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New Drugs 2018:

PART 1

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

- two new combination formulations for hepatitis C virus infection.
- the first anticoagulant approved for in-hospital and extended-duration venous thromboembolism prophylaxis in acutely ill patients.
- the second drug approved to treat amyotrophic lateral sclerosis.

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

SELECTED REFERENCES

Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, Inc.; 2018.

Nursing2018 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2018.

Physician's Desk Reference. 71st ed. Montvale, NJ: Medical Economics; 2018.

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DRUG FOR *C. DIFFICILE* INFECTION

Bezlotoxumab

Neutralizing the effects of *C. difficile* toxin B

Clostridium difficile is a spore-forming, anaerobic Gram-positive bacillus that produces two exotoxins (toxins A and B). In hospitalized patients, *C. difficile* infection (CDI) is the most common cause of healthcare-associated diarrhea.[1]

C. difficile represents an important challenge in many healthcare settings because it can survive in the environment for long periods and can be spread by healthcare personnel. In addition, patients who develop CDI face a high risk of CDI recurrence: typically 20% to 25% experience a recurrence after the initial episode, and the odds increase with multiple recurrences.[1] Bezlotoxumab (*Zinplava,* Merck) is a human monoclonal antibody that binds to *C. difficile* toxin B (but not to toxin A, which is less virulent) and neutralizes its effects.[1,2] Because it's not an antibacterial drug, it isn't a treatment for CDI. Administered as a single I.V. dose in conjunction with antibacterial treatment, bezlotoxumab is indicated to reduce recurrence of CDI in adults who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

The effectiveness of bezlotoxumab was evaluated in two placebo-controlled clinical trials that included approximately 1,500 patients. In both trials, a single I.V. infusion of bezlotoxumab or placebo was given to patients with CDI in addition to standard-of-care treatment: a 10- to 14-day course of metronidazole, vancomycin, or fidaxomicin. Patients were monitored for CDI recurrence, defined as the development of a new episode of diarrhea associated with a positive stool test for toxigenic *C. difficile* through 12 weeks after administration of the new drug or placebo. A sustained clinical response was defined as clinical cure of the presenting CDI episode and no CDI recurrence through 12 weeks after infusion.

In Trial 1, the sustained clinical response rates in the patients receiving bezlotoxumab or placebo were 60% and 55%, respectively, a difference that wasn't statistically significant. However, a statistically significant difference was observed in Trial 2, in which the sustained clinical response rates were 67% and 52%, respectively.

Precaution: Use caution in patients with a history of heart failure (HF), which was reported more frequently in patients with a history of HF treated with bezlotoxumab (13%) than placebo (5%). In addition, in patients with a history of HF, more deaths were reported in bezlotoxumab-treated patients (20%) than in placebo-treated patients (13%) during the 12-week study period. Patients with such a history should receive the new drug only if the anticipated benefit outweighs the risk.

Adverse reactions: nausea, pyrexia, headache

Supplied as: single-dose vials containing 1,000 mg of the drug in 40 mL (25 mg/mL)

Dosage: 10 mg/kg administered as an I.V. infusion over 60 minutes

Nursing considerations: (1) Store vials in a refrigerator in the original cartons. (2) Dilute the drug prior to I.V. administration by transferring the volume of drug needed to provide the prescribed dose into an I.V. bag containing either 0.9% Sodium Chloride Injection or 5% Dextrose Injection. The diluted solution should contain the drug in a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix the diluted solution using gentle inversion; don't shake. (3) Administer the solution using a sterile, nonpyrogenic, low-protein binding 0.2 to 5 micron in-line or add-on filter. (4) The diluted solution may be stored at room temperature for up to 16 hours or under refrigeration for up to 24 hours. If the bag is refrigerated, allow it to reach room temperature before use. (5) Administer the drug as an I.V. infusion only, not as a bolus injection.

REFERENCES

1. Bezlotoxumab (Zinplava) for prevention of recurrent *Clostridium difficile* infection. *Med Lett Drugs Ther.* 2017;59(1517):49-50.

2. Zinplava (bezlotoxumab) injection, for intravenous use. Prescribing information. http://www.merck.com/product/usa/pi_circulars/z/zinplava/zinplava_pi.pdf.

