New Drugs 2016

PART 2

By Daniel A. Hussar, PhD
Remington Professor of Pharmacy
Philadelphia College of Pharmacy
University of the Sciences
Philadelphia, Pa.

CE

3.0
ANCC
CONTACT HOURS

Rx

3.0
PHARMACOLOGY
CREDITS

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

> the first medication approved for female sexual dysfunction.

> a specific reversal agent for dabigatran that neutralizes its anticoagulant activity.

> two human monoclonal antibodies that are the first drugs in a new class of lipid-lowering agents.

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 package insert, 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.; 2016.

Nursing2015 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2016.

Physician's Desk Reference. 69th ed. Montvale, NJ: Medical Economics; 2016.

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

ANTIPSYCHOTIC DRUG

Brexpiprazole

Treatment option for schizophrenia and major depressive disorder.

Classified as an atypical antipsychotic agent, brexpiprazole (*Rexulti*, Otsuka) has properties and uses that are most similar to those of aripiprazole. It's indicated for treatment of adults with schizophrenia and for adjunctive treatment in adults with major depressive disorder (MDD). Its mechanism of action isn't well understood, but it may involve a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_2 receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

The effectiveness of brexpiprazole for treating schizophrenia was demonstrated in two 6-week, placebo-controlled studies in which the new drug was demonstrated to be superior to placebo in reducing the occurrence of schizophrenia symptoms. It was also evaluated in two 6-week, placebo-controlled studies as an add-on treatment in patients with MDD who hadn't responded adequately to an antidepressant alone. Patients treated with brexpiprazole plus an antidepressant reported fewer symptoms of depression than those receiving placebo plus an antidepressant. Brexpiprazole hasn't been directly compared with other antipsychotic agents in clinical studies.

No well-controlled studies of brexpiprazole have been conducted in pregnant women, but neonates whose mothers have been exposed to similar antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. A pregnancy exposure registry (1-866-961-2388) has been created to monitor pregnancy outcomes in women exposed to brexpiprazole during pregnancy.

Precautions: (1) As with other antipsychotic agents, the labeling for brexpiprazole includes a boxed warning that older adults with dementia-related psychosis are at increased risk for death if treated with an antipsychotic agent (dementia-related psychosis isn't an approved indication for any antipsychotic drug). Use of an antipsychotic agent in these patients also increases the risk of cerebrovascular adverse events such as stroke and transient ischemic attack. (2) The labeling includes a boxed warning regarding an increased risk of suicidal thoughts and behaviors in children, adolescents, and young adults through the age of 24, a warning that also applies to other antidepressants. The safety and effectiveness of brexpiprazole in pediatric patients hasn't been established and it's not approved for use in these patients. (3) Other serious risks associated with the use of atypical antipsychotics include neuroleptic malignant syndrome, tardive dyskinesia, seizures, orthostatic hypotension and syncope, body temperature dysregulation, dysphagia, metabolic changes (such as hyperglycemia/diabetes, dyslipidemia, and weight gain), leukopenia, neutropenia, agranulocytosis, and cognitive and motor impairment (including sedation and hypersomnia). Closely monitor patients who are at greater risk or who have experienced symptoms that are characteristic of these events. Discontinue treatment as indicated by the type and/or extent of the adverse event; for example, development of neuroleptic malignant syndrome or severe neutropenia (absolute neutrophil count less than 1,000/mm^3). (4) The maximum recommended dosage should be reduced in patients with moderate, severe, or end-stage renal impairment, and in patients with moderate or severe hepatic impairment. (5) The concentration and action of brexpiprazole is increased by the concurrent use of a strong CYP3A4 inhibitor (such as clarithromycin and itraconazole), a moderate CYP3A4 inhibitor (such as fluconazole), a strong CYP2D6 inhibitor (such as fluoxetine, paroxetine, and quinidine), or a moderate CYP2D6 inhibitor (such as duloxetine). Conversely, brexpiprazole's action may be reduced by the concurrent use of a strong CYP3A4 inducer (such as rifampin and St. John's wort). See the full prescribing information for dosage adjustment guidelines for patients concurrently taking drugs affecting brexpiprazole metabolism. (6) Reduce dosages as prescribed for patients known to be CYP2D6 poor metabolizers. Approximately 8% of White patients and 3% to 8% of Black patients may experience higher concentrations of brexpiprazole because of a reduced capacity to metabolize CYP2D6 substrates. See the full prescribing information for guidelines.

