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PART 2

BY DANIEL A. HUSSAR, PhD
DEAN EMERITUS AND REMINGTON PROFESSOR EMERITUS • 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: amifampridine, bremelanotide, lefamulin, rifamycin, risankizumab-rzaa, siponimod, upadacitinib

THIS ARTICLE reviews seven recently marketed drugs, including:

- a new treatment for relapsing forms of multiple sclerosis.
- the third Janus kinase inhibitor approved to treat rheumatoid arthritis.
- the second drug approved to treat female sexual dysfunction.

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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Lefamulin

New treatment for community-acquired pneumonia in adults

Lefamulin acetate (*Xenleta*, Nabriva) is the first pleuromutilin antibacterial drug to be approved for treatment of a systemic infection. The only other pleuromutilin antibacterial that is available, retapamulin, was first marketed in 2007 in an ointment formulation for the topical treatment of impetigo caused by *Staphylococcus aureus* (methicillin-susceptible isolates only) or *Streptococcus pyogenes*.

Administered orally and I.V., lefamulin is indicated to treat adults with community-acquired bacterial pneumonia caused by certain susceptible microorganisms, including *Streptococcus pneumoniae* and methicillin-susceptible *S. aureus*.[1] It inhibits bacterial protein synthesis and is bactericidal *in vitro* against *S. pneumoniae*, *Haemophilus influenzae*, and *Mycoplasma pneumoniae*, but bacteriostatic against most other susceptible bacteria. It is not active against Enterobacteriaceae and *Pseudomonas aeruginosa*. Treatment that is initiated I.V. may be switched, when appropriate, to oral administration during the course of treatment.

The effectiveness of lefamulin was evaluated in two clinical trials in which it was compared with moxifloxacin. Efficacy was determined by Early Clinical Response (ECR) rates at 72 to 120 hours after the first dose. The ECR rates in the first trial were 87% and 90%, respectively, for lefamulin and moxifloxacin, and 91% for both drugs in the second study.

Investigator-assessed clinical response (IACR) rates were also assessed at the Test of Cure Visit 5 to 10 days after the last dose of the study drug. The IACR rates in the first trial were 81% and 84%, respectively, for lefamulin and moxifloxacin, and 87% and 89% in the second study.

Precautions: (1) Lefamulin may prolong the QT interval and increase the risk of cardiac dysrhythmias. Avoid using in patients with known QT prolongation, ventricular dysrhythmias including torsades de pointes, and in patients being treated with other medications that may prolong the QT interval, such as Class IA (quinidine, procainamide, disopyramide) and Class III (amiodarone, sotalol) antiarrhythmic drugs; antipsychotic drugs such as ziprasidone and thioridazine; and antibacterial drugs such as moxifloxacin and erythromycin. (2) The risk of QT prolongation is increased in patients with hepatic impairment or patients in renal failure who require dialysis. Lefamulin tablets have not been studied in patients with hepatic impairment, and their use is not recommended in patients with moderate or severe hepatic impairment. When lefamulin is administered I.V. to patients with severe hepatic impairment, the dosage should be reduced. (3) The concurrent use of lefamulin tablets with sensitive CYP3A substrates known to prolong the QT interval such as pimozide is contraindicated because of the increased action and risk of toxicity with the latter agent. (4) Strong and moderate CYP3A and/or P-glycoprotein (P-gp) inducers such as rifampin and carbamazepine may reduce the effectiveness of lefamulin, and concurrent use should be avoided. (5) The activity and risk for toxicity from use of lefamulin tablets may be increased by strong CYP3A and/or P-gp inhibitors such as ketoconazole, and concomitant use should be avoided. (6) The concurrent use of lefamulin tablets with moderate CYP3A and/or P-gp inhibitors should be closely monitored. Consult the Prescribing Information for more warnings and precautions involving potential drug interactions. (7) Monitor patients for *Clostridioides* (formerly *Clostridium*) *difficile*-associated diarrhea, which has been reported with the use of almost all systemic antibacterial drugs.

Adverse reactions: *With oral administration:* diarrhea, nausea, vomiting, hepatic enzyme elevation. *With I.V. administration:* administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache.

Supplied as: film-coated tablets in an amount equivalent to 600 mg of lefamulin for oral administration. For I.V. administration, single-dose vials containing lefamulin acetate in an amount equivalent to 150 mg of lefamulin in 15 mL of 0.9% sodium chloride for further dilution prior to infusion. Before administration, vial contents are diluted in a bag of 250 mL of 10 mM citrate buffered (pH 5) 0.9% sodium chloride solution; this diluent is supplied with the drug.

Dosage: *For oral administration*: 600 mg every 12 hours for 5 days. *For I.V. administration:* 150 mg infused over 60 minutes every 12 hours for 5 to 7 days. In patients with severe hepatic impairment, the I.V. dosage should be reduced to 150 mg infused over 60 minutes every 24 hours.

Nursing considerations: (1) Store vials in a refrigerator. (2) Tell patients to swallow tablets whole with 6 to 8 oz of water, and to take each dose at least 1 hour before a meal or 2 hours after a meal. Concurrent administration with a high-fat meal may reduce the drug's bioavailability. (3) Teach patients about possible adverse reactions and tell them to report diarrhea to the healthcare provider. (4) Advise women of reproductive potential to use effective contraception during

treatment and for 2 days after the final dose. Lactating women should pump and discard milk for the duration of treatment and for 2 days after the final dose. (5) Teach patients to take the entire course of therapy as prescribed and warn them not to skip doses or discontinue therapy unless directed to do so by the healthcare provider.

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Rifamycin

Treatment for travelers' diarrhea

The most common travel-related illness, travelers' diarrhea is defined as three or more unformed stools in 24 hours in a person who is traveling.[1] Patients may experience other signs and symptoms such as cramps, fever, severe abdominal pain, bloody diarrhea, and vomiting. Travelers' diarrhea is most often caused by enterotoxigenic *Escherichia coli* present in food and water, but may also be caused by various other bacteria and, less commonly, certain viruses and protozoa.[2] The highest-risk destinations for travelers' diarrhea are Mexico, Central and South America, Africa, the Middle East, and most of Asia.[1]

The treatment of travelers' diarrhea often includes the use of an antimotility agent and/or replacement of fluid and electrolytes. Moderate or severe travelers' diarrhea is often treated with an antibacterial drug such as azithromycin. A fluoroquinolone such as ciprofloxacin may also be considered, but drugs in this class are more likely to be associated with adverse reactions and antibiotic resistance.

Rifamycin sodium (*Aemcolo*, Aries), a member of the ansamycin class of antibacterial drugs, acts by blocking one of the steps in DNA transcription that results in inhibition of bacterial synthesis and growth.[3] Its properties and use are most similar to those of rifaximin, another antibacterial that is labeled to treat travelers' diarrhea. Both drugs are minimally absorbed following oral administration.

Rifamycin is provided in delayed-release tablets coated with a pH-resistant polymer film that breaks down above pH 7, resulting in the release of most of the drug in the terminal ileum and colon. Active against most isolates of *E. coli*, it is indicated to treat travelers' diarrhea caused by noninvasive strains of *E. coli* in adults. It is not indicated to treat diarrhea complicated by fever and/or bloody stool, or diarrhea caused by pathogens other than noninvasive strains of *E. coli*.

The effectiveness of rifamycin was evaluated in two clinical trials. In a placebo-controlled trial, the percentage of patients who achieved clinical cure was significantly higher in those treated with rifamycin (81%) compared with those receiving placebo (57%). The second trial compared the effectiveness of rifamycin and ciprofloxacin. The percentage of patients who achieved clinical cure was 85% with both treatments, demonstrating noninferiority of rifamycin to ciprofloxacin. Rifamycin was well tolerated in the clinical trials.

Precautions: (1) Contraindicated in patients with known hypersensitivity to any of the rifamycin class antibacterial agents. (2) Because *C. difficile*-associated diarrhea has been reported with the use of almost all systemic antibacterial agents, this possibility should be considered in patients who experience diarrhea while being treated with rifamycin. (3) Because rifamycin may inhibit P-gp in the gastrointestinal tract, it may interact with medications that are P-gp inhibitors or substrates.

Adverse reactions: headache, constipation

Supplied as: delayed-release tablets containing 200 mg of rifamycin sodium equivalent to 194 mg of rifamycin

Dosage: 388 mg (two tablets) twice a day in the morning and evening for 3 days

Nursing considerations: (1) Doses may be taken without regard to food. (2) Instruct patients not to break, crush, or chew tablets. Tablets should be swallowed whole with a full glass (6 to 8 ounces) of liquid. (3) Warn patients not to take rifamycin with alcohol, which may alter the release of the drug from the delayed-release tablet. (4) Tell patients to contact the healthcare provider if diarrhea worsens or persists for more than 48 hours following initiation of treatment. (5) Teach patients to take the entire course of therapy as prescribed, even if they feel well, and warn them not to skip doses or discontinue therapy unless directed to do so by the healthcare provider.

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DRUG FOR PSORIASIS

Risankizumab-rzaa

Therapy for patients with moderate-to-severe plaque psoriasis

Psoriasis is the most common autoimmune disease in the US, affecting approximately 8 million people.[1] It is characterized by overactivation of the immune system

and widespread inflammation that causes scaly, raised skin plaques that may be pruritic or painful. Plaques commonly appear on the elbows, knees, or scalp, but may develop at any location.[2]

Certain naturally occurring interleukins (primarily IL-23 and IL-17A) have been identified as having a role in the occurrence and worsening of psoriasis. Seven monoclonal antibodies that inhibit specific interleukins that have been implicated in psoriasis have been approved in the last 10 years and these provide the most effective treatments for moderate-to-severe plaque psoriasis.

The p19 and p40 subunits of IL-23 are present in higher concentrations in psoriatic lesions. Risankizumab-rzaa (*Skyrizi*, AbbVie) joins guselkumab and tildrakizumab as monoclonal antibodies that selectively bind to the p19 subunit of IL-23. Like the other two drugs, it is administered subcutaneously to treat moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[3]

Except for ustekinumab, with which some of the newest drugs have been compared, the IL inhibitors have not been directly compared with each other in clinical studies. (Ustekinumab, which targets the p40 subunit, was the first IL inhibitor to be marketed for moderate-to-severe psoriasis.) However, in the separate studies of the IL inhibitors, risankizumab appears to be at least as or possibly more effective than the other drugs.

Risankizumab is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject doses after appropriate education and training in subcutaneous injection technique.

Precautions: (1) As with any drug that suppresses immune function, risankizumab increases the risk of infection. Treatment should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated. (2) Patients should be evaluated for tuberculosis (TB) infection before treatment starts. The drug should not be used in patients with active TB. In patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, anti-TB therapy should be considered before treatment with risankizumab is initiated. (3) If a clinically important infection develops during treatment or an infection is not responding to standard therapy, the patient should be closely monitored and risankizumab should not be administered until the infection resolves.

Adverse reactions: upper respiratory infections, headache, fatigue, injection site reactions, tinea infections

Supplied as: single-dose prefilled syringes containing 75 mg of the drug in 0.83 mL of solution

Dosage: 150 mg (two injections) at Weeks 0 and 4, and every 12 weeks thereafter

Nursing considerations: (1) Teach patients how to self-administer the drug as prescribed. A Medication Guide and detailed instructions are provided with the medication. (2) Tell patients to store syringes in a refrigerator in the original carton to protect the drug from light, but to let syringes reach room temperature (15 to 30 minutes) out of direct sunlight before administration. (3) Teach patients to administer the two injections of risankizumab at different anatomic locations such as the thigh or abdomen. Injection into the upper, outer arm should be performed only by a healthcare professional or caregiver. (4) Tell patients to avoid live vaccines during treatment. (5) Inform patients about the risk of infection during treatment and instruct them to notify the healthcare provider if they experience signs or symptoms of a clinically significant infection.

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ANTIARTHRITIC DRUG

Upadacitinib

Indicated for rheumatoid arthritis

Janus kinase (JAK) enzymes are intracellular enzymes that transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Four JAK enzymes (JAK1, JAK2, JAK3, and TYK2) have been implicated in the pathogenesis of various inflammatory and autoimmune diseases, including rheumatoid arthritis. Within the signaling pathway, JAKs, acting in pairs, phosphorylate and activate signal transducers and activators of transcription (STATs), which modulate intracellular activity. Inhibition of these enzymes blocks the activation of mediators of inflammation.[1]

Upadacitinib (*Rinvoq*, AbbVie) is the third JAK inhibitor to be approved to treat patients with rheumatoid arthritis, joining tofacitinib and baricitinib. It appears to have greater inhibitory potency at JAK1 and JAK2 relative to JAK3 and TYK2, but the relationship of inhibition of specific enzymes to therapeutic effectiveness is not known.[1]

Upadacitinib is indicated for adults with moderately-to-severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. Like

tofacitinib and baricitinib, upadacitinib may be used as monotherapy or in combination with methotrexate or another nonbiologic disease-modifying antirheumatic drug (DMARD). However, concurrent use with another JAK inhibitor, biologic DMARD, or a potent immunosuppressant such as azathioprine or cyclosporine is not recommended.

The effectiveness of upadacitinib was evaluated in four studies in which the primary endpoint was the proportion of patients who achieved an ACR20 response (representing a 20% improvement in criteria established by the American College of Rheumatology), as well as one study in which the primary endpoint was the ACR50 response (representing a 50% improvement).[2] The latter study included patients who had not previously been treated with methotrexate.

Patients treated with upadacitinib had higher ACR20, ACR50, and ACR70 responses compared with placebo or methotrexate. Upadacitinib also met secondary endpoints in the clinical studies, including the Disease Activity Score and the Health Assessment Questionnaire Disability Index, and achieved clinical remission in many patients, characterized by almost no disease activity and symptoms, even without methotrexate. In addition, it significantly inhibited radiographic progression.[1]

The labeling for upadacitinib contains boxed warnings about the risks of serious infections, malignancy, and thrombosis. Most patients who developed infections were being treated concurrently with immunosuppressants such as methotrexate or corticosteroids.

Precautions: (1) None of the JAK inhibitors should be used in patients with an active, serious infection, including localized infections. If a serious infection develops during treatment, therapy should be interrupted until the infection is controlled. (2) Before initiating treatment with upadacitinib, patients should be evaluated for latent or active TB infection. The drug should not be used in patients with active TB. Anti-TB therapy should be considered in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and in patients with a negative test for latent TB who have risk factors for TB infection. (3) Patients are also at greater risk of invasive fungal infections, as well as bacterial, viral, and other infections caused by opportunistic pathogens. Reactivation of latent viruses such as herpes viruses has occurred. If a patient develops herpes zoster, treatment with upadacitinib should be interrupted until the episode resolves. (4) Because lymphomas and other malignancies have occurred in patients treated with upadacitinib and other JAK inhibitors, this risk should be considered before initiation of treatment in patients with a known malignancy other than a successfully treated nonmelanoma skin cancer. (5) Because upadacitinib increases the risk of deep vein thrombosis, pulmonary embolism, and other thrombotic events that may be fatal, risks and benefits must be carefully weighed before initiating treatment in patients at increased risk for thrombosis. (6) Use upadacitinib with caution in patients at risk for gastrointestinal perforation, including those with a history of diverticulitis. (7) Monitor patients for lab abnormalities, including neutropenia, lymphopenia, anemia, elevated liver enzymes, and elevated lipid concentrations. Treatment should not be initiated, or should be interrupted, in patients with an absolute neutrophil count less than 1,000 cells/mm^3, an absolute lymphocyte count less than 500 cells/mm^3, or hemoglobin less than 8 g/dL. Lab parameters should be evaluated at baseline and periodically thereafter. (8) Upadacitinib is not recommended for use in patients with severe hepatic impairment. (9) Strong CYP3A4 inducers such as rifampin may reduce the activity of upadacitinib, and concurrent use is not recommended. (10) Strong CYP3A4 inhibitors such as ketoconazole may increase the action of the new drug and concurrent use should be closely monitored.

Adverse reactions: upper respiratory tract infections, nausea, cough, pyrexia

Supplied as: extended-release tablets in a 15 mg potency

Dosage: 15 mg once a day

Nursing considerations: (1) This drug may be taken without regard to food. Instruct patients to swallow the tablets whole, without crushing, splitting, or chewing them. (2) Tell patients to avoid live vaccines during treatment. (3) Advise patients at increased risk for skin cancer to undergo periodic skin examinations. (4) Advise women of reproductive potential to use effective contraception during treatment and for 4 weeks following completion of therapy. Women treated with upadacitinib should also be advised not to breastfeed.

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DRUG FOR MULTIPLE SCLEROSIS

Siponimod

Approved for adults with relapsing forms of MS

A chronic inflammatory autoimmune disease of the central nervous system, multiple sclerosis (MS) is

one of the most common causes of neurologic disability in young adults. It is more common in women than in men, and most individuals first experience symptoms between ages 20 and 40.[1]

Relapsing-remitting MS (RRMS), the most common form of MS, accounts for approximately 85% of all MS diagnoses.[1,2] It is characterized by episodes of worsening function (relapses) that are followed by recovery periods (remissions) of varying duration.

Most patients with MS experience some degree of persistent disability that gradually worsens over time. In some of these patients, disability progresses independent of relapses, representing an extension of the disease designated as *secondary progressive MS (SPMS)*. This may be characterized by reduced ambulation necessitating a walking aid or wheelchair, bladder dysfunction, and cognitive decline.[1]

Active SPMS is one of the relapsing forms of MS, but many patients subsequently stop experiencing new relapses although disability continues to worsen. This is designated as *nonactive SPMS*.[1]

Approximately 15% of patients with MS have *primary progressive MS (PPMS)*, which is characterized by steadily worsening function from the onset of symptoms, sometimes without relapses and remissions.[3]

Siponimod (*Mayzent*, Novartis) is a sphingosine 1-phosphate receptor modulator indicated to treat adults with relapsing forms of MS, including clinically isolated syndrome, RRMS, and active SPMS.[4] A clinically isolated syndrome is the first clinical episode suggestive of MS.[5] Administered orally, siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood and their migration into the central nervous system.

The effectiveness of siponimod was demonstrated in a placebo-controlled study that included 1,651 patients with SPMS who had evidence of disability progression in the prior 2 years, no evidence of relapse in the 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at study entry. The primary endpoint was the time to 3-month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher), sustained for 3 months. Additional endpoints included annualized relapse rate (relapses/year) and magnetic resonance imaging measures of inflammatory disease activity. The proportion of patients with CDP was significantly lower in the group of patients treated with siponimod (26% versus 32% with placebo), and the annualized relapse rate was also lower (0.07 versus 0.16). Although the effectiveness of siponimod was demonstrated in patients with active SPMS, the differences were not statistically significant in the subgroup of patients with nonactive SPMS.

The activity of siponimod is increased in patients who are CYP2C9 poor metabolizers. All patients should have CYP2C9 genotype testing before treatment is initiated. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype and should be used in a reduced dosage in patients with CYP2C9 genotypes *1/*3 or *2/*3.

In addition to CYP2C9 genotype testing, other assessments that should be performed prior to starting treatment with siponimod include a complete blood cell count, an electrocardiogram, liver function tests, varicella zoster virus (VZV) antibody testing, and an ophthalmic evaluation; macular edema was reported in 2% of the patients treated with siponimod, and the risk is higher in patients with diabetes or a history of uveitis. The potential for additive immunosuppressive effects of other current or prior medications should also be evaluated.

When siponimod treatment is discontinued, the drug remains in the blood for up to 10 days and residual pharmacodynamic effects may persist for 3 to 4 weeks after the last dose. The use of other drugs with immunosuppressive activity during this period may result in an additive effect on the immune system.

Precautions: (1) Because initiation of treatment results in a transient decrease in heart rate and atrioventricular (AV) conduction delays, siponimod is contraindicated in patients with Mobitz type II second-degree AV block, third-degree AV block, or sick sinus syndrome, unless the patient has a functioning pacemaker. (2) Siponimod is contraindicated in patients who have experienced within the previous 6 months a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III/IV heart failure. (3) Use caution in patients being treated with a beta-blocker when initiating treatment with siponimod because of the additive effects on lowering heart rate. To reduce the risk of bradycardia and associated complications, treatment should be initiated with a low dose and titrated upwards. (4) For patients with sinus bradycardia, first- or second-degree (Mobitz type I) AV block, or a history of myocardial infarction or heart failure, patients should be monitored for 6 hours after the first dose (first-dose monitoring) for symptomatic bradycardia; this includes hourly heart rate and BP measurements. (5) Because of the risk of bradycardia and other cardiac complications,

treatment with siponimod should generally not be initiated in patients who are concurrently treated with QT-prolonging drugs with known arrhythmogenic properties, heart rate-lowering calcium channel blockers such as diltiazem and verapamil, or other drugs that may decrease heart rate such as digoxin and ivabradine. (6) The use of Class IA (quinidine, procainamide) and Class III (amiodarone, sotalol) antiarrhythmic drugs has been associated with torsades de pointes in patients with bradycardia. If concurrent use of siponimod with one of these drugs is being considered, a cardiologist should be consulted. (7) Siponimod may increase BP and elevations may persist with continuing treatment, so monitor BP periodically. (8) Siponimod may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed if clinically indicated. (9) Use caution in patients with a history of significant liver disease. Elevations of serum transaminases were experienced by some patients in the clinical study of siponimod. (10) Siponimod causes a dose-dependent reduction in peripheral lymphocyte count to 20% to 30% of baseline values, and the immunosuppression may increase the risk of infection. Complete blood cell counts should be determined and treatment should not be initiated in patients with severe active infection until the infection is resolved. (11) Rare cases of cryptococcal meningitis have been reported, as have increased rates of herpes viral infections, including herpes zoster. Patients without a confirmed history of varicella (chickenpox) or without documentation of vaccination against VZV should be tested for antibodies to VZV before initiating treatment with siponimod. (12) Although not reported in the clinical trial for siponimod, progressive multifocal leukoencephalopathy, a potentially fatal opportunistic viral infection of the brain, has been rarely reported with the use of other MS treatments. The risk of this infection is increased in immunocompromised patients and in patients being concurrently treated with antineoplastic agents, immune-modulating, or immunosuppressive therapies including corticosteroids, because of the risk of additive immune system effects. Initiating treatment with siponimod following treatment with alemtuzumab is not recommended and caution should be exercised when switching from other drugs with prolonged immune effects. (13) The use of live attenuated vaccines should be avoided while patients are taking siponimod and for 4 weeks after stopping treatment. Vaccinations may be less effective if administered during siponimod treatment. (14) CYP2C9 and CYP3A4 inhibitors increase siponimod exposure and activity of siponimod, and the concurrent use of a moderate CYP2C9 and moderate or strong CYP3A4 dual inhibitor such as fluconazole, or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor, is not recommended. (15) CYP2C9 and CYP3A4 inducers decrease the exposure and activity of siponimod, and the concurrent use of a moderate CYP2C9 and strong CYP3A4 dual inducer such as carbamazepine or rifampin, or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer, is not recommended. Exercise caution when siponimod is administered concomitantly with a moderate CYP2C9 inhibitor or a moderate CYP2C9 inducer.

Adverse reactions: headache, hypertension, serum transaminase increase

Supplied as: 0.25 mg film-coated tablets in a starter/blister pack; 0.25 mg and 2 mg film-coated tablets in bottles

Dosage: To reduce the risk of bradydysrhythmias and AV conduction delays, treatment in most patients is initiated with a 5-day titration using a starter pack containing 0.25 mg tablets. The usual dosage is 0.25 mg on Days 1 and 2, 0.5 mg on Day 3, 0.75 mg on Day 4, 1.25 mg on Day 5, and 2 mg once a day thereafter. Consult the Prescribing Information for recommended dosage modifications for specific patient populations, such as those with CYP2C9 genotypes *1/*3 or *2/*3 and those with certain preexisting cardiac conditions.

Nursing considerations: (1) Tell patients to store unopened containers in a refrigerator. After opening, the starter pack may be stored at room temperature for up to 1 week. Opened bottles may be stored at room temperature for up to 1 month. (2) Teach patients to take siponimod exactly as prescribed, and not to discontinue it without first contacting the healthcare provider. Also tell them to contact the provider if they accidently take more siponimod than prescribed. (3) Teach patients to recognize and report potentially serious adverse reactions and complications of therapy, such as infection, symptomatic bradycardia, vision changes, sudden severe headache or altered mental status, new-onset or worsening dyspnea, and signs and symptoms of liver injury such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and dark urine. (4) Tell women of childbearing potential to use effective contraception during siponimod treatment and for 10 days after stopping treatment. (5) Inform patients that a severe increase in disability has been reported in some patients after discontinuation of a drug similar

to siponimod. Advise them to inform the provider if they develop worsening MS symptoms after siponimod therapy ends.

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DRUG FOR LEMS

Amifampridine phosphate

First therapy for adults with a rare autoimmune disorder

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disease of the neuromuscular junction leading to a gradual onset of muscle weakness. Affecting about 400 people in the US, LEMS is caused by autoantibodies against voltage-gated calcium channels in the neuromuscular junction.[1,2] This disrupts the ability of nerve cells to send signals to muscle cells, resulting in progressive muscle weakness. Early manifestations include difficulty in climbing stairs or rising from a sitting position. Other signs and symptoms include extraocular, pharyngeal, tongue, and neck muscle weakness; and changes in autonomic nervous system function leading to dry mouth, constipation, and blurred vision. The disease can be life-threatening when the weakness involves respiratory muscles.

In approximately 50% of patients, LEMS is associated with an underlying malignancy, most commonly small cell lung cancer. In some cases, LEMS is the first symptom of the malignancy.[2]

The first drug to be approved to treat LEMS in adults, amifampridine phosphate (*Firdapse*, Catalyst), is an aminopyridine that acts as a potassium channel blocker.[3] Its properties are most similar to those of dalfampridine, also known as fampridine and by its chemical name 4-aminopyridine, which was initially marketed to improve walking in patients with MS.

The potassium-blocking action of amifampridine results in the opening of slow voltage-dependent calcium channels, allowing for a subsequent influx of calcium. This leads to greater release of acetylcholine from synaptic vesicles into the synaptic cleft, enhancing neuromuscular transmission and improving muscle function.

The effectiveness of amifampridine was evaluated in two placebo-controlled studies involving 64 adult patients. Efficacy was measured using the Quantitative Myasthenia Gravis score (a 13-item physician-rated categorical scale assessing muscle weakness) and the Subject Global Impression score (a 7-point scale on which patients rated their global impression of the effects of the study treatment on their physical well-being). For both measures, patients experienced greater benefit with amifampridine than with placebo.

The most important concern with the new drug is a risk of seizures, which occurred in 2% of the patients in the studies who did not have a history of seizures.

Subsequent to the approval of this drug, which is labeled for adults only, the FDA approved another amifampridine drug (*Ruzurgi*, Jacobus) for children ages 6 to less than 17 years.[4] This product is not included in this discussion.

Precautions: (1) Amifampridine is contraindicated in patients with a history of seizures. If seizures occur during treatment in patients without such a history, a reduction in dosage or discontinuation of treatment should be considered. The concurrent use of amifampridine with other medications that lower the seizure threshold may increase the risk of seizures. (2) No hypersensitivity reactions were reported in the clinical studies of amifampridine, but such events (including anaphylaxis) have been experienced with the use of another aminopyridine. Consequently, amifampridine is contraindicated in patients with a history of hypersensitivity to any drug in the aminopyridine class. (3) The concurrent use of drugs with cholinergic effects (such as the peripherally acting cholinesterase inhibitor pyridostigmine) may increase the cholinergic effects of amifampridine and the risk of adverse reactions. Patients using these drugs concurrently should be closely monitored for cholinergic adverse events. (4) In patients with hepatic impairment or renal impairment, and in those who are known to be N-acetyltransferase 2 (NAT2) poor metabolizers (also called slow acetylators), treatment should be initiated with the lowest recommended starting dosage.

Adverse reactions: paresthesia, upper respiratory tract infection, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, muscle spasms

Supplied as: 10 mg functionally scored oral tablets

Dosage: The recommended starting dosage of amifampridine is 15 to 30 mg daily in divided doses (3 to 4 times a day). In patients with hepatic or renal impairment and in those who are NAT2 poor metabolizers, treatment should be initiated at the lower dosage of 15 mg/day. The initial dosage can

be increased by 5 mg daily every 3 to 4 days. The maximum recommended dosage is 80 mg a day using maximum single doses of 20 mg (20 mg four times a day).

Nursing considerations: (1) Teach patients to take the drug exactly as prescribed and not to take more than 2 tablets at one time or more than 8 tablets in a 24-hour period. If they accidentally take too much, they should contact the healthcare provider or go to an ED immediately. (2) If a dose is missed, patients should skip that dose and take the next dose at the next scheduled dose time. Warn them not to double a dose to make up the missed dose. (3) Tell patients that amifampridine can be taken with or without food. (4) Warn patients about the seizure risk and tell them to stop taking the drug and contact the healthcare provider immediately if they experience a seizure. (5) Advise women of childbearing potential to use effective contraception.

