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ZERBOR / SHUTTERSTOCK

PART 3

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

Keywords: brexanolone, brolucizumab-dbll, elexacaftor/tezacaftor/ivacaftor, imipenem monohydrate/cilastatin sodium/relebactam monohydrate, onasemnogene abeparvovec-xioi, pretomanid, segesterone acetate/ethinyl estradiol, trifarotene

THIS ARTICLE reviews eight recently marketed drugs, including:

- an important therapeutic advance for patients with spinal muscular atrophy.
- the first drug specifically approved to treat postpartum depression.
- a combination product that can help treat approximately 90% of patients with cystic fibrosis.

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.

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

DRUG FOR SMA

Onasemnogene abeparvovec-xioi

One-time therapy to replace a defective gene.

Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disease that impairs muscle strength and movement. It is caused by a defective or missing survival motor neuron 1 (SMN1) gene. Infants without a functional SMN1 gene lose the motor neurons responsible for muscle functions such as swallowing, breathing, speaking, and walking.

SMN1 gene-related SMA, also known as SMA type 1 and infantile-onset SMA, is a severe form in which muscle weakness leads to paralysis and ultimately progressive respiratory failure requiring ventilatory support or death by age 2 years in more than 90% of cases. In general, early onset of symptoms correlates with the degree of functional impairment.[1,2] SMA may affect 10,000 to 25,000 children and adults in the US and is considered one of the most common rare diseases.[3]

Onasemnogene abeparvovec-xioi (*Zolgensma,* AveXis) is an adeno-associated virus (AAV) vector-based gene therapy indicated for pediatric patients under age 2 years with SMA with bi-allelic mutations in the SMN1 gene.[4] It replaces the defective or missing SMN1 gene with a single, one-time I.V. infusion. This increases production of SMN protein, which blocks or delays the worsening of SMA.

The effectiveness of onasemnogene abeparvovec was evaluated in two clinical trials, one of which was still ongoing at the time the drug was approved. The completed trial involved 15 patients with infantile-onset SMA. Twelve infants received a high dose of the drug and three received a lower dose. By 24 months following treatment, all 12 patients in the high-dose cohort were alive without the need for permanent ventilatory support. Nine of these patients were able to sit without support for at least 30 seconds and two were able to stand and walk without assistance. None of the three patients in the low-dose cohort was able to sit without support, or to stand or walk. The dose-response relationship that occurred supports the drug's effectiveness.

Twenty-one patients (mean age at the time of treatment, 3.9 months) were enrolled in the other study. As of the March 2019 data cutoff, 19 patients were alive without the need for permanent ventilatory support (that is, event-free survival) and were continuing in the trial, one patient died, and one patient withdrew from the study. Thirteen of the 19 patients reached 14 months without permanent ventilatory support, one of the study's coprimary efficacy endpoints. Ten patients achieved the ability to sit without support for at least 30 seconds. Based on the natural progression of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive without permanent ventilatory support beyond 14 months.

The use of onasemnogene abeparvovec in patients with advanced SMA (complete paralysis of extremities and permanent ventilator dependence) has not been evaluated, nor has the effectiveness and safety of repeated doses of the drug. Its use in premature neonates before they reach full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurologic development.

The labeling includes a boxed warning about the risk of acute serious liver injury. This risk may be higher in patients with preexisting liver impairment.

The development of onasemnogene abeparvovec is a lifesaving advance in treatment. However, it is extremely expensive, costing $2,125,000 for the single dose.[5]

Precautions: (1) Starting 1 day before the infusion, the patient should receive a systemic corticosteroid equivalent to oral prednisolone at 1 mg/kg of body weight each day for 30 days. Consult the product labeling for recommendations for continuing or tapering the dose based on an evaluation of liver function. (2) Liver function tests should be performed before treatment. Following treatment, liver function should be monitored weekly for the first month and then every other week for the second and third months until results are unremarkable. (3) Perform baseline testing for the presence of anti-AAV9 antibodies before the infusion. The presence of these antibodies may interfere with the effectiveness of therapy. The safety and efficacy of this therapy in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated. (4) Transient increases in serum platelets and cardiac-specific troponin I levels have been observed with the use of onasemnogene abeparvovec. Monitor these values before treatment and regularly following treatment until values return to baseline.

Adverse reactions: elevated aminotransferases, vomiting

Supplied as: single-use vials provided in a kit containing 2 to 9 vials. Vials are provided in two fill volumes: 5.5 mL or 8.3 mL.

Dosage: 1.1×10^{14} vector genomes (vg) per kg of body weight. The drug is administered as a single-dose I.V. infusion over 60 minutes. Consult the product labeling for details on dosage calculation, drug preparation, and drug administration.