Adverse reactions: *In patients treated for schizophrenia:* weight gain. *In patients treated for MDD:* akathisia, weight gain

Supplied as: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg tablets

Dosage: *To treat schizophrenia:* the recommended starting dosage is 1 mg once a day titrated to the recommended target dosage of 2 mg to 4 mg once a day. The maximum recommended daily dose is 4 mg. *As adjunctive treatment for MDD:* the recommended starting dosage is 0.5 mg or 1 mg once a day, titrated to the recommended target dosage of 2 mg once a day. The maximum recommended daily dose is 3 mg. See the full prescribing information for titration guidelines and dosage adjustments for patients with renal or hepatic impairment.

Nursing considerations: (1) Tell patients that brexpiprazole can be taken without regard to food. (2) Because brexpiprazole may impair judgment, thinking, and motor skills,

caution patients to avoid driving and other hazardous activities requiring alertness until they determine whether the drug impairs their ability to safely engage in such activities. (3) Teach patients to take the medication exactly as prescribed and not to skip doses. Patients should take a missed dose as soon as they remember, unless it's nearly time for the next dose. In that case, they should skip the missed dose and take the next dose at the regular time. Warn them not to take two doses at the same time. (4) Educate patients about possible adverse reactions and make sure they know which ones require immediate medical attention.

REFERENCE

Rexulti (brexpiprazole) tablets, for oral use. Prescribing information. http://otsuka-us.com/products/Documents/Rexulti.PI.pdf.

DRUG FOR FEMALE SEXUAL DYSFUNCTION

Flibanserin

First drug approved for hypoactive sexual desire disorder

An estimated 10% of premenopausal women experience hypoactive sexual desire disorder (HSDD), which is designated as "acquired" when it develops in a woman who previously had no problems with sexual desire. HSDD is considered "generalized" when it occurs regardless of the type of sexual activity, the situation, or the sexual partner.

Flibanserin (*Addyi*, Sprout; Valeant), the first drug to be approved to treat HSDD, acts as an agonist at serotonin 5-HT_{1A} receptors and as an antagonist at serotonin 5-HT_{2A} receptors; however, its specific mechanism of action in treating HSDD isn't known. Flibanserin is indicated to treat premenopausal women with acquired, generalized HSDD characterized by low sexual desire that causes marked distress or interpersonal difficulty. It's not indicated to treat sexual dysfunction due to a coexisting medical or psychiatric condition, problems within the relationship, or the effects of a medication or other substance. The new drug hasn't been evaluated or approved to treat HSDD in postmenopausal women or in men, and it's not indicated to enhance sexual performance.

The effectiveness of flibanserin was demonstrated in three 24-week placebo-controlled studies that included approximately 2,400 premenopausal women with acquired, generalized HSDD. Compared with placebo, flibanserin increased the number of satisfying sexual events, increased sexual desire, and decreased the occurrence of distress. Additional analyses investigated whether the improvements with the drug were meaningful to patients (that is, they felt much improved or very much improved). Approximately 10% more flibanserin-treated patients than placebo-treated patients reported meaningful improvements.

Dizziness, somnolence, and fatigue were the most commonly reported adverse reactions. Women who were using hormonal contraceptives experienced a higher incidence of dizziness, somnolence, and fatigue than women not using hormonal contraceptives. The discontinuation rate due to adverse reactions was 13% among patients treated with flibanserin compared with 6% among those receiving placebo.