ANTIVIRAL DRUGS FOR HCV

More than three million Americans have chronic hepatitis C virus (HCV) infection.[1] HCV has at least six different genotypes; approximately 75% of Americans with HCV have genotype 1 infection and 20% to 25% have genotype 2 or 3 infection.[2] The recent development of direct-acting antiviral drugs that are highly effective against HCV has resulted in cure rates of HCV infection exceeding 90%, representing an important advance over previous regimens, with which cure rates were less than 50%.[3]

For optimum effectiveness, at least two of the new antiviral drugs are used together to treat patients with HCV infection. Fixed-dose combination formulations have permitted convenient once-a-day treatment regimens; for example, Harvoni (sofosbuvir/ledipasvir), Zepatier (elbasvir/grazoprevir), and Viekira XR (dasabuvir, ombitasvir, and paritaprevir, with ritonavir). The specific HCV genotype infections for which these combination formulations have been approved vary, as do their treatment regimens. Epclusa (sofosbuvir/velpatasvir) was the first combination product approved to treat all six major HCV genotype infections (1, 2, 3, 4, 5, or 6).

Antiviral agents approved for chronic HCV infections inhibit enzymes/proteins essential for HCV replication. In 2017, two additional combination formulations that include new antiviral agents were approved. Sofosbuvir/velpatasvir/voxilaprevir includes the new antiviral agent voxilaprevir, an HCV NS3/4A protease inhibitor. Glecaprevir/pibrentasvir includes the new HCV NS3/4A protease inhibitor glecaprevir and the new HCV NS5A inhibitor pibrentasvir. These new combination formulations are considered individually in the following discussions.

REFERENCES

1. Centers for Disease Control and Prevention. Hepatitis C FAQs for the public. 2016. https://www.cdc.gov/hepatitis/hcv/cfaq.htm#cFAQ21.

2. FDA approves Vosevi for hepatitis C. Food and Drug Administration. News release. July 17, 2017.

3. Hepatitis C treatments give patients more options. Food and Drug Administration. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm405642.htm.

Sofosbuvir/velpatasvir/voxilaprevir

Approved for certain patients with any of the six major HCV genotypes

Sofosbuvir/velpatasvir/voxilaprevir (*Vosevi*, Gilead) is the first product to be approved for patients who've been previously treated unsuccessfully with certain other antiviral regimens for HCV infection. Administered orally, it's specifically indicated for:

- adults with chronic HCV infection without cirrhosis or with compensated cirrhosis who have genotype 1, 2, 3, 4, 5, or 6 infection and who've previously been treated with an HCV regimen containing an NS5A inhibitor.
- patients who have genotype 1a or 3 infection and who've been previously treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.[1,2]

The effectiveness of sofosbuvir/velpatasvir/voxilaprevir was evaluated in two studies in patients without cirrhosis or with compensated cirrhosis who'd been previously treated with an HCV regimen. The primary endpoint in both studies was sustained virologic response (SVR12), defined as HCV RNA less than the lower limit of quantification at 12 weeks after the cessation of treatment.

In the first study, a 12-week treatment regimen with the new combination was compared with 12 weeks of placebo in NS5A inhibitor-experienced adults. An SVR12 response was experienced by 96% of the patients across all 6 HCV genotypes who were treated with the new regimen. No patients in the placebo group achieved SVR12.

The second study was conducted in patients with genotype 1, 2, 3, or 4 HCV infection who'd previously failed an HCV antiviral regimen that didn't include an NS5A inhibitor. Patients were treated for 12 weeks with either sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir/velpatasvir. Treatment with the new combination resulted in higher SVR12 rates than treatment with sofosbuvir/velpatasvir in patients with HCV genotype 1a (97% versus 82%) and 3 (96% versus 85%) infection. Comparable SVR12 rates were observed in patients with HCV genotype 1b (94% versus 92%) and 2 (100% versus 97%) infection. Comparison data aren't available for patients with HCV genotypes 4, 5, and 6 infection. Consequently, in patients who previously received sofosbuvir without an NS5A inhibitor, sofosbuvir/velpatasvir/voxilaprevir is indicated only for treatment of genotypes 1a or 3 infection because additional benefit over sofosbuvir/velpatasvir for the other genotype infections hasn't been demonstrated.

