolithiasis is suspected. (3) Because abaloparatide may cause hypercalcemia, it is not recommended in patients with preexisting hypercalcemia or in patients who have an underlying hypercalcemic disorder, such as primary hyperparathyroidism. (4) Patients may experience orthostatic hypotension, typically within 4 hours of injection. The first several doses should be administered where the patient can sit or lie down if necessary. (5) Cumulative use of abaloparatide and parathyroid hormone analogues such as teriparatide for more than 2 years during a patient's lifetime is not recommended.

Adverse reactions: hypercalciuria, dizziness, nausea, headache, palpitations, fatigue, upper abdominal pain, vertigo

Supplied as: single-patient-use prefilled pens. Each pen delivers 30 doses, each containing 80 mcg of the drug in 40 mcL of sterile solution.

Dosage: 80 mcg once a day at approximately the same time each day

Nursing considerations: (1) Advise patients to sit or lie down if they experience signs and symptoms of hypotension, such as dizziness and palpitations. (2) Teach patients how to administer abaloparatide subcutaneously into the periumbilical region. (3) Instruct patients to promptly report signs and symptoms of osteosarcoma, such as persistent localized pain or a new soft tissue mass that is tender to palpation. (4) Instruct patients to promptly report signs and symptoms of hypercalcemia, such as nausea, vomiting, constipation, lethargy, and muscle weakness. (5) Tell patients to store the pens in a refrigerator before use. After first use, they may store pens at room temperature for up to 30 days.

REFERENCES

1. FDA approves Radius Health's Tymlos™ (abaloparatide), a bone building agent for the treatment of postmenopausal women with osteoporosis at high risk for fracture. Radius. News release. April 28, 2017.

2. Tymlos (abaloparatide) injection, for subcutaneous use. Prescribing Information. http://radiuspharm.com/wp-content/uploads/tymlos/tymlos-prescribing-information.pdf.

Drugs approved in 2017 for certain rare disorders[1-4]

Drug (*trade name,* manufacturer, description)	Route	Indications
Cerliponase alfa (*Brineura*, BioMarin) A recombinant human tripeptidyl peptidase-1 (rhTPP1), a lysosomal exopeptidase, and an enzyme replacement therapy	Intraventricular infusion into cerebrospinal fluid via a surgically implanted reservoir and catheter followed by Intraventricular Electrolytes Injection	Indicated to slow the loss of ambulation in symptomatic pediatric patients age 3 years and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), a form of Batten disease also known as tripeptidyl peptidase 1 (TPP1) deficiency
Deflazacort (*Emflaza*, PTC) A corticosteroid prodrug whose active metabolite exerts anti-inflammatory and immunosuppressive effects	Oral	Indicated to treat Duchenne muscular dystrophy in patients age 5 years and older
Emicizumab-kxwh (*Hemlibra*, Genentech) A humanized monoclonal antibody with a bispecific antibody structure binding factor IXa and factor X. By bridging activated factor IX and factor X, it restores the function of missing activated factor VIII needed for effective hemostasis.	Subcutaneous injection	Indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors
Vestronidase alfa-vjbk (*Mepsevii*, Ultragenyx) A recombinant human lysosomal beta glucuronidase; this is an enzyme replacement therapy	I.V. infusion	Indicated to treat pediatric and adult patients with mucopolysaccharidosis VII (MPS VII, Sly syndrome)

REFERENCES

1. Brineura (cerliponase alfa) injection, for intraventricular use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf.
2. Emflaza (deflazacort) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208684s000,208685s000lbl.pdf.
3. Hemlibra (emicizumab-kxwh) injection, for subcutaneous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761083s000lbl.pdf.
4. Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761047s000lbl.pdf.

DRUG FOR HYPERPARATHYROIDISM

Etelcalcetide hydrochloride

Treatment for secondary hyperparathyroidism in adults with chronic kidney disease on hemodialysis

The parathyroid glands secrete parathyroid hormone (PTH), which helps maintain the appropriate balance of calcium and phosphorus in the body. Hyperparathyroidism (HPT) disrupts this balance and serum calcium concentrations increase. The secretion of PTH is regulated by changes in extracellular calcium concentrations and, when the concentration of extracellular calcium is decreased, the amount of PTH secreted is increased. This autoregulation is controlled by calcium-sensing receptors in the parathyroid glands.[1]

Secondary HPT involves the excessive secretion of PTH in response to decreased renal function and impaired mineral metabolism. The elevated concentrations of PTH can increase the release of calcium and phosphate from the bones. Approximately 470,000 patients in the US are receiving dialysis, and almost 90% of patients with chronic kidney disease (CKD) on hemodialysis will develop secondary HPT. Treatment options for secondary HPT include phosphate binders, active vitamin D analogues such as calcitriol, and calcimimetics. Cinacalcet, the first marketed calcimimetic agent, acts by increasing the sensitivity of the calcium-sensing receptors in the parathyroid glands to activation by extracellular calcium.[1]

Etelcalcetide hydrochloride (*Parsabiv*, Amgen) is a synthetic peptide calcium-sensing receptor agonist with properties similar to those of cinacalcet. However, unlike cinacalcet, which is administered orally, the new drug is administered I.V.[2]

Indicated to treat secondary HPT in adults with CKD on hemodialysis, etelcalcetide is administered three times a week by the dialysis healthcare team at the end of hemodialysis treatment. Its effectiveness was demonstrated in two placebo-controlled studies involving more than 1,000 patients who were also receiving standard of care that could include vitamin D and/or phosphate binders. The primary endpoint of both studies was the proportion of patients achieving greater than a 30% reduction in PTH concentrations from baseline to the efficacy assessment

phase (mean PTH concentrations for weeks 20 through 27, inclusive). Secondary endpoints included the proportion of patients with a mean PTH of less than or equal to 300 pg/mL percent reductions in PTH, corrected serum calcium, and phosphate concentrations. In both studies, significantly more patients treated with etelcalcetide had a greater than 30% reduction in PTH (77% and 79%) than in those receiving placebo (11% in each study). PTH concentrations of 300 pg/mL or less were achieved in 52% and 56% of the patients treated with the new drug, compared with 6% and 5% of those in the placebo groups. In addition, patients treated with etelcalcetide experienced greater reductions in corrected calcium and phosphate concentrations in patients.

Because etelcalcetide has not been studied in patients with CKD who are not on hemodialysis or in patients with other parathyroid disorders, it is not recommended for use in these patients.

Precautions: (1) Hypocalcemia is associated with symptomatic reductions in corrected serum calcium less than 8.3 mg/dL and may be severe. Significant lowering of serum calcium can cause paresthesias, myalgia, muscle spasms, seizures, QT interval prolongation, and ventricular dysrhythmias; patients at added risk for these adverse reactions should be closely monitored. (2) Corrected serum calcium should be determined before initiation of treatment with etelcalcetide, and treatment should not be started if the corrected serum calcium is less than the lower limit of normal. Corrected serum calcium levels should be monitored within 1 week after initiation or dose adjustment, and every 4 weeks during treatment. (3) The concurrent use of etelcalcetide with cinacalcet could result in life-threatening hypocalcemia. Patients switching to the new drug should discontinue cinacalcet for at least 7 days before initiating etelcalcetide. (4) Some patients in the clinical studies experienced hypotension and worsening heart failure; heart failure requiring hospitalization occurred in 2% of the patients treated with etelcalcetide, compared with 1% of those receiving placebo. (5) Patients with risk factors for upper gastrointestinal (GI) bleeding such as gastritis or ulcers may be at increased risk for GI bleeding while being treated with etelcalcetide. Patients who experience worsening of GI symptoms such as nausea and vomiting should be monitored for GI bleeding and ulceration. (6) If PTH concentrations are chronically suppressed and decrease below the recommended target range, adynamic bone may develop. The dosage of etelcalcetide and/or vitamin D should be reduced or therapy discontinued. Following discontinuation of treatment, therapy can be resumed at a lower dose to maintain PTH concentrations in the target range.

Adverse reactions: muscle spasms, diarrhea, nausea, vomiting, headache, hypocalcemia, paresthesia

Supplied as: single-dose vials in etelcalcetide concentrations of 2.5 mg/0.5 mL, 5 mg/mL, and 10 mg/2 mL

Dosage: *Starting dosage:* 5 mg administered by I.V. bolus injection into the venous line of the dialysis circuit three times a week at the end of hemodialysis treatment. *Maintenance dosage:* individualized according to titration based on PTH and corrected serum calcium response, ranging from 2.5 mg three times a week to a maximum maintenance dosage of 15 mg three times a week. The dosage may be increased in 2.5 mg or 5 mg increments no more frequently than every 4 weeks. Consult the Prescribing Information for details regarding the determination of PTH and calcium concentrations, dosage adjustments, and suspension/discontinuation of treatment.

Nursing considerations: (1) Teach patients to recognize and report signs and symptoms of hypocalcemia, heart failure, and GI bleeding. (2) Inform patients about the importance of regular blood tests as directed by the healthcare provider. (3) Store vials in the refrigerator in the original carton to protect the medication from light.

REFERENCES

1. FDA approves Amgen's Parsabiv™ (etelcalcetide), first new treatment In more than a decade for secondary hyperparathyroidism in adult patients on hemodialysis. Amgen. News release. February 7, 2017.

2. Parsabiv (etelcalcetide) injection, for intravenous use. Prescribing Information. https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/parsabiv/parsabiv_pi.pdf.

DRUG FOR GLAUCOMA

Latanoprostene bunod

Managing intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Latanoprostene bunod (*Vyzulta*, Valeant) is a prostaglandin analogue with properties similar to those of bimatoprost, latanoprost, tafluprost, and travoprost. These drugs are available in solutions for ophthalmic administration to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Prostaglandin analogues lower IOP by increasing the outflow of aqueous humor. Latanoprostene is thought to act via both the trabecular meshwork and uveoscleral routes. Following ocular administration, it is rapidly metabolized in the eye to latanoprost acid and butanediol mononitrate.[1]

The effectiveness of the new drug was demonstrated in clinical studies of up to 12 months in duration in patients with average baseline IOP of approximately 27 mm Hg. The IOP-lowering effect of latanoprostene was 7 to 9 mm Hg. Its effectiveness appears to be similar to that of the related drugs.

Like the other prostaglandin analogues used to reduce elevated IOP, latanoprostene may cause brownish pigmentation of the iris and eyelid due to increased melanin content in the melanocytes. Increased pigmentation of the eyelid is reversible in most patients but pigmentation of the iris is likely to be permanent. Use in pediatric patients younger than age 16 years is not recommended because of potential safety concerns related to increased pigmentation following long-term use.

Changes in eyelash length, color, thickness, shape, and number may also occur. These changes are likely to be reversible upon discontinuation of treatment.

Precautions: (1) Use latanoprostene with caution in patients with risk factors for macular edema. (2) Use caution in patients with a history of intraocular inflammation such as iritis or uveitis. Latanoprostene is generally not recommended for patents with active intraocular inflammation because it may exacerbate inflammation. (3) Patients who experience increased iris pigmentation should be closely monitored because the long-term effects of increased pigmentation are not known.

Adverse reactions: conjunctival hyperemia, eye irritation, eye pain, instillation site pain

Supplied as: sterile ophthalmic solution containing the drug in a concentration of 0.024% (0.24 mg/mL). Five milliliters of solution are provided in polyethylene bottles with a dropper tip.

Dosage: one drop in the conjunctival sac of the affected eye(s) once a day in the evening

Nursing considerations: (1) Warn patients not to administer the drug more often than once a day because more frequent administration may actually lessen the IOP-lowering effect. (2) Instruct patients who take more than one ophthalmic drug to administer latanoprostene at least 5 minutes apart from another ophthalmic medication. (3) Tell patients who wear contact lenses to remove them before drug administration to prevent damaging them. Lenses may be reinserted 15 minutes after administration. (4) Inform patients about the risk of potentially permanent changes in iris pigmentation, which may not be noticeable for months or years. (5) Tell patients to store unopened bottles in a refrigerator. Once a bottle is opened, it may be stored at room temperature for 8 weeks. ■

REFERENCE

1. Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use. Prescribing Information. www.bausch.com/Portals/69/-/m/BL/United%20States/USFiles/Package%20Inserts/Pharma/vyzulta-prescribing-information.pdf.

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