The risk of hypotension and syncope is the most serious concern in patients taking flibanserin. In patients taking no other medications known to cause hypotension or syncope, hypotension and syncope were reported in 0.2% and 0.4%, respectively, of patients treated with flibanserin, and in <0.1% and 0.2%, respectively, in those receiving placebo. However, numerous factors increase the risk of hypotension and syncope; for example, taking more than the recommended dose or administering it during waking hours. The daily dose should be administered at bedtime.

The risk of hypotension and syncope is also increased by the consumption of alcoholic beverages, the concurrent use of moderate or strong CYP3A4 inhibitors, and hepatic impairment. These risks are the subject of a boxed warning in the labeling and represent contraindications to use of the drug. Before flibanserin is prescribed, patients must be assessed for the likelihood of their abstaining from alcohol, taking into account their current and past drinking behavior.

Approximately 0.2% of the patients treated with flibanserin experienced appendicitis, which wasn't reported in any patients receiving placebo. However, a cause-and-effect relationship hasn't been established.

This drug is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy, in which prescribers and pharmacies must be certified. If a patient doesn't experience improvement after 8 weeks of treatment, the medication should be discontinued.

Precautions: (1) Contraindicated in patients with any degree of hepatic impairment. (2) Contraindicated for concurrent use with a moderate or strong CYP3A4 inhibitor such as clarithromycin, itraconazole, diltiazem, fluconazole, or grapefruit juice. If treatment with one of these CYP3A4 inhibitors is required, flibanserin should be discontinued at least 2 days before treatment starts with the CYP3A4 inhibitor. If the use of flibanserin is to be initiated in a patient being treated with a moderate or strong CYP3A4 inhibitor, the latter agent should be discontinued for 2 weeks before starting the new drug. The activity of flibanserin may also be increased by the concurrent use of multiple weak CYP3A4 inhibitors such as oral contraceptives, cimetidine, ginkgo, and resveratrol. (3) The concomitant use of a CYP3A4 inducer (such as carbamazepine, rifampin, and St. John's wort) significantly reduces flibanserin exposure, and concurrent use should be avoided. (4) Flibanserin may increase the action of digoxin and other P-glycoprotein (P-gp) substrates. Concentrations of drugs that are transported by P-gp that have a narrow therapeutic index should be

closely monitored. Consult the product insert for a full listing of potential drug interactions. (5) Because flibanserin may depress the central nervous system (CNS), patients must avoid concurrent use of other CNS depressants, including alcoholic beverages, to prevent excessive CNS depression. Patients should avoid activities requiring full alertness for at least 6 hours after taking flibanserin, until they know how the drug affects them. (6) Flibanserin hasn't been studied in pregnant women. Whether the drug is excreted in human milk isn't known, but breastfeeding isn't recommended during treatment.

Adverse reactions: dizziness, somnolence, nausea, fatigue, insomnia

Supplied as: 100 mg tablets

Dosage: 100 mg once a day at bedtime.

Nursing considerations: (1) If patients miss a dose, tell them to take the next scheduled dose at bedtime on the next day. (2) Warn patients about the risk of somnolence and teach them not to take more flibanserin than prescribed, to take it at bedtime, and to avoid alcoholic beverages. Tell them to avoid driving and other activities requiring alertness for at least 6 hours after taking a dose. (3) Tell patients not to consume grapefruit products while taking flibanserin.

REFERENCE

Addyi (flibanserin). Prescribing information. www.addyi.com.

REVERSAL AGENT

Idarucizumab

Neutralizing dabigatran's anticoagulant effect

Several orally administered anticoagulants that may be considered as alternatives to warfarin have been approved and marketed in the last 6 years: the direct thrombin inhibitor dabigatran and the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban. However, unlike warfarin for which vitamin K is an antidote, antidotes (reversal agents) for the newer oral anticoagulants haven't been available.

Idarucizumab (*Praxbind*, Boehringer Ingelheim) is a humanized monoclonal antibody fragment that binds to dabigatran and its acylglucuronide metabolites with a higher affinity than the binding affinity of dabigatran to thrombin. The new drug is a specific reversal agent for dabigatran and neutralizes its anticoagulant activity. However, it doesn't reverse the action of the factor Xa inhibitor anticoagulants.

Administered I.V., idarucizumab is indicated when reversal of dabigatran's anticoagulant effects is needed for emergency surgery/urgent procedures or to treat life-threatening or uncontrolled bleeding. Its approval was based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers, and its effectiveness in a study of 123 patients who received idarucizumab due to uncontrolled bleeding or because they required emergency surgery. In the latter study, dabigatran's anticoagulant activity was fully reversed in 89% of patients within 4 hours of receiving idarucizumab.

Hypersensitivity reactions (such as rash, pruritus, pyrexia, and bronchospasm) have been experienced by some patients treated with idarucizumab. If anaphylaxis or another serious hypersensitivity reaction occurs, idarucizumab should be immediately discontinued and appropriate treatment instituted.

A few patients in the clinical study experienced elevated coagulation parameters (such as activated partial thromboplastin time) 12 to 24 hours after administration of idarucizumab. If clinically relevant rebleeding occurs, administration of a second dose of the reversal agent may be considered. However, the effectiveness and safety of repeat treatment hasn't been evaluated.

Reversing dabigatran's action exposes patients to the thrombotic risk of the underlying disease for which the anticoagulant was prescribed. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate. Dabigatran treatment can be initiated 24 hours after administration of idarucizumab.

Precaution: Some individuals with hereditary fructose intolerance experience serious adverse reactions following the parenteral administration of sorbitol; for example, hypoglycemia, hypophosphatemia, metabolic acidosis, increased uric acid, and acute liver failure. The recommended dose of idarucizumab contains 4 g of sorbitol in the formulation as an excipient. If idarucizumab is being considered for a patient with hereditary fructose intolerance, the combined daily metabolic load of sorbitol/fructose from all sources should be evaluated.

Adverse reactions: hypokalemia, delirium, constipation, pyrexia, pneumonia, headache

Supplied as: a sterile solution in single-use vials containing 2.5 g of the drug in 50 mL

Dosage: 5 g (two vials) administered I.V. as two consecutive infusions, or as bolus injections by injecting the contents of both vials consecutively, one after another via syringe.

Nursing considerations: (1) Store the vials in a refrigerator. (2) Once the solution has been removed from the vial, administration should begin promptly or within 1 hour. (3) A preexisting I.V. line may be used for administration, but first flush it with 0.9% Sodium Chloride Injection. Don't mix idarucizumab with other medications. (4) Teach patients about the risk of hypersensitivity reactions, bleeding, and thrombosis, and tell them to call 911 if they experience serious signs and symptoms.

REFERENCE

Praxbind (idarucizumab) injection, for intravenous use. Prescribing information. www.praxbind.com.

Familial hypercholesterolemia is an inherited disorder that's associated with high concentrations of low-density lipoprotein cholesterol (LDL-C). High concentrations of LDL-C are linked to heart disease, the number one cause of death in the United States from which more than 600,000 Americans die every year.[1] Statins such as atorvastatin have been highly effective and widely prescribed as the standard of therapy for reducing elevated LDL-C concentrations and the related risks of cardiovascular disease (CVD). However, some patients who are treated with a maximally tolerated dose of a statin still require additional lowering of LDL-C.

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a protein that binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation in the liver. Because LDLR is the primary receptor that clears circulating LDL, a decrease in LDLR by PCSK9 results in higher blood concentrations of LDL-C.

In mid-2015, the FDA approved two human monoclonal antibodies that target PCSK9 and inhibit its activity: alirocumab and evolocumab. These are the first drugs to be approved in this new class of lipid-lowering agents. By inhibiting the binding of PCSK9 to LDLR, the new drugs increase the amount of LDLR available to clear LDL, thereby lowering LDL-C concentrations.

Both alirocumab and evolocumab are administered subcutaneously and are indicated as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (HeFH) and for adults with clinical atherosclerotic CVD who require additional lowering of LDL-C. Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (such as statins, ezetimibe, and LDL apheresis) for patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. In clinical trials, the addition of either of the new drugs to the regimen resulted in a substantial further reduction in LDL-C concentrations compared with placebo. In addition, treatment regimens that include the new drugs are more effective than other regimens in reducing LDL-C concentrations. Thus, the new drugs represent important additions to the options available for reducing LDL-C concentrations.

Although the statins have been shown to reduce the risk of myocardial infarction or stroke, the effects of alirocumab and evolocumab on cardiovascular morbidity and mortality haven't been established.

REFERENCE

1. Centers for Disease Control and Prevention. Heart disease facts. www.cdc.gov/heartdisease/facts.htm.

Alirocumab

Significant reduction in LDL-C concentrations

The effectiveness of alirocumab (*Praluent*, Regeneron; Sanofi) was demonstrated in five placebo-controlled studies in patients who were already being treated with a maximally tolerated dosage of a statin, with or without other lipid-modifying therapy. The addition of alirocumab to the regimen resulted in a further lowering of LDL-C concentrations by approximately 50% compared with placebo.

Some patients have experienced hypersensitivity reactions with the use of alirocumab including serious events that required hospitalization. Hypersensitivity reactions resulted in discontinuation of treatment in 0.6% of patients, compared with 0.2% of patients receiving placebo.

As with other therapeutic proteins, a potential for immunogenicity exists with alirocumab and approximately 5% of patients developed antidrug antibodies (ADA). Patients who developed ADA had a higher incidence of injection site reactions compared with patients who didn't develop ADA. A total of 1.2% of patients who were treated with alirocumab developed neutralizing antibodies and 0.3% of patients both tested positive for neutralizing antibodies and exhibited loss of efficacy.

Adverse reactions: nasopharyngitis, injection site reactions, influenza, urinary tract infection, diarrhea

Precaution: Monitor patients for hypersensitivity reactions. Discontinue therapy if serious signs and symptoms develop, initiate treatment according to the standard of care, and monitor until signs and symptoms resolve.

Supplied as: single-dose, prefilled pens and syringes containing 75 mg and 150 mg of the drug

Dosage: initially, 75 mg injected subcutaneously once every 2 weeks. If indicated, dosage may be increased to the maximum of 150 mg once every 2 weeks.

Nursing considerations: (1) LDL-C concentrations should be determined within 4 to 8 weeks of initiating treatment or changing the dosage. (2) Tell patients who miss a dose to administer it within 7 days of the missed dose, then resume the regular dosage schedule. If the missed dose isn't administered within 7 days, patients should wait to administer the next dose on the original schedule. (3) Teach patients how to inject the medication in the thigh, abdomen, or upper arm, and how to rotate injection sites. (4) Tell patients to store the medication in the refrigerator, and to allow the medication to warm to room temperature for 30 to 40 minutes before administration. They should administer the medication as soon as possible after it warms up, and not use medication that's been at room temperature for 24 hours or more.

REFERENCE

Praluent (alirocumab) injection, for subcutaneous use. Prescribing information. http://products.sanofi.us/praluent/praluent.pdf.

Evolocumab

Approved for an additional indication

In addition to the indications for which alirocumab has been approved, evolocumab (*Repatha*, Amgen) is also indicated as an adjunct to diet and other LDL-lowering therapies for treatment of patients with HoFH who require additional lowering of LDL-C. The effectiveness of evolocumab has been demonstrated in multiple placebo-controlled studies in patients with clinical atherosclerotic CVD or HeFH who were already being treated with a maximally tolerated dosage of a statin. The addition of evolocumab to the regimen resulted in a further lowering of LDL-C concentrations by approximately 60% compared with placebo. In patients with HoFH, evolocumab reduced LDL-C by approximately 30% compared with placebo.

Approximately 5% of the patients treated with evolocumab experienced hypersensitivity reactions (rash, eczema, erythema, and/or urticaria) but these reactions didn't require discontinuation of treatment in most cases.

As with alirocumab and other therapeutic proteins, a potential for immunogenicity exists with evolocumab. However, only 0.1% of the patients tested positive for ADA and none of the patients tested positive for neutralizing antibodies.

The effectiveness and safety of evolocumab in pediatric patients with HeFH or clinical atherosclerotic CVD, and in patients with HoFH who are younger than 13 years, hasn't been established. The study in patients with HoFH included a small number of adolescents (ages 13 to 17) in whom effectiveness and safety were demonstrated.

Precaution: If signs or symptoms of serious allergic reactions occur, discontinue treatment with evolocumab, treat according to the standard of care, and monitor until signs and symptoms resolve.

Adverse reactions: nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, urinary tract infection, cough

Supplied as: single-use prefilled autoinjectors and syringes containing 140 mg of the drug.

Dosage: *To treat primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH*: 140 mg once every 2 weeks or 420 mg once monthly in the abdomen, thigh, or upper arm. *To treat HoFH*: 420 mg once monthly. To administer a 420 mg dose, give three injections of 140 mg consecutively within 30 minutes.

Nursing considerations: (1) In patients with HoFH, LDL-C concentrations should be measured 4 to 8 weeks after initiating treatment because responses to therapy will depend on the degree of LDL-receptor function. (2) If a dose is missed, patients should administer it as soon as possible if more than 7 days remain until the next scheduled dose, or omit the missed dose and administer the next dose according to the original schedule. (3) Tell patients they can store the medication in the refrigerator and let it warm to room temperature for at least 30 minutes before administration. Or, they can store it at room temperature in the original carton, but it must be used within 30 days. ■

REFERENCE

Repatha (evolocumab) injection, for subcutaneous use. Prescribing information. http://pi.amgen.com/united_states/repatha/repatha_pi_hcp_english.pdf.

ANTIVIRAL DRUG

Daclatasvir dihydrochloride

Inhibiting HCV replication

HCV genotype 3 causes less than 10% of chronic hepatitis C virus (HCV) infections in the United States, although the incidence in certain other countries such as India is considerably higher.[1]

Daclatasvir dihydrochloride (*Daklinza*, Bristol-Myers Squibb) is the third inhibitor of the HCV NS5A protein, which is required for viral replication, to be marketed in the United States, joining ledipasvir, which is included in the combination formulation Harvoni, and ombitasvir, which is included in the combination formulation Technivie and in a combination formulation included in the Viekira Pak regimen.

Daclatasvir is indicated for use with sofosbuvir to treat patients with chronic HCV genotype 1 or 3 infection, with or without ribavirin.[2] This is the first regimen that has proven effective for the treatment of chronic HCV genotype 3 infection without interferon or ribavirin.

The effectiveness of the daclatasvir and sofosbuvir regimen was evaluated in a study in which patients were treated for 12 weeks and were monitored for 24 weeks posttreatment. In treatment-naive patients, 98% of the patients with no cirrhosis and 58% of the patients with cirrhosis achieved a sustained virologic response (SVR). In treatment-experienced patients, 92% of those without cirrhosis and 69% of those with cirrhosis achieved SVR. The lower SVR in patients with cirrhosis is identified as a limitation of use in the labeling for daclatasvir.

Precautions: (1) Coadministration of amiodarone in patients treated with daclatasvir and sofosbuvir isn't recommended. Symptomatic bradycardia requiring pacing has been reported when amiodarone is coadministered with sofosbuvir in combination with another HCV direct-acting antiviral agent such as daclatasvir. Patients also taking a beta-blocker, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at particular risk for bradycardia with coadministration of amiodarone. For patients for whom other treatment options aren't available, cardiac monitoring in an inpatient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of heart rate should occur

daily through at least the first 2 weeks of treatment. (2) The effectiveness of daclatasvir may be significantly reduced by strong CYP3A inducers such as carbamazepine, phenytoin, rifampin, and St. John's wort, and concurrent use is contraindicated. (3) The dosage of daclatasvir should be reduced when it's used concurrently with a strong CYP3A inhibitor such as clarithromycin or itraconazole. (4) If daclatasvir is used concurrently with a moderate CYP3A inhibitor such as diltiazem or fluconazole, no dosage adjustment is recommended, but response to daclatasvir should be monitored for the occurrence of adverse events. (5) Daclatasvir may increase the action of dabigatran, digoxin, and HMG-CoA reductase inhibitors (statins). (6) The efficacy and safety of daclatasvir haven't been established in patients with decompensated cirrhosis.

Adverse reactions: *In combination with sofosbuvir:* headache, fatigue. *In combination with sofosbuvir and ribavirin:* headache, anemia, fatigue, nausea.

Supplied as: 30 mg, 60 mg, and 90 mg tablets

Dosage: 60 mg/day in combination with sofosbuvir for 12 weeks. See the prescribing information for dosage adjustments when used concurrently with a strong CYP3A inhibitor or a moderate CYP3A inducer.

Nursing considerations: (1) Teach patients taking amiodarone concurrently with daclatasvir and sofosbuvir to monitor their heart rate as directed and report symptoms such as near-syncope or syncope. (2) Tell patients that daclatasvir can be taken without regard to food. (3) Teach patients to take the medication exactly as prescribed and not to skip doses. If they miss a dose, they should contact their healthcare provider or pharmacist for instructions. If they take an overdose, they should call their healthcare provider immediately or seek emergency medical attention.

REFERENCES

1. FDA approves new treatment for chronic hepatitis C genotype 3 infections. FDA news release. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455888.htm.

2. Daklinza (daclatasvir) tablets, for oral use. Prescribing information. http://packageinserts.bms.com/pi/pi_daklinza.pdf.

ANTIFUNGAL DRUG

Isavuconazonium sulfate

Orphan drug approved to treat certain rare infections

Isavuconazonium sulfate (*Cresemba*, Astellas) is a prodrug that's converted to isavuconazole following administration. Isavuconazole is an azole antifungal drug with an antifungal spectrum that's generally similar to those of posaconazole and voriconazole. It acts by inhibiting the synthesis of ergosterol, a key component of the fungal cell membrane.

Administered orally or I.V., isavuconazonium is indicated to treat patients age 18 and older with invasive aspergillosis or invasive mucormycosis (caused by Mucorales fungi).[1] Both are rare fungal infections for which patients with immunocompromise are at greatest risk.

The new drug has been granted orphan drug status and is the sixth antibacterial or antifungal drug to be designated as a Qualified Infectious Disease Product. This designation is given to a product used in the treatment of serious or life-threatening infections under the provisions of the FDA Safety and Innovation Act.

The effectiveness of isavuconazonium for treating invasive aspergillosis was demonstrated in a clinical trial involving 516 patients who received either isavuconazonium or voriconazole. Overall success at the end of treatment was found in 35% of the patients treated with the new drug and 39% of patients treated with voriconazole.

The approval of isavuconazonium for treating invasive mucormycosis was based on the results of a clinical trial in which 37 patients were treated with the new drug and compared with the natural disease progression associated with untreated mucormycosis. The overall response success rate at the end of treatment was 31%.

The type and incidence of adverse events with isavuconazonium are generally similar to those reported with voriconazole.

Precautions: (1) Monitor liver function test results at the start and during the course of therapy; serious hepatic adverse reactions have occurred in some patients. (2) Contraindicated in patients with familial short QT syndrome; isavuconazonium shortens the QT interval in a dose-related manner predisposing affected patients to a risk of atrial and ventricular dysrhythmias.[2] (3) Contraindicated for concurrent use with strong CYP3A4 inhibitors such as ketoconazole, which may significantly increase the plasma concentration of isavuconazole. (4) Contraindicated for concurrent use with strong CYP3A4 inducers such as carbamazepine, rifampin, long-acting barbiturates, and St. John's wort, which may significantly decrease the plasma concentration of isavuconazole. Consult the prescribing information for cautions and dosage adjustments recommended for concurrent use with immunosuppressants, certain antiviral medications, and many other drugs that may interact with isavuconazole. (5) Discontinue treatment if a patient develops a severe cutaneous adverse reaction. Serious hypersensitivity reactions such as anaphylaxis and severe skin reactions such as Stevens-Johnson syndrome have been reported with other azole antifungal agents. (6) Use caution if the new drug is used in patients with hypersensitivity to other azoles. Whether cross-sensitivity exists between isavuconazonium and other azole antifungal agents isn't known. (7) Infusion-related reactions such as hypotension, dyspnea, chills, dizziness, and paresthesia have occurred during I.V. administration

of isavuconazonium. Discontinue the infusion if these reactions occur. (8) Isavuconazonium hasn't been studied in patients with severe hepatic impairment; if it's used in these patients, they should be closely monitored for adverse reactions.

Adverse reactions: nausea, vomiting, diarrhea, headache, hypokalemia, constipation, dyspnea, cough, peripheral edema, back pain, elevated liver function test results

Supplied as: 186 mg capsules for oral use; a lyophilized powder in single-dose vials containing 372 mg of the drug for I.V. use

Dosage: for both oral and I.V. administration, a loading dose of 372 mg (equivalent to 200 mg of isavuconazole) every 8 hours for 6 doses (48 hours). The maintenance dosage is 372 mg once a day starting 12 to 24 hours after the last loading dose. The I.V. and oral formulations of isavuconazonium are bioequivalent and, if the route of administration is changed, another loading dose isn't required when switching between formulations.

Nursing considerations: (1) Keep capsules in their aluminum blister pack until use to protect them from moisture. Tell patients not to put the capsules in pill boxes or pill organizers. (2) Teach patients to swallow capsules whole; capsules shouldn't be opened, chewed, crushed, or dissolved. (3) Store unreconstituted vials of isavuconazonium sulfate for injection in a refrigerator. (4) Reconstitute vial contents by adding 5 mL of Water for Injection to the vial. Shake the vial gently to completely dissolve the powder. The reconstituted solution should be clear and free from visible particulate. (5) Remove a volume of 5 mL of the reconstituted solution from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Gently mix the solution to minimize formation of particulates. (6) Add an in-line filter with a microporous membrane pore size of 0.2 to 1.2 micron to the infusion bag. Translucent to white particulates of insoluble isavuconazole may be visible in the diluted solution; these will be removed by in-line filtration. (7) Flush the I.V. line with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before and after each infusion of isavuconazonium. Infuse the diluted solution immediately over a minimum of 1 hour to reduce the risk of infusion-related reactions. I.V. administration should be completed within 6 hours of dilution at room temperature. (8) If the infusion can't be started immediately after dilution, refrigerate the infusion solution and complete the infusion within 24 hours. (9) Educate patients about the risk of liver problems and other serious adverse reactions and ensure that they know when to report problems and/or seek medical attention.

REFERENCES

1. Cresemba (isavuconazonium sulfate). Capsules for oral administration. For Injection for intravenous administration. Prescribing information. https://www.astellas.us/docs/cresemba.pdf.

2. Antzelevitch C, Cordeiro JM. Short QT syndrome. UptoDate. 2016. www. uptodate.com.

DOI-10.1097/01.NURSE.0000484020.74264.06