Precautions: (1) Before therapy begins, patients should be tested for evidence of current or prior hepatitis B virus (HBV) infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). Some patients who are coinfected with HCV and HBV who've been treated with HCV direct-acting antivirals without receiving HBV antiviral therapy have experienced reactivation of the HBV infection, and this is the subject of a boxed warning in the labeling. Patients coinfected with HCV/HBV should be monitored for HBV reactivation or hepatitis flare during HCV treatment and posttreatment follow-up. Treatment of the HBV infection should be initiated as clinically indicated. (2) Concurrent therapy with amiodarone isn't recommended. Symptomatic bradycardia has been reported in patients taking amiodarone concurrently with a sofosbuvir-containing regimen, and some patients have required pacemaker intervention. Patients also taking beta-blockers and those with underlying cardiac comorbidities and/or advanced liver disease may be at risk for this response when amiodarone is administered concurrently with sofosbuvir/velpatasvir/voxilaprevir. If no other treatment option is available, the drugs may be used concomitantly

with cardiac monitoring in an inpatient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur daily through at least the first 2 weeks of treatment. Because amiodarone has a long half-life, patients discontinuing this drug just before treatment initiation with sofosbuvir/velpatasvir/voxilaprevir should also undergo similar cardiac monitoring. (3) Not recommended for use in patients with moderate or severe hepatic impairment. Dosage adjustment isn't necessary for patients with mild hepatic impairment. (4) Not recommended for use in patients with severe renal impairment or end-stage renal disease requiring dialysis because the product's safety and effectiveness in these patients hasn't been studied. Dosage adjustment isn't necessary in patients with mild or moderate renal impairment. (5) The concurrent use of CYP450 and drug transporter (such as P-glycoprotein) inducers may reduce the plasma concentrations and activity of sofosbuvir/velpatasvir/voxilaprevir. The concomitant use of rifampin is contraindicated, and the use of other inducers (such as rifabutin, rifapentine, carbamazepine, oxcarbazepine, phenytoin, efavirenz, and St. John's wort) isn't recommended. The activity of sofosbuvir and velpatasvir may also be reduced by tipranavir/ritonavir, and concomitant use is not recommended. (6) Cyclosporine, atazanavir, and lopinavir have been reported to substantially increase the plasma concentration of voxilaprevir, and the concurrent use of these drugs with the new combination isn't recommended. (7) Administration of the new combination and an antacid should be separated by at least 4 hours. The solubility of velpatasvir decreases as pH increases, so drugs that increase gastric pH may reduce its concentration and activity. (8) Consult the product labeling for a complete listing of possible drug interactions and clinical recommendations for drugs that may interact with the sofosbuvir/velpatasvir/voxilaprevir combination.

Adverse reactions: headache, fatigue, diarrhea, nausea

Supplied as: tablets containing 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir. Each bottle contains 28 tablets that should be dispensed in the original container.

Dosage: one tablet once a day with food for 12 weeks

Nursing considerations: (1) Instruct patients at risk for bradycardia to self-monitor heart rate as directed and to immediately seek medical evaluation if they experience signs or symptoms of bradycardia, such as dizziness, lightheadedness, syncope, weakness, or shortness of breath. (2) Tell patients to take doses on a regular schedule with food. Warn them not to skip doses and to complete the course of treatment as directed. (3) Instruct patients who take antacids to separate administration of the drugs by at least 4 hours or the new drug's therapeutic effectiveness may be diminished. (4) Inform patients that this combination may interact with many other drugs and over-the-counter products. Advise them to check with their healthcare provider before using any other prescription or nonprescription medication or herbal products, including St. John's wort.

REFERENCES

1. FDA approves Vosevi for hepatitis C. Food and Drug Administration. News release. July 17, 2017.

2. Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209195s000lbl.pdf.

Glecaprevir/pibrentasvir

An 8-week course of treatment for all HCV genotypes

Glecaprevir/pibrentasvir (*Mavyret*, AbbVie) is the first antiviral combination that's used in an 8-week course of treatment for all HCV genotypes 1-6 infections in patients without cirrhosis who haven't been previously treated. The usual duration of treatment with other regimens is 12 weeks or longer.

The new combination is specifically indicated for adults with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis. It's also indicated for adults with HCV genotype 1 infection who were previously treated with a regimen containing an HCV NS5A inhibitor or an HCV NS3/4A protease inhibitor, but not both.[1]

The effectiveness of glecaprevir/pibrentasvir was evaluated in multiple studies enrolling approximately 2,300 patients with HCV genotypes 1-6 infection without cirrhosis or with compensated (mild) cirrhosis. Patients were treated for 8, 12, or 16 weeks, and the primary endpoint across all clinical trials was SVR12. An SVR12 response was experienced by 95% to 100% of the patients in most of the studies. An 8-week course of treatment is recommended for treatment-naive patients without cirrhosis; a 12-week course of treatment is recommended for treatment-naive patients with compensated cirrhosis.

When glecaprevir/pibrentasvir was also evaluated in treatment-experienced patients, 92% to 100% attained SVR12 responses. However, a longer duration of treatment (12 to 16 weeks) is recommended for most of these groups of patients.

Some patients in the studies had severe renal impairment and were

on dialysis, but the efficacy of treatment wasn't affected. Efficacy was also demonstrated in patients with HCV infection who were coinfected with HIV-1.

Some patients coinfected with HCV and HBV who've been treated with HCV direct-acting antivirals and weren't receiving HBV antiviral therapy have experienced reactivation of the HBV infection; this is the subject of a boxed warning in the labeling for glecaprevir/pibrentasvir and related products.

Precautions: (1) Contraindicated in patients with severe hepatic impairment; not recommended in patients with moderate hepatic impairment. (2) Before beginning treatment, patients should be tested for current or prior HBV infection by measuring HBsAg and anti-HBc. (3) Concurrent use with atazanavir is contraindicated because it increases the concentration of glecaprevir and pibrentasvir and increases the risk of elevated alanine aminotransferase (ALT). Ethinyl estradiol-containing products (such as combination oral contraceptives) may also increase the risk of ALT elevations and coadministration isn't recommended. (4) The concomitant use of the HIV antiviral drugs darunavir, lopinavir, or ritonavir may increase the concentration of both of the new HCV antivirals and concurrent use isn't recommended. (5) Cyclosporine may also increase concentrations of the new HCV combination products. Concurrent use isn't recommended in patients requiring stable cyclosporine doses higher than 100 mg per day. (6) Concurrent use of rifampin is contraindicated, and the concurrent use of carbamazepine, efavirenz, or St. John's wort isn't recommended. Consult the product labeling for a complete listing of possible drug interactions and clinical recommendations for drugs that may interact with the glecaprevir/pibrentasvir combination.

Adverse reactions: headache, fatigue, nausea, diarrhea

Supplied as: tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir, provided in cartons containing 4-week and 8-week supplies of medication

Dosage: three tablets (total daily dose: glecaprevir 300 mg and pibrentasvir 120 mg) once a day with food. Consult the product labeling for recommended dosage adjustments for specific patient groups.

Nursing considerations: (1) Tell patients to take doses with food exactly as directed. Warn them not to skip doses and to complete the course of treatment as prescribed. (2) Inform patients that this combination product may interact with many other drugs and over-the-counter products. Tell them to check with their healthcare provider before using any other prescription or nonprescription medication or herbal products.

REFERENCE

1. Mavyret (glecaprevir and pibrentasvir) tablets, for oral use. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209394s000lbl.pdf.

ANTICOAGULANT

Betrixaban

First anticoagulant approved for in-hospital and extended-duration VTE prophylaxis in acutely ill patients

Joining rivaroxaban, apixaban, and edoxaban, betrixaban (*Bevyxxa*, Portola) is the fourth orally administered anticoagulant that acts by inhibiting Factor Xa (FXa) activity. Betrixaban selectively blocks the active site of FXa and inhibits free FXa and prothrombinase activity. It decreases thrombin generation but has no direct effect on platelet aggregation. It's specifically indicated for the prophylaxis of venous thromboembolism (VTE) in adults hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.[1,2]

Many VTE events and VTE-related deaths occur in acutely ill medical patients, despite the standard use of injectable enoxaparin and other heparins in the hospital. More than half of VTE events occur after patients are discharged from the hospital.[3] Betrixaban is the first anticoagulant to be approved for in-hospital and extended-duration VTE prophylaxis in acutely ill medical patients.

The new drug's effectiveness was evaluated in a study of over 7,500 patients that compared extended duration betrixaban (35 to 42 days) to short duration enoxaparin (6 to 14 days) for preventing VTE in patients hospitalized for acute medical conditions such as decompensated heart failure, infection, respiratory failