1.5 ANCC CONTACT HOURS CE 1.5 PHARMACOLOGY CREDITS

New Drugs 2019 PART 1

BY DANIEL A. HUSSAR, PhD
REMINGTON PROFESSOR OF PHARMACY • PHILADELPHIA COLLEGE OF PHARMACY • UNIVERSITY OF THE SCIENCES • PHILADELPHIA, PA

Abstract: This article reviews seven drugs recently approved by the FDA, including indications, precautions, adverse reactions, and nursing considerations.

Keywords: benralizumab, ertugliflozin L-pyroglutamic acid, netarsudil dimesylate, ozenoxacin, semaglutide, tezacaftor/ivacaftor, voretigene neparvovec-rzyl

THIS ARTICLE reviews seven drugs recently approved by the FDA, including:

- two antidiabetic medications.
- a new combination medication for patients with cystic fibrosis.
- the first gene therapy that targets a disease caused by mutations in a specific gene.

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

Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, Inc.; 2019.

Nursing2019 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2019.

Physician's Desk Reference. 71st ed. Montvale, NJ: Medical Economics; 2019.

The author and planners have disclosed no potential conflicts of interest, financial or otherwise.

EPIC CREATIONS / SHUTTERSTOCK

ANTIDIABETIC DRUGS

Semaglutide

Another GLP-1 receptor agonist joins the arsenal

Glucagon-like peptide-1 (GLP-1) is a peptide hormone that is released soon after a person eats a meal. It has multiple actions that include suppressing glucagon secretion, stimulating glucose-dependent insulin secretion, slowing gastric emptying, and promoting satiety.[1]

Semaglutide (*Ozempic*, Novo Nordisk) is the sixth GLP-1 receptor agonist to be marketed in the US, joining exenatide, extended-release exenatide, liraglutide, lixisenatide, dulaglutide, and albiglutide (which has been discontinued due to lack of competitive success in the marketplace[2]).

Like the other drugs in this class, semaglutide is administered via subcutaneous injection in the abdomen, thigh, or upper arm. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] As with dulaglutide and extended-release exenatide, semaglutide is administered just once a week, whereas liraglutide and lixisenatide are administered once a day, and the Byetta formulation of exenatide is administered twice a day.

Semaglutide is not recommended as first-line therapy for patients with diabetes that is not adequately controlled with diet and exercise. Metformin is the usual initial treatment of choice in patients with type 2 diabetes who do not have risk factors, such as severe renal impairment, that preclude its use.[3] However, many patients do not experience adequate glycemic control with the use of metformin alone, and a GLP-1 receptor agonist is among the options that may be added to the regimen.

The effectiveness of semaglutide was evaluated 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. Semaglutide reduced A1C and fasting plasma glucose concentrations, and many patients experienced weight loss. In a 30-week, placebo-controlled study of semaglutide monotherapy, patients treated with the new drug (0.5 mg or 1 mg once a week) experienced 1.4% and 1.6% reductions, respectively, in A1C concentrations compared with a 0.1% reduction in patients receiving placebo.

The efficacy of semaglutide was also compared with sitagliptin, exenatide extended-release, and insulin glargine in studies of combination regimens of antidiabetic agents. Semaglutide in a dosage of 1 mg once a week provided a greater reduction in A1C concentrations than sitagliptin (-1.5% versus -0.7% at week 56), exenatide extended-release (-1.4% versus -0.9% at week 56), and insulin glargine (-1.5% versus -0.9% at week 30).

Many patients with diabetes are overweight, and some antidiabetic agents such as insulin and sulfonylureas have been associated with weight gain during treatment. In contrast, patients treated with a GLP-1 receptor agonist often experience weight loss. In the studies of semaglutide, the mean changes from baseline were a weight reduction in the range of 4 to 5 kg.