Nursing considerations: (1) The drug is shipped and delivered frozen. Upon receipt, the kit should be immediately placed in a refrigerator.

The drug is stable for 14 days from receipt when stored in the refrigerator and must not be refrozen. It must be used within 14 days of receipt. (2) Inform the patient's caregivers about the risk of liver injury and the need for regular blood tests to monitor liver function. Advise them to contact their healthcare provider immediately if the patient develops jaundice or conjunctival icterus, misses a dose of corticosteroid, or vomits after taking the dose. (3) Tell caregivers to consult with their healthcare provider to determine if the patient's vaccination schedule should be adjusted during corticosteroid use. (4) Inform caregivers that a cold or other viral respiratory infection before or after treatment could lead to more serious complications such as respiratory insufficiency. Advise them to immediately report any signs or symptoms of a respiratory infection, such as coughing, wheezing, sneezing, rhinorrhea, pharyngitis, or fever. (5) Because the drug may decrease platelet counts, tell caregivers to inform the provider of any unusual bruising or bleeding. (6) After treatment, temporary vector shedding occurs primarily through body waste. Teach caregivers about the proper handling of patient feces; for example, sealing disposable diapers in disposable trash bags and then discarding into regular trash. Emphasize the importance of hand hygiene. These precautions should be followed for 1 month after treatment.

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DRUG FOR POSTPARTUM DEPRESSION

Brexanolone

First drug specifically approved for postpartum depression.

Postpartum depression (PPD) affects approximately one in nine women who give birth in the US, and about 400,000 annually, although many cases are undiagnosed.[1] It is considered a major depressive episode that occurs following childbirth, although symptoms can start during pregnancy. Characterized by feelings of sadness and/or loss of interest in activities that were previously enjoyed, it can become severe to the point that some women may consider harming themselves or their child. The ability of the mother to bond with, care for, and nurture her child is often impaired, as may be the child's emotional and behavioral development.

Counseling and therapy with antidepressants such as a selective serotonin reuptake inhibitor (SSRI) are standard treatments. However, patients usually don't experience the full benefit of SSRIs and other antidepressants for several weeks or more following initiation of treatment, and some patients experience only minimal benefit.

Brexanolone (*Zulresso*, Sage), the first drug specifically approved to treat PPD, is administered by continuous I.V. infusion over 60 hours (2.5 days).[2] It is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator that is chemically identical to endogenous allopregnanolone, a major metabolite of progesterone. Concentrations of allopregnanolone rise during pregnancy, but then significantly fall following delivery.

The effectiveness of brexanolone was evaluated in two placebo-controlled studies in women who experienced the onset of depressive symptoms in the third trimester or within 4 weeks following delivery. In both studies, patients received a 60-hour continuous I.V. infusion of brexanolone or placebo and were then followed for 4 weeks. Brexanolone demonstrated superiority to placebo in improvement of depressive symptoms at the end of the infusion, and the improvement was maintained at the end of the 30-day follow-up period. However, in one study, the improvement of symptoms at Day 30 in the women receiving placebo was similar to the improvement in those treated with brexanolone.

A reduction of depressive symptoms was experienced by some women as early as 24 hours. The new drug's rapid onset of action is an important advantage when compared with other therapies for PPD.

Excessive sedation and sudden loss of consciousness are the most important concerns associated with brexanolone and are the subject of a boxed warning in its labeling. Because of the risks associated with these events, the new drug was approved with a Risk Evaluation and Mitigation Strategy (REMS) and is available only through a restricted distribution program. Under the provisions of the REMS program, wholesalers and distributors of brexanolone must be registered with the program and may distribute the drug only to certified healthcare facilities and pharmacies. Patients must also be enrolled in the program. During treatment, a healthcare provider must be available on site to continuously monitor the patient and intervene as necessary for the 60-hour duration of the infusion.

Brexanolone may cause adverse developmental effects if used during pregnancy. Patients who are pregnant during treatment should be registered in the National Pregnancy Registry for Antidepressants (1-844-405-6185), which monitors pregnancy outcomes.

Precautions: (1) Monitor patients for excessive sedation, especially if they are taking an oral antidepressant concurrently. Concomitant use of other medications with central

nervous system depressant activity, including benzodiazepines and opioids, increases the likelihood and severity of sedation. (2) Patients with depression and/or those who are taking antidepressant medications may experience suicidal thoughts and behaviors. Discontinuation of brexanolone should be considered in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors during treatment. (3) Brexanolone is included in Schedule IV under the provisions of the Controlled Substances Act. Because it has the potential to cause physical dependence, withdrawal symptoms may occur if it is abruptly discontinued. Consult the prescribing information for recommendations regarding tapering the dosage during the latter part of the infusion. These recommendations should be followed unless adverse reactions warrant immediate discontinuation of treatment. (4) Brexanolone should not be used in patients with end-stage renal disease because the solubilizing agent (betadex sulfobutyl ether sodium) used in the formulation may accumulate.

Adverse reactions: sedation/somnolence, dry mouth, loss of consciousness, flushing/hot flush

Supplied as: single-dose vials containing 100 mg/20 mL that must be diluted before administration. Consult the prescribing information for directions on preparing the drug for administration.

Dosage: Initially, 30 mcg/kg/h for the first 4 hours. The initial dosage is first increased and then tapered incrementally over the course of treatment. Consult the prescribing information for detailed administration instructions.

Nursing considerations: (1) After the drug has been diluted, the infusion bag should be immediately refrigerated until use. The diluted drug can be stored in infusion bags under refrigerated conditions for up to 96 hours. (2) The diluted product can be used for only 12 hours at room temperature, so each 60-hour infusion requires the preparation of at least five infusion bags. Patients weighing 90 kg or more may require additional bags. (3) Treatment should be initiated early during the day to allow for recognition of excessive sedation. Monitor patients for hypoxia using continuous pulse oximetry equipped with an alarm. Assess the patient for sedation every 2 hours during planned, nonsleep periods. If excessive sedation occurs at any time during the infusion, alert the healthcare provider. The infusion should be stopped until the symptoms resolve, and then resumed at the same or lower dosage. (4) Inform the patient about possible adverse reactions, including sedation and suicidal ideation. Tell her to report excessive sleepiness or any disturbing thoughts or mood changes. (5) During treatment, the patient must not be the primary caregiver of dependents and must be accompanied during interactions with any children.

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CONTRACEPTIVE

Segesterone acetate/ethinyl estradiol

Combination hormonal vaginal system that can be used for an entire year.

Segesterone acetate/ethinyl estradiol (*Annovera*, TherapeuticsMD) is a combination hormonal contraceptive (CHC) vaginal system that includes the new progestin segesterone with the estrogen that is included in many oral and other CHC formulations.[1] The vaginal system is in the shape of a ring and is most similar to NuvaRing, a progestin/estrogen combination of etonogestrel and ethinyl estradiol. However, the NuvaRing must be replaced every month, whereas the segesterone/ethinyl estradiol ring is used for an entire year (although it is removed for 1 week in each 28-day cycle). The use of a contraceptive formulation that is administered less frequently can be an advantage for women who may forget to take an oral contraceptive every day.

Segesterone/ethinyl estradiol is indicated for women of reproductive potential to prevent pregnancy. Its effectiveness was evaluated in two clinical trials in more than 2,000 healthy women ranging from ages 18 to 40. The product was highly effective, with results suggesting that out of 100 women using the product, 2 to 4 may become pregnant during the first year of use.

Return to fertility was assessed in almost 300 women who either desired pregnancy or switched to nonhormonal contraception following the trials. All of them reported a return to fertility (defined as a return of menses or pregnancy) during the 6-month follow-up period. The clinical trials did not include women with a body mass index greater than 29 kg/m^2, and this is identified as a limitation of use for the product.

Precautions: (1) Contraindicated in women with a high risk of arterial or venous thrombotic diseases (such as coronary artery disease, cerebrovascular disease, uncontrolled hypertension, history of deep vein thrombosis or pulmonary embolism), current or history of breast cancer or other estrogen- or progestin-sensitive cancer, abnormal uterine bleeding, hypersensitivity to any of the product's components, hepatic tumors, acute hepatitis, or severe (decompensated) cirrhosis. (2) Contraindicated in women with chronic hepatitis C infection being treated with ombitasvir/paritaprevir/ritonavir because of the risk of liver

enzyme elevations. (3) Contraindicated in women over age 35 who smoke. CHCs are associated with a risk of thrombotic disorders and other vascular problems, and cigarette smoking increases the risk of serious cardiovascular events. This is the subject of a boxed warning in the labeling. Providers should consider cardiovascular risk factors before prescribing the product for all women, particularly those over age 35. (4) Use of segesterone/ethinyl estradiol should be stopped at least 4 weeks before and 2 weeks after major surgery to decrease the risk of venous thromboembolism. (5) Contraindicated in women with diabetes over age 35; those who have diabetes with hypertension, nephropathy, retinopathy, neuropathy, or other vascular disease; and those with diabetes of more than 20 years' duration. CHCs may cause adverse carbohydrate and lipid metabolic effects such as decreased glucose tolerance and an increased risk of pancreatitis. (6) Closely monitor women with diabetes or prediabetes. Because CHCs may cause adverse lipid changes, alternative contraception should be considered for women with uncontrolled dyslipidemia. (7) Chloasma (also called melasma), a disorder of hyperpigmentation, may occur with the use of segesterone/ethinyl estradiol. Women who tend to experience this response should avoid excessive exposure to sunlight or UV radiation. (8) Women who become pregnant should discontinue use of the product. (9) Concurrent use of a CYP3A4 inducer such as carbamazepine, rifampin, or St. John's wort may reduce exposure to contraceptive hormones. Advise women to use an alternative or back-up contraception method during concurrent use and for 28 days after discontinuation of the enzyme inducer. (10) CHCs may increase the glucuronidation of lamotrigine, resulting in decreased seizure control with the latter agent and a need for dosage adjustment. (11) Oil-based (including silicone-based) vaginal lubricants and oil-based vaginal suppositories may increase the exposure of contraceptive hormones and should not be used.

Adverse reactions: headache/migraine, nausea/vomiting, vulvovaginal mycotic infection/candidiasis, abdominal pain, dysmenorrhea, vaginal discharge, urinary tract infection, breast tenderness/pain/discomfort, bleeding irregularities including metrorrhagia, diarrhea, genital pruritus

Supplied as: a ring-shaped, nonbiodegradable, flexible, silicone elastomer vaginal system that contains 103 mg of segesterone acetate and 17.4 mg of ethinyl estradiol

Dosage: When the ring is placed in the vagina, it releases an approximate average of 0.15 mg/day and 0.013 mg/day of the two hormones, respectively, over 21 days of each cycle for up to thirteen 28-day cycles (1 year). Each cycle of use is 28 days with 21 days in and 7 days out.

Nursing considerations: (1) Teach the patient how to use the product, including how to insert and remove the ring, and review with her the detailed patient instructions provided with the product. She should remove the ring for a 1-week dose-free interval; during this time withdrawal bleeding usually occurs. She should clean the removed vaginal system with mild soap and warm water, pat it dry with a clean cloth towel or paper towel, and place it in its case during the 1-week dose-free interval. At the end of the dose-free interval, she should again clean the ring before replacing it in the vagina for another 21 continuous days (3 complete weeks). (2) Tell the patient that scheduled ring removals and insertions should be on the same day of the week for each monthly cycle and at about the same time of day. Consult the prescribing information for recommendations based on the patient's prior use of hormonal contraceptives and considerations for women with irregular menstrual cycles. (3) Following childbirth, segesterone/ethinyl estradiol should not be started sooner than 4 weeks postpartum and only in women who choose not to breastfeed. If the woman has not yet had a menstrual period, initiation of the product should be accompanied by an additional method of contraception during coitus for the first 7 days. (4) Inform the patient that the ring can be accidentally expelled while removing a tampon, during coitus, or when straining during a bowel movement. If it is expelled once during the 21 days of intravaginal use and is replaced within 2 hours, contraceptive efficacy should not be reduced. If it is out of the vagina for more than 2 continuous hours or more than 2 cumulative hours (multiple removals or expulsions adding up to 2 hours), advise her to use back-up contraception until the ring has been in the vagina for 7 consecutive days. (5) Following completion of 13 cycles of use, the patient should place the product in the case provided and discard it via a drug take-back option if available, or in a waste receptacle out of the reach of children or pets. Warn her not to flush it down the toilet.

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DRUG FOR CYSTIC FIBROSIS

Elexacaftor/tezacaftor/ivacaftor

Combination treatment is an important advance for 90% of patients with CF.

In the US, cystic fibrosis (CF) affects approximately 30,000 people. Although most are diagnosed before age 2, more than half of people living with CF are over age 18.[1,2] It is caused by

a defective or missing cystic fibrosis transmembrane conductance regulator (CFTR) protein resulting from mutations in the CFTR gene. Children must inherit two defective CFTR genes, one from each parent, to have CF.

CFTR protein regulates chloride and water transport in the body, including the lungs, sweat glands, gastrointestinal (GI) tract, and pancreas. Defective functioning of this protein results in the formation of thick mucus in the lungs, GI tract, and other affected areas, causing malnutrition, poor growth, frequent respiratory infections, and eventually permanent lung damage. Lung disease is the most common cause of death in patients with CF.[2]

The F508del mutation is the most common cause of CF. Patients who have two copies of this mutation account for approximately one-half of cases in the US. Elexacaftor/tezacaftor/ivacaftor (*Trikafta*, Vertex) is a combination formulation indicated to treat CF in patients age 12 years and older who have at least one F508del mutation in the CFTR gene.[3] If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation. Elexacaftor facilitates the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface. Elexacaftor and tezacaftor, which bind to different sites on the CFTR protein, have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR. This increases the amount of CFTR protein delivered to the cell surface compared with either drug alone. Ivacaftor potentiates the channel-open probability (gating) of the CFTR protein at the cell surface. The new combination can be used to treat approximately 90% of patients with CF and represents an important advance in therapy.

Precautions: (1) Liver function tests should be assessed before treatment starts, every 3 months during the first year of treatment, and annually thereafter. In patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring may be indicated. (2) Noncongenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up ophthalmologic examinations are recommended in pediatric patients. (3) Concurrent use with a strong CYP3A inducer such as carbamazepine, rifampin, or St. John's wort is not recommended because the medication's activity is likely to be significantly reduced. (4) The concurrent use of a strong CYP3A inhibitor such as clarithromycin, telithromycin, itraconazole, or ketoconazole, or a moderate CYP3A inhibitor such as fluconazole or erythromycin increases the exposure of elexacaftor, tezacaftor, and ivacaftor. Accordingly, the dosage of the new combination product should be reduced. (5) The exposure of all three drugs in the combination is also increased by certain components of grapefruit that moderately inhibit CYP3A. The product labeling recommends that patients avoid food or drink containing grapefruit during treatment. (6) Patients with severe hepatic impairment should not be treated with the new product, and the dosage should be reduced in patients with moderate hepatic impairment. (7) Caution is recommended in patients with severe renal impairment or end-stage renal disease.

Adverse reactions: headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increased alanine aminotransferase, nasal congestion, increased serum creatine kinase, increased aspartate aminotransferase, rhinorrhea, rhinitis, influenza, sinusitis, increased blood bilirubin

Supplied as: tablets containing 100 mg of elexacaftor, 50 mg of tezacaftor, and 75 mg of ivacaftor, copackaged with tablets containing 150 mg of ivacaftor

Dosage: two combination tablets in the morning and one tablet containing 150 mg of ivacaftor in the evening, approximately 12 hours apart. Consult the prescribing information for recommended dosage adjustments for certain patient populations.

Nursing considerations: (1) Teach patients to swallow the tablets whole and to take each dose with food containing fat such as eggs, cheeses, nuts, whole milk, or meat. (2) Review the patient information sheet with the patient and reinforce what to do if a dose is missed. If more than 6 hours have passed since a missed morning dose, the patient should take the missed dose as soon as possible and *not* take the evening dose. If more than 6 hours have passed since a missed evening dose, the patient should *not* take the missed dose. Make sure the patient understands that morning and evening doses should not be taken at the same time. (3) The medication can be stored at room temperature.

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ANTIBACTERIAL DRUG

Imipenem monohydrate/ cilastatin sodium/ relebactam monohydrate

Indicated for certain complicated drug-resistant bacterial infections.

Beta-lactam antibacterial agents (penicillins, cephalosporins, and carbapenems) are highly effective for

treating many bacterial infections. However, an increasing number of bacteria (penicillinases, cephalosporinases, carbapenemases) can produce beta-lactamase enzymes that break the beta-lactam ring and inactivate the antibacterial agent. To address this common mechanism of resistance, pharmaceutical companies have developed beta-lactamase inhibitors that protect and extend the activity of the beta-lactam antibacterial agents with which they are used in combination.

The carbapenems have a broad spectrum of antibacterial activity and imipenem was the first of this class of agents to be approved. Because it is extensively metabolized by renal dehydropeptidase, it is supplied and used in combination with the renal dehydropeptidase inhibitor cilastatin. Three other carbapenems (meropenem, ertapenem, and doripenem) have been subsequently approved.

Some bacteria, such as *Klebsiella pneumoniae,* have become resistant to the carbapenem antibacterial agents by developing carbapenemase enzymes that inactivate them. In 2017, the first combination of a carbapenem (meropenem) with a beta-lactamase inhibitor (vaborbactam) was approved.

In 2019, the FDA approved imipenem monohydrate/cilastatin sodium/relebactam monohydrate (*Recarbrio*, Merck).[1] This medication is a combination of imipenem and cilastatin with the new beta-lactamase inhibitor relebactam. Relebactam has no intrinsic antibacterial activity but it protects imipenem from degradation by certain serine beta-lactamases such as *K. pneumoniae* carbapenemase.

Administered I.V., the new product is indicated for adults with limited or no alternative treatment options to treat complicated urinary tract infections, including pyelonephritis, caused by susceptible Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*. It is also indicated for adults with limited or no treatment options to treat complicated intra-abdominal infections caused by numerous susceptible aerobic and anaerobic Gram-negative bacteria.

To preserve the effectiveness of imipenem/cilastatin/relebactam by reducing or delaying the development of resistance that is likely to result from extensive use, the labeled indications include the provision that the new combination be reserved for patients with limited or no alternative treatment options.

Precautions: (1) Contraindicated in patients with a history of known severe hypersensitivity to any of the medication's components. Before treatment, patients should be assessed for any previous hypersensitivity reaction to carbapenems, penicillins, cephalosporins, other beta-lactams, or other allergens. (2) Almost all systemic antibacterial agents, including imipenem, have been reported to cause *Clostridioides difficile*-associated diarrhea. This possibility should be considered in all patients who experience diarrhea during and after use of an antibacterial agent, including for a period of time after treatment ends. (3) Use particular caution in patients with a history of seizures and/or compromised renal function. Imipenem/cilastatin has been infrequently associated with seizures and other central nervous system effects, such as confusion, disorientation, and delirium. The use of carbapenems has been reported to reduce the concentration of the antiepileptic drugs (AEDs) valproic acid and divalproex sodium, increasing the risk of breakthrough seizures. Avoid concurrent use of imipenem/cilastatin/relebactam with these AEDs; alternative antibacterial agents should be considered in patients whose seizures are well controlled with these AEDs. Also avoid concomitant use with ganciclovir unless the anticipated benefit outweighs the risk because of an increased risk of seizures. (4) The dosage of imipenem/cilastatin/relebactam should be reduced in patients with impaired renal function.

Adverse reactions: diarrhea, nausea, headache, vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, phlebitis/infusion site reactions, pyrexia, hypertension

Supplied as: a sterile powder for constitution in single-dose vials containing imipenem monohydrate in an amount equivalent to 500 mg of imipenem, cilastatin sodium in an amount equivalent to 500 mg of cilastatin, and relebactam monohydrate in an amount equivalent to 250 mg of relebactam. The sterile powder should be constituted and further diluted using 0.9% Sodium Chloride Injection or another appropriate diluent as directed in the prescribing information.

Dosage: 1.25 grams (imipenem 500 mg, cilastatin 500 mg, relebactam 250 mg) by I.V. infusion over 30 minutes every 6 hours in patients age 18 and older with creatinine clearance of 90 mL/min or greater. Consult the prescribing information for dosage adjustments in patients with renal impairment.

Nursing considerations: (1) Complete the I.V. infusion of the diluted solution within 2 hours if stored at room temperature or within 24 hours if stored in a refrigerator. (2) Assess patients for any previous hypersensitivity reactions to antibiotics and educate them about potentially serious adverse reactions that may develop after treatment, including anaphylaxis, seizures, and *C. difficile* diarrhea.

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ANTIMYCOBACTERIAL DRUG

Pretomanid

Bactericidal activity against actively replicating *M. tuberculosis*.

Tuberculosis (TB) is the leading cause of infectious disease-related deaths in the world. In the US, 8,920 cases were provisionally reported to the CDC in 2019.[1]

The infection is caused by *Mycobacterium tuberculosis*, a slow-growing acid-fast bacillus. Empiric treatment of drug-susceptible TB often consists of rifampin, isoniazid, pyrazinamide, and ethambutol for 2 months, followed by rifampin and isoniazid for 4 to 7 months. However, emergence of resistance to first-line agents has led to multidrug-resistant (MDR)-TB. Emergence of resistance to first-line agents, a fluoroquinolone, and an injectable second-line agent has led to extensively drug-resistant (XDR)-TB. These developments are posing a public health crisis.

Pretomanid (*TB Alliance*, Mylan) is a nitroimidazooxazine antimycobacterial agent that exhibits bactericidal activity against actively replicating *M. tuberculosis* by inhibiting mycolic acid synthesis and thereby blocking cell wall production. It is indicated to treat adults with pulmonary XDR-TB, treatment-intolerant MDR-TB, or nonresponsive MDR-TB, as part of a combination regimen with bedaquiline and linezolid. It is not indicated for patients with drug-sensitive TB, latent TB, extra-pulmonary TB, or MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy.[2]

The labeling for pretomanid includes warnings regarding hepatic adverse reactions, myelosuppression, peripheral and optic neuropathy, QT prolongation, reproductive effects, and lactic acidosis.

Pretomanid must be used in combination with bedaquiline and linezolid. The entire regimen should be administered with food by directly observed therapy.

Precautions: (1) Patients should undergo liver function tests and be monitored for signs and symptoms of hepatic injury. Treatment with the entire regimen should be interrupted if evidence of liver injury occurs. (2) Complete blood cell counts should be monitored. If significant myelosuppression develops or worsens, the dosage of linezolid should be reduced or treatment with linezolid interrupted. (3) Patients should also be monitored for peripheral and optic neuropathy. The dosage of linezolid should be reduced or treatment interrupted if neuropathy develops or worsens, and an ophthalmologic evaluation should be obtained if the patient develops vision impairment. (4) Patients should have ECGs and be monitored for QT prolongation. The concurrent use of other drugs that prolong the QT interval (such as moxifloxacin) may cause additive QT prolongation. If a significant ventricular dysrhythmia occurs or if corrected QT by Fridericia/Framingham (QTcF) interval prolongation greater than 500 ms develops, treatment with the entire antitubercular regimen should be discontinued. (5) Lactic acidosis has been reported with the pretomanid regimen. If significant lactic acidosis develops, interruption of linezolid or the entire combination regimen should be considered. (6) Avoid the use of pretomanid with strong or moderate CYP3A4 inducers such as rifampin or efavirenz. (7) When organic anion transporter-3 (OAT3) substrate drugs such as methotrexate are used concomitantly with pretomanid, OAT3 substrate drug-related adverse events should be monitored and a reduction in dosage of these drugs should be considered.

Adverse reactions: peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, anorexia, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal weight loss, diarrhea

Supplied as: 200 mg tablets

Dosage: *For pretomanid:* 200 mg once a day for 26 weeks. *For bedaquiline*: 400 mg once daily for 2 weeks, followed by 200 mg 3 times a week, with at least 48 hours between doses, for 24 weeks (for a total of 26 weeks). *For linezolid*: 1,200 mg once a day for 26 weeks. The dosage of linezolid can be reduced to 600 mg daily or 300 mg daily, or treatment with this drug can be interrupted if necessary to manage adverse reactions.

Nursing considerations: (1) Teach patients the importance of adhering to the full course of treatment exactly as prescribed. Tablets should be swallowed whole with water and the entire regimen taken with food. (2) If the regimen is interrupted for safety reasons, missed doses can be made up at the end of treatment; however, doses of linezolid missed due to linezolid adverse reactions should not be made up. The duration of the entire regimen can be extended beyond 26 weeks if necessary. (3) If linezolid is permanently discontinued during the initial 4 consecutive weeks of treatment, pretomanid and bedaquiline should also be discontinued. However, if linezolid is discontinued after the initial 4 weeks of consecutive treatment, pretomanid and bedaquiline should be continued. If either pretomanid or bedaquiline is discontinued, the entire regimen should also be discontinued. (4) Tell the patient to avoid alcohol during therapy.

REFERENCES

1. Centers for Disease Control and Prevention. Tuberculosis. Data and statistics. www.cdc.gov/tb/statistics/default.htm.

2. Pretomanid tablets, for oral use. Prescribing information. www.tballiance.org/sites/default/files/assets/Pretomanid_Full-Prescribing-Information.pdf.

DRUG FOR MACULAR DEGENERATION

Brolucizumab-dbll

Administered by intravitreal injection to treat wet AMD.

The macula is the area of the retina that is responsible for the sharp, central vision necessary for activities such as reading, driving, and recognizing faces. Age-related macular degeneration (AMD) is a chronic progressive disease of the macula that is a common cause of blindness in older adults.

The two general types of AMD are neovascular (wet) and nonneovascular (dry). In wet AMD, abnormal blood vessels form underneath the macula and leak blood and fluid into the retina, disrupting the normal retinal structure. Subsequent damage to the macula impairs central vision. Wet AMD accounts for only 10% of all AMD cases but is more severe and rapidly progressive than the dry type.

The growth of abnormal blood vessels is thought to primarily result from the overexpression of vascular endothelial growth factor (VEGF). VEGF-A has three major isoforms that interact with receptors VEGFR-1 and VEGFR-2 that are present on the surface of endothelial cells. Activation of these receptors may result in endothelial cell proliferation, neovascularization, and vascular permeability. Several VEGF inhibitors have been approved to treat wet AMD and all are administered via intravitreal injection.

Brolucizumab-dbll (*Beovu*, Novartis) is a humanized monoclonal single-chain antibody fragment that binds with the three major isoforms of VEGF-A and suppresses neovascularization and vascular permeability.[1] Like the previously approved drugs, it is administered by intravitreal injection and is indicated for wet AMD. The risks and adverse reactions of VEGF inhibitors are similar and are often associated with the intravitreal injection procedure rather than the drugs themselves. The other VEGF inhibitors have been approved for certain other retinal disorders as well, but wet AMD is currently the only approved indication for brolucizumab.

Precautions: (1) Contraindicated in patients with ocular or periocular infections, and/or active intraocular inflammation. (2) Intravitreal injection of VEGF inhibitors carries a potential risk for arterial thromboembolic events such as nonfatal stroke. (3) Increases in intraocular pressure, endophthalmitis, and retinal detachment may also occur. Patients should be advised to immediately report any signs or symptoms of these possible complications.

Adverse reactions: blurred vision, cataract, conjunctival hemorrhage, eye pain, vitreous floaters

Supplied as: single-use vials designed to deliver 0.05 mL of solution containing 6 mg of the drug

Dosage: 6 mg (0.05 mL) administered by intravitreal injection monthly (approximately every 25 to 31 days) for the first 3 doses, followed by 6 mg every 8 to 12 weeks.

Nursing considerations: (1) Store vials in a refrigerator. (2) Adequate anesthesia and a topical broad-spectrum microbicide should be administered before the injection to disinfect the periocular skin, eyelid, and ocular surface. (3) Tell patients they may experience temporary visual disturbances after an intravitreal injection and the associated eye examination. Warn them not to drive or use machinery until visual function has recovered sufficiently. (4) Tell patients to seek immediate care from an eye care provider if the eye becomes red, sensitive to light, or painful, or if they experience any vision changes in the days following the injection due to the risk of developing endophthalmitis, retinal detachment, retinal vasculitis, and/or retinal vascular occlusion.

REFERENCE

1. Beovu (brolucizumab-dbll) injection, for intravitreal use. Prescribing information. www.novartis.us/sites/www.novartis.us/files/beovu.pdf.

DRUG FOR ACNE

Trifarotene

Fourth topical retinoid approved to treat acne.

Joining tretinoin, tazarotene, and adapalene, trifarotene (*Aklief*, Galderma) is the fourth topical retinoid to be approved to treat acne. It is specifically indicated to treat acne vulgaris in patients age 9 and older.[1]

The retinoids act as agonists at retinoic acid receptors (RAR). Stimulation of these receptors is associated with cell differentiation and mediation of inflammation. Topical retinoids are sometimes used in conjunction with a topical antibiotic or benzoyl peroxide, and combination formulations of adapalene/benzoyl peroxide and tretinoin/clindamycin are available.

Trifarotene cream was evaluated in two vehicle-controlled studies in patients with moderate facial and truncal acne, with moderate acne defined as a score of 3 on a 5-point assessment scale. In the two studies, 29% and 42% of the patients treated with trifarotene experienced success on the Investigator's Global Assessment scale compared with 20% and 26%, respectively, in those treated with the vehicle cream. The new drug was also more effective in reducing the number of facial inflammatory and noninflammatory lesions and more effective for improving truncal lesions.

Trifarotene exhibits selective activity at the gamma subtype of RAR, but it is not known whether this greater selectivity is of clinical importance, and it has not been directly compared

with other topical retinoids in clinical studies.

Precaution: Use of any topical retinoid during pregnancy should be approached with caution because systemic exposure to retinoids has been associated with teratogenic effects.

Adverse reactions: application site irritation, application site pruritus, sunburn.

Supplied as: topical cream containing 0.005% trifarotene in a pump container

Dosage: apply a thin layer of cream to the affected areas of the face and/or trunk once a day, in the evening, on clean and dry skin

Nursing considerations: (1) Teach patients how and when to apply the medication. One pump actuation usually provides enough cream to cover the face, and two actuations of the pump should provide enough cream to cover the upper trunk. If acne is present in the middle or lower back, an additional pump actuation may be needed. (2) Reinforce that the medication is for topical use only and should not come in contact with the eyes, lips, paranasal creases, and mucous membranes. (3) Advise patients to use a moisturizer from the beginning of treatment to prevent or minimize irritation. In the clinical studies, patients applied moisturizer approximately 1 hour before or after treatment. (4) Tell patients not to apply trifarotene to skin that is compromised with cuts, abrasions, eczema, or sunburn. (5) Warn patients that trifarotene increases the risk of sunburn and tell them to minimize unprotected exposure to UV rays, including sunlight, sunlamps, and tanning beds. Recommend using a sunscreen with an SPF of 15 or more and wearing protective clothing over treated areas when high levels of sun exposure cannot be avoided. ■

REFERENCE

1. Aklief (trifarotene) cream, for topical use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2019/211527s000lbl.pdf.

DOI-10.1097/01.NURSE.0000697144.04917.4a