REFERENCES

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DRUG FOR FEMALE SEXUAL DYSFUNCTION

Bremelanotide acetate

Second drug approved to treat HSDD

An estimated 10% of premenopausal women experience hypoactive sexual desire disorder (HSDD). HSDD is designated as "acquired" when it is experienced by a woman who previously had no problems with sexual disorder. It is designated as "generalized" when it is not apparently related to a specific partner, the situation, or type of sexual activity.[1] HSDD had been included in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition, but has recently been removed and replaced by sexual interest/arousal disorder.

Psychotherapy and behavioral therapy have been used to treat HSDD. In 2015, flibanserin (Addyi) was the first drug to be specifically approved for the treatment of premenopausal women with HSDD, but it has not been widely used due to interactions with alcohol resulting in severe hypotension and syncope, and other adverse experiences.

Bremelanotide acetate (*Vyleesi*, AMAG), the second drug to be approved to treat HSDD, is administered subcutaneously at least 45 minutes before anticipated sexual activity.[2] It is a melanocortin receptor agonist that activates melanocortin receptors, but the mechanism by which it improves sexual desire and related distress is unknown.[1]

Bremelanotide is specifically indicated to treat premenopausal women with acquired, generalized HSDD as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a coexisting medical or psychiatric disorder, problems with the relationship, or the effects of a medication or drug substance. This labeled indication is identical to the one for the oral use of flibanserin. Neither drug is indicated for the treatment of HSDD in postmenopausal women or in men, or to enhance sexual performance.

The effectiveness of bremelanotide was evaluated in two 24-week placebo-controlled studies. Measures of sexual desire and distress were the coprimary endpoints. In both studies, bremelanotide provided statistically significant improvement in the assessments compared with placebo, as demonstrated by an increase in the desire measure over time and a decrease in the distress measure over time. However, fewer than 40% of patients in both studies experienced improvement in either measure, and no statistically significant difference was found between the drug and placebo groups in the number of satisfying sexual events, a secondary endpoint. Nausea, the most common adverse reaction, was experienced by 40% of patients, and the incidence was highest following the first dose. Eight percent of patients discontinued participation in the clinical studies due to nausea.

Bremelanotide may cause adverse developmental effects if used during pregnancy. Women should use effective contraception while using the new drug and discontinue use if pregnancy is suspected. Encourage women who are exposed to the drug during pregnancy to contact the Vyleesi Pregnancy Exposure Registry at (877)411-2510.

Precautions: (1) Bremelanotide is contraindicated in patients with uncontrolled hypertension or known cardiovascular disease, and cardiovascular risk should be assessed before treatment starts. The drug may cause a transient increase in BP and a decrease in heart rate, which may occur after each dose and usually resolves within 12 hours. (2) Use with caution in patients with severe hepatic or renal impairment; these patients may experience an increase in the incidence and severity of adverse reactions such as nausea and vomiting. (3) Focal hyperpigmentation, including involvement of the face, gingiva, and breasts, was reported in 1% of the patients who received up to 8 doses of bremelanotide per month. Patients with dark skin are more likely to experience this response, as are patients who use the drug daily or who take more

than 8 doses a month. (4) Bremelanotide may slow gastric emptying and reduce the rate and extent of absorption of concomitantly administered oral medications. Patients should not use the new drug while taking other oral drugs that are dependent on threshold concentrations for efficacy, such as antibiotics. Discontinuing bremelanotide should be considered in women taking other medications for which a fast onset of action is important; for example, analgesics. (5) Bremelanotide has been reported to markedly decrease the systemic exposure of orally administered naltrexone, and concurrent use should be avoided.

Adverse reactions: nausea, flushing, injection site reactions, headache, vomiting

Supplied as: 1.75 mg bremelanotide in 0.3 mL solution in a single-dose, disposable prefilled autoinjector provided in a carton of 4 autoinjectors

Dosage: 1.75 mg at least 45 minutes before anticipated sexual activity, administered subcutaneously in the abdomen or thigh

Nursing considerations: (1) Teach patients how to administer the drug subcutaneously using correct injection technique. (2) Warn patients to administer no more than one dose within a 24-hour period and inform them that more than 8 doses per month is not recommended because of the increased risk of adverse reactions. (3) Advise patients that focal hyperpigmentation on the face, gingiva, and breasts may occur and changes may not resolve completely when bremelanotide is discontinued. Tell them to contact the healthcare provider if they have any concerns about changes to their skin. ■

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