A 2-year study of patients with type 2 diabetes and high cardiovascular risk found a higher incidence of diabetic retinopathy complications in patients treated with semaglutide (3%) compared with those receiving placebo (1.8%). It is not known whether this response is drug-related or whether it represents a temporary worsening of diabetic retinopathy, which is sometimes associated with rapid improvement in glucose control.[4]

Semaglutide and the other GLP-1 receptor agonists are not likely to cause hypoglycemia. However, the risk of hypoglycemia is increased if semaglutide is used in combination with insulin or an insulin secretagogue such as a sulfonylurea, and a reduction in the dosage of the latter may be necessary.

Precautions: (1) Not indicated for patients with type 1 diabetes or patients with diabetic ketoacidosis. (2) Contraindicated for patients with a personal or family history of medullary thyroid carcinoma and patients with multiple endocrine neoplasia syndrome type 2. Semaglutide and other GLP-1 receptor agonists have been reported to cause thyroid C-cell tumors in animal studies. This risk is the subject of a Boxed Warning in the labeling. (3) Promptly discontinue treatment if the patient develops signs and symptoms of pancreatitis; acute pancreatitis has been infrequently reported with the GLP-1 receptor agonists. Other antidiabetic drugs should be considered for patients with a history of pancreatitis. (4) Discontinue semaglutide if the patient experiences signs and symptoms of a hypersensitivity reaction. Serious hypersensitivity reactions have infrequently occurred with other GLP-1 receptor agonists. (5) A few patients treated with a GLP-1 receptor agonist have experienced acute kidney injury or worsening of chronic renal failure. Most of these events have been reported in patients who had experienced gastrointestinal (GI) adverse reactions such as diarrhea and dehydration. Monitor renal

function when initiating treatment or increasing the dosage of semaglutide in patients reporting severe GI reactions. (6) Because GLP-1 receptor agonists slow gastric emptying, use semaglutide with caution in patients with gastroparesis. This action also has the potential to alter the absorption of medications that are administered orally.

Adverse reactions: nausea, vomiting, diarrhea, abdominal pain, constipation

Supplied as: 2 mg/1.5 mL supplied in prefilled, disposable, single-patient-use pens that deliver 0.25 mg (for treatment initiation), 0.5 mg (for maintenance treatment), or 1 mg (for maintenance treatment) of the drug per injection. Cartons of the product contain the pens and a supply of needles.

Dosage: Initially, 0.25 mg once a week for 4 weeks. This dosage is subtherapeutic and is intended only for treatment initiation. After 4 weeks, the dosage should be increased to 0.5 mg once a week. If additional glycemic control is needed after the patient has been on the 0.5 mg dose for at least 4 weeks, the dosage may be increased to 1 mg once a week, which is the maximum recommended dosage.

Nursing considerations: (1) Teach patients how to administer the medication as directed in the Medication Guide and Instructions for Use provided with the product. Tell them to administer the drug on the same day each week, at any time of the day, without regard to food, and to use a new needle for each injection. After the first use of the pen, it can be stored for 56 days at room temperature or in a refrigerator. (2) If a dose is missed, tell patients to administer it as soon as possible within 5 days after the missed dose. If more than 5 days have passed, tell them to skip the missed dose and administer the next dose on the regularly scheduled day. (3) Tell patients to store the product in a refrigerator prior to first use. (4) Monitor patients with a history of diabetic retinopathy for worsening of this complication. (5) Warn patients about the risk of pancreatitis and instruct them to report signs and symptoms such as severe abdominal pain that may radiate to the back, with or without vomiting. (6) Because the risk of fetal abnormalities is unknown, advise women to discontinue the drug at least 2 months before a planned pregnancy.

REFERENCES

1. Ozempic. Semaglutide injection 0.5 mg/1 mg. Prescribing Information. www.novo-pi.com/ozempic.pdf.

2. US Food and Drug Administration. FDA drug shortages. Current and resolved drug shortages and discontinuations reported to FDA. 2017. www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Albiglutide+%28Tanzeum%29+Injection&st=d&tab=tabs-2.

3. Glucophage (metformin hydrochloride) tablets, for oral use. Prescribing Information. https://packageinserts.bms.com/pi/pi_glucophage.pdf.

4. Feldman-Billard S, Larger É, Massin P, et al. Early worsening of diabetic retinopathy after rapid improvement of blood glucose control in patients with diabetes. *Diabetes Metab.* 2018; 44(1):4-14.

Ertugliflozin L-pyroglutamic acid

Effective as monotherapy or as part of a combination regimen

Administered orally, ertugliflozin (*Steglatro*, Merck) is the fourth drug in a class of oral antidiabetic drugs designated as sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 is expressed in the proximal renal tubules and is responsible for the reabsorption of most of the glucose that is filtered by the kidneys. By inhibiting SGLT2, ertugliflozin and the other agents in this class (canagliflozin, dapagliflozin, and empagliflozin) reduce the reabsorption of filtered glucose, increase urinary glucose excretion, and reduce blood glucose and A1C concentrations.[1]

Like the other SGLT2 inhibitors, ertugliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Its effectiveness in reducing A1C and fasting plasma glucose concentrations has been demonstrated in studies in which it was used as monotherapy or as part of a combination regimen with metformin and/or other antidiabetic agents.[2]

Ertugliflozin was also evaluated in a study of patients with type 2 diabetes and moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to less than 60 mL/min/1.73 m^2). The A1C reductions from baseline to week 26 were not significantly different between placebo and the drug in a dosage of either 5 mg or 15 mg once a day, so the results did not demonstrate efficacy of the drug in these patients.

After empagliflozin was approved in 2014, studies have demonstrated a benefit with respect to cardiac risk. Accordingly, the labeled indications for empagliflozin have been expanded to include use to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. This is not a labeled indication for the other SGLT2 inhibitors.

Precautions: (1) Not indicated for treatment of patients with type 1 diabetes mellitus or diabetic ketoacidosis. If ketoacidosis is suspected during the period of treatment, the drug should be discontinued, the patient assessed, and prompt treatment instituted. (2) Contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) or end-stage renal disease, and in patients on dialysis. The SLGT2 inhibitors have been associated with increases in serum

creatinine concentrations and decreases in eGFR. Older patients and others with impaired renal function are more susceptible to the related risks. (3) Not recommended for use in patients with moderate renal impairment. Evaluate renal function before initiating treatment and periodically thereafter. Initiation of treatment with ertugliflozin is not recommended in patients with an eGFR of 30 to less than 60 mL/min/1.73 m^2. If the eGFR falls to and persists within this range during treatment, continued use of the drug is not recommended. (4) Assess volume status and BP before initiating treatment with ertugliflozin and monitor these values periodically during treatment. Ertugliflozin and the other SGLT2 inhibitors cause an osmotic diuresis, which may lead to intravascular volume contraction and symptomatic hypotension. In studies with ertugliflozin in which BP was monitored, the mean change from baseline in systolic BP was a reduction of about 5 mm Hg. Older adults, patients with low systolic BP, and patients treated with a diuretic are at greatest risk for hypotension. Temporary discontinuation of treatment should be considered in patients who experience fluid losses or reduced oral intake. (5) The labeling for ertugliflozin contains a warning (but not a more severe Boxed Warning) about the risk of lower limb amputation. This is the subject of a Boxed Warning for canagliflozin but not any of the other SGLT2 inhibitors. Before treatment with any SGLT2 inhibitor is initiated, assess for risk factors, such as a history of prior amputation, peripheral arterial disease, neuropathy, and diabetic foot ulcers, that may predispose patients to a need for amputation. (6) Although ertugliflozin is not likely to cause hypoglycemia, it can increase the risk of hypoglycemia when used in combination with insulin or an insulin secretagogue such as a sulfonylurea. A lower dosage of the latter agent may be necessary when such combination regimens are used. (7) Dose-dependent increases in low-density lipoprotein cholesterol have been reported with the use of the SGLT2 inhibitors, so monitor serum lipids as appropriate. (8) Because SGLT2 inhibitors increase urinary glucose secretion, positive urine glucose tests will result and alternative methods to monitor glycemic control should be used. (9) Measurements of 1,5-anhydroglucitol (1,5-AG) are unreliable in patients treated with an SGLT2 inhibitor, so this method is also not recommended in assessing glycemic control. (10) Not recommended for use in patients with severe hepatic impairment because of a lack of study data. Dosage adjustment is not necessary in patients with mild or moderate hepatic impairment.

Adverse reactions: female genital mycotic infections, male genital mycotic infections such as balanitis, urinary tract infections (UTIs), headache, back pain

Supplied as: 5 mg and 15 mg film-coated tablets

Dosage: Initially, 5 mg once a day in the morning. The dosage may be increased to 15 mg once a day in patients who tolerate the drug and need additional glycemic control.

Nursing considerations: (1) Tell patients to take each dose in the morning without regard to food. (2) If a dose is missed, tell patients to take it as soon as they remember, unless it is almost time for the next dose. In that case, they should skip the missed dose and take the medication at the next regularly scheduled time. Warn patients not to take two doses at the same time. (3) Teach patients to report any signs and symptoms of a UTI, such as dysuria, urinary frequency, and urinary urgency, to the healthcare provider. Serious UTIs, including pyelonephritis, have been infrequently reported. (4) Because of a potential risk for lower limb amputations, monitor patients for signs and symptoms of infection, new pain or tenderness, and sores or ulcers involving the lower limbs. The medication should be discontinued if these complications occur.

REFERENCES

1. Novikov A, Vallon V. SGLT2 inhibition in the diabetic kidney—an update. *Curr Opin Nephrol Hypertens.* 2016; 25(1):50-56.

2. Steglatro (ertugliflozin) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/209803s000lbl.pdf.

ANTIASTHMATIC DRUG

Benralizumab

Add-on maintenance treatment for certain patients age 12 and older

Multiple cell types, including eosinophils and mediators such as cytokines, are involved in the inflammatory process affecting the lungs of patients with asthma. Benralizumab (*Fasenra*, AstraZeneca) is the third monoclonal antibody to be approved for reducing the activity of interleukin-5 (IL-5), the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Benralizumab directly binds to the alpha subunit of IL-5 receptors, preventing IL-5 from binding to its receptors and leading to apoptosis of eosinophils through antibody-dependent cell-mediated cytotoxicity.[1]

Administered subcutaneously, benralizumab is indicated as add-on maintenance treatment for patients age 12 and older with severe asthma and an eosinophilic phenotype. Like the other IL-5 antagonists, benralizumab is not indicated for relief of acute bronchospasm or status asthmaticus.[2]

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 requiring oral or systemic corticosteroid treatment in the past 12 months despite regular treatment with an inhaled corticosteroid, a long-acting beta agonist, and/or additional medications for asthma. 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 28 weeks. The median percent reduction in the daily oral corticosteroid dose from baseline was 75% in patients treated with benralizumab compared with 25% in patients receiving placebo.

The change from baseline in mean forced expiratory volume in 1 second (FEV_1) was assessed as a secondary endpoint in all three studies. Patients treated with the new drug experienced consistent improvements over time in the mean increase in FEV_1 from baseline.

Benralizumab is administered by subcutaneous injection into the upper arm, thigh, or abdomen. The labeling recommends that it be administered by a healthcare professional.

Precautions: (1) The use of any drug that reduces IL-5 activity may permit a reduced dosage of corticosteroids that have been part of a patient's maintenance treatment. Treatment with a systemic or inhaled corticosteroid should be discontinued gradually, not abruptly. Dosage reduction of a corticosteroid may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. (2) Any preexisting helminth infections should be treated before starting therapy with the new drug because eosinophils may be involved in the immunologic response to some helminth infections. If a helminth infection occurs during treatment with benralizumab and does not respond to antihelminth treatment, benralizumab should be discontinued until the infection resolves.

Adverse reactions: headache, pharyngitis

Supplied as: single-dose prefilled syringes containing 30 mg of the drug in 1 mL

Dosage: 30 mg once every 4 weeks for the first three doses, then once every 8 weeks for maintenance

Nursing considerations: (1) Inform patients that hypersensitivity reactions to benralizumab have occurred within hours or in some cases days after administration. Tell them to contact their healthcare professional immediately if they experience signs and symptoms of hypersensitivity, such as angioedema, urticaria, or rash. (2) Remind patients that benralizumab is not used to treat acute or worsening asthma symptoms. Tell them to seek medical advice if their asthma worsens. (3) Warn patients not to discontinue any systemic or inhaled corticosteroids except under the direct supervision of their healthcare provider. (4) Store the drug in the refrigerator in the original carton to protect it from light.

REFERENCES

1. Benralizumab (Fasenra) for severe eosinophilic asthma. *JAMA*. 2018;319(14):1501-1502.

2. Fasenra (benralizumab) injection, for subcutaneous use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf.

DRUG FOR CYSTIC FIBROSIS

Tezacaftor/ivacaftor

Combination product gives therapy a boost

Cystic fibrosis is a genetic disorder affecting approximately 30,000 people in the US.[1] It is caused by a defective or missing cystic fibrosis transmembrane conductance regulator (CFTR) protein resulting from mutations in the CFTR gene. Approximately 2,000 mutations in the CFTR gene have been identified.[2]

CFTR protein regulates chloride and water transport throughout the body, including in the lungs, sweat glands, GI tract, and pancreas; defective functioning of this protein results in the formation of thick mucus in the affected areas.[1,3] Signs and symptoms can include chronic cough, persistent lung and sinus infections, pancreatic insufficiency, and other severe digestive problems.[4]

The F508del mutation is the most common cause of cystic fibrosis; patients with two copies of this mutation account for approximately one-half of patients with this disease in the US. It is usually diagnosed during infancy or childhood.[1]

Tezacaftor/ivacaftor (*Symdeko*, Vertex) is a new combination formulation indicated for patients with cystic fibrosis age 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the CFTR gene that is responsive to the combination based on in vitro data and/or clinical evidence.[5] Ivacaftor was the first treatment for cystic fibrosis that targeted the underlying cause of the disease. It is thought to facilitate increased chloride transport by potentiating the channel-open probability ("gating") of the G551D-CFTR protein; that is, increasing the amount of time the protein stays open at the cell surface.[6]

Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the gating of the CFTR protein at the cell surface. However, CFTR protein must be present at the cell surface for ivacaftor to function. Tezacaftor increases the delivery of CFTR protein to the cell surface. Its use in combination with ivacaftor enhances chloride transport beyond what either drug given alone can provide. Tezacaftor/ivacaftor is supplied as fixed-dose combination tablets that are administered in the morning and copackaged with ivacaftor tablets that are administered in the evening.

The effectiveness of the tezacaftor/ivacaftor regimen was demonstrated in two placebo-controlled trials. In both studies, patients treated with the new combination experienced statistically significant and clinically meaningful improvements in lung function and other measures of disease that were sustained for up to 48 weeks of treatment.

Precautions: (1) Because elevated transaminases have been reported, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be assessed before treatment starts, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of transaminase elevations, more frequent monitoring should be considered. Treatment should be interrupted in patients with significant elevations (for example, ALT or AST greater than five times the upper limit of normal). (2) Noncongenital lens opacities/cataracts have been reported in pediatric patients treated with tezacaftor/ivacaftor. Baseline and follow-up ophthalmologic examinations are recommended in pediatric patients. (3) Concurrent use of a CYP3A inducer such as carbamazepine, rifampin, or St. John's wort is not recommended because of the probability of a significant reduction in the new product's activity. The concurrent use of a moderate or strong CYP3A inhibitor, such as fluconazole, itraconazole, and clarithromycin, increases the exposure of tezacaftor/ivacaftor and the dosage of the new product should be reduced in patients taking these drugs. Patients should be instructed to avoid food containing grapefruit, grapefruit juice, and Seville oranges, which also increases the exposure of tezacaftor/ivacaftor. (4) Consult the Prescribing Information for recommended dosage adjustments for patients with moderate or severe renal or hepatic impairment.

Adverse reactions: headache, nausea, sinus congestion, dizziness

Supplied as: tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor, copackaged with tablets containing 150 mg of ivacaftor

Dosage: one combination tablet (100 mg/150 mg) in the morning and one 150 mg ivacaftor tablet in the evening, approximately 12 hours apart

Nursing considerations: (1) Teach patients to take the yellow tablet (tezacaftor/ivacaftor) in the morning and the blue tablet (ivacaftor) in the evening, about 12 hours apart. Instruct them to swallow tablets whole and to take each dose with a food containing fat, such as eggs, butter, peanut butter, cheese pizza, or whole-milk dairy products. (2) Tell patients to avoid food and drink that contain grapefruit or Seville oranges while being treated with tezacaftor/ivacaftor. (3) Warn patients to avoid driving and other activities requiring alertness until they learn how the medication affects them. (4) If they miss a dose, patients should take the missed dose as soon as they remember unless more than 6 hours have lapsed since the last dose. In that case, they should not take the missed dose and instead take the next dose as scheduled. Warn them not to double the dose to make up for a missed dose.

REFERENCES

1. National Institutes of Health. National Heart, Lung, and Blood Institute. Facts about cystic fibrosis. www.cdc.gov/scienceambassador/documents/cystic-fibrosis-fact-sheet.pdf.

2. Cutting GR. Cystic fibrosis genetics: from molecular understanding to clinical application. *Nat Rev Genet*. 2015;16(1):45-56.

3. Cystic Fibrosis Foundation. Types of CFTR mutations. www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations.

4. *Merck Manual*. 20th ed. Kenilworth, NJ: Merck and Co., Inc.; 2018.

5. Symdeko (tezacaftor/ivacaftor) tablets; (ivacaftor) tablets, for oral use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/210491lbl.pdf.

6. Tezacaftor/ivacaftor (Symdeko) for cystic fibrosis. *The Medical Letter*. Issue 1558; October 22, 2018.

ANTIBACTERIAL DRUG

Ozenoxacin

Treatment for patients with impetigo age 2 months and up

A highly contagious superficial bacterial skin infection, impetigo is usually caused by *Staphylococcus aureus* or *Streptococcus pyogenes* and is considered the most common bacterial skin infection in children.[1] It occurs most often in infants and young children, and spreads easily in child-care settings, schools, and other settings in which people are in close contact. Impetigo that is localized and involves limited areas of skin is usually treated with a topically applied antibacterial agent such as mupirocin or retapamulin. More extensive lesions are usually treated with an oral antibiotic.

Ozenoxacin (*Xepi*, Medimetriks) is a quinolone antibacterial agent. Applied topically, it inhibits bacterial DNA replication enzymes, DNA gyrase A, and topoisomerase IV. It also

exhibits a bactericidal action against *S. aureus* and *S. pyogenes*.[2]

Ozenoxacin is indicated for the topical treatment of impetigo caused by *S. aureus* or *S. pyogenes* in adult and pediatric patients age 2 months and older. Its action against *S. aureus* includes both methicillin-susceptible and methicillin-resistant isolates.

The effectiveness of ozenoxacin was evaluated in two placebo-controlled clinical trials that included 723 patients. Overall clinical 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 studies of the individual drugs suggests that ozenoxacin is less effective.

For treatment of impetigo, ozenoxacin is used in a cream formulation, whereas mupirocin and retapamulin are used in ointment formulations. Ozenoxacin was very well tolerated in the clinical studies with only one adult patient experiencing adverse reactions (rosacea and seborrheic dermatitis).

Precaution: Prolonged use of ozenoxacin may result in overgrowth of nonsusceptible bacteria and fungi. If such infections occur, use should be discontinued and alternative therapy instituted.

Adverse reactions: rosacea, seborrheic dermatitis

Supplied as: cream containing the drug in a 1% concentration (10 mg/g)

Dosage: apply a thin layer to the affected area twice a day for 5 days.

Nursing considerations: (1) Instruct the patient (or the patient's parents) to apply a thin layer of cream twice a day for 5 days as directed. The treated area may be up to 100 cm^2 in adult and pediatric patients age 12 and older, or 2% of the total body surface area and not exceeding 100 cm^2 in pediatric patients younger than 12 years. The treated area may be covered with a sterile bandage or gauze dressing to protect the area. (2) Tell patients to wash their hands after applying the cream (unless the hands are being treated). Warn them to avoid accidental transfer of the cream to the eyes or other areas. (3) Tell patients to use the drug only as prescribed. It should not be used to treat other disorders, including ocular, nasal, or vaginal infections.

REFERENCES

1. Lewis LS. Impetigo. Medscape. 2018. https://emedicine.medscape.com/article/965254-overview.

2. Xepitm (ozenoxacin) cream, for topical use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208945lbl.pdf.

DRUG FOR GLAUCOMA

Netarsudil dimesylate

Unique medication for lowering IOP

Netarsudil dimesylate (*Rhopressa*, Aerie) ophthalmic solution is indicated to reduce elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.[1] Classified as a Rho kinase inhibitor, it has a unique mechanism of action. It is thought to reduce IOP by increasing the outflow of aqueous humor through the trabecular meshwork, but the exact mechanism 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%, one drop into the affected eye[s] once daily in the evening) was demonstrated in three controlled clinical trials in which it was compared with an ophthalmic solution of the beta-adrenergic blocking agent timolol (0.5% twice a day). Patients treated with the new drug experienced up to 5 mm Hg reductions in IOP. In patients with a baseline IOP less than 25 mm Hg, the IOP reductions were similar to those with timolol. However, in patients with a baseline IOP of 25 mm Hg or greater, the mean IOP reductions were smaller with netarsudil than with timolol.

Precautions: (1) Reports of bacterial keratitis have been associated with the use of multiple-dose containers of topical ophthalmic products. Instruct patients to prevent the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize the risk of contaminating the solution. (2) Twice-a-day dosing is not well tolerated and is not recommended.

Adverse reactions: conjunctival hyperemia, corneal verticillata (opacities), instillation site pain, conjunctival hemorrhage

Supplied as: a sterile ophthalmic solution in an amount equivalent to 0.2 mg/mL (0.02%) of netarsudil. The medication is contained in opaque white low-density polyethylene bottles and tips with white polypropylene caps.

Dosage: one drop in the affected eye(s) per day in the evening

Nursing considerations: (1) Tell patients to report any unusual ocular signs and symptoms. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were each reported in 5% to 10% of patients in clinical trials. Corneal verticillata were first noted approximately 4 weeks following initiation of treatment but did not cause any apparent visual

functional changes. (2) Teach patients how to properly instill the medication without contaminating the dispenser tip or medication. (3) If they miss a dose, patients should skip it and take the next scheduled evening dose. Warn them not to take more than one dose a day. (4) Instruct patients taking other ophthalmic medications concurrently to administer them at least 5 minutes apart. (5) Like many ophthalmic formulations, netarsudil solution contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Tell patients to remove contact lenses before instilling the medication; lenses may be reinserted 15 minutes following administration. (6) Unopened medication containers should be stored in a refrigerator. After being opened, containers may be kept at room temperature for up to 6 weeks.

REFERENCE

1. Rhopressa (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use. Prescribing Information. www.accessdata.fda.gov/drugsatfda_docs/label/2017/208254lbl.pdf.

DRUG FOR RETINAL DYSTROPHY

Voretigene neparvovec-rzyl

First gene therapy approved to target a disease caused by mutations in a specific gene

Hereditary retinal dystrophies are a group of genetic retinal disorders that are associated with worsening visual dysfunction and are caused by any one of more than 220 different genes.[1] Voretigene neparvovec-rzyl (*Luxturna*, Spark) is indicated for patients with confirmed biallelic human retinal pigment epithelial 65 kDa gene (RPE65) mutation-associated retinal dystrophy. This is the first gene therapy that targets a disease caused by mutations in a specific gene.[1,2]

The RPE65 gene provides instructions for making an enzyme essential for normal vision.[3] This occurs in the visual (retinoid) cycle, which is necessary for the biological conversion of light into an electrical signal in the retina. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 isomerohydrolase activity, blocking the visual cycle and impairing vision.[3] Loss of vision often occurs during childhood or adolescence and may eventually result in complete blindness. Biallelic RPE65 mutation-associated retinal dystrophy affects between 1,000 and 2,000 individuals in the US.[1] Voretigene is indicated only for those patients who have viable retinal cells.[2]

Voretigene is provided in a suspension of an adeno-associated virus vector-based gene therapy for subretinal injection. It uses a naturally occurring, live, nonreplicating adeno-associated virus serotype 2, which has been genetically modified using recombinant DNA techniques, to deliver the normal human RPE65 gene to the retinal cells.

The effectiveness of voretigene was evaluated in a study with 31 patients ranging in age from 4 to 44 years; almost two-thirds were under age 18. The multiluminance mobility testing evaluation was used to measure changes 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. The evaluation of the change from baseline to 1 year demonstrated significant improvements in the patients treated with voretigene being able to complete the obstacle course at low light levels compared with those in the control group. The benefit was sustained over the 2-year study period. Patients who were initially in the control group were treated with voretigene after 1 year and experienced similar improvement with the drug compared with the patients in the initial treatment group.

Additional clinical outcomes were also evaluated, including full-field light sensitivity threshold (FST) testing and visual acuity. Patients treated with voretigene experienced significant improvement from baseline to Year 1 in the analysis of white light FST testing. However, the change in visual acuity was not significantly different between the voretigene and control groups.

Voretigene should be administered in a surgical suite under controlled aseptic conditions by a surgeon experienced in performing intraocular surgery.

Precautions: (1) Monitor patients for endophthalmitis or other infection, decline in visual acuity, retinal abnormalities, cataract formation, and increased intraocular pressure (IOP). (2) Instruct patients to avoid air travel, travel to high elevations, or scuba diving until the intraocular air bubble formed following administration of voretigene has completely dissipated from the eye. This may take 1 week or more following injection of the drug. A change in altitude while air bubbles are still present can result in irreversible vision loss. (3) Not recommended for pediatric patients younger than 12 months because the retinal cells are still undergoing cell proliferation and the drug may be diluted or lost during cell proliferation.

Adverse reactions: conjunctival hyperemia, cataract, increased IOP, retinal tear, corneal dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula)

Supplied in: a 0.5 mL extractable volume in a single-dose 2 mL vial for a single administration in one eye. The vial and the two vials of diluent (single-use 2 mL vials) provided should be stored in the frozen state. The drug

must be diluted before administration. Consult the product labeling for detailed recommendations for diluting, preparing, and administering the injection.

Dosage: for each eye, 1.5 x 10^{11} vector genomes, 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.

Nursing considerations: (1) Maintain supine head positioning in the post-op period. Advise patients to rest in a supine position as much as possible for 24 hours after treatment. (2) Because voretigene is an adeno-associated virus vector-based gene therapy, universal biohazard precautions should be observed during handling. Transient and low-level shedding may occur in patient tears. Instruct patients and/or their caregivers on proper handling of waste material generated from dressing, tears, and nasal secretions. These handling precautions should be followed for up to 7 days following voretigene administration. (3) Teach patients or their caregivers how and when to administer the prescribed medication regimen. A systemic oral corticosteroid is recommended for a total of 7 days (starting 3 days before the administration of voretigene in the first eye) and followed by dosage tapering during the following 10 days. The same corticosteroid dosing regimen should be used for treatment of the second eye. If the corticosteroid taper following voretigene administration to the first eye is not completed 3 days before the planned administration of the drug in the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye. (4) Store voretigene and diluent frozen. After vials are thawed, store them at room temperature. Also store diluted voretigene at room temperature. ■

REFERENCES

1. FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. US Food and Drug Administration. News release. December 19, 2017.

2. Luxturna (voretigene neparvovec-rzyl) intraocular suspension for subretinal injection. Prescribing Information. www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM589541.pdf.

3. Genetics Home Reference. RPE65 gene. US National Library of Medicine. 2018. https://ghr.nlm.nih.gov/gene/RPE65#conditions.

DOI-10.1097/01.NURSE.0000552697.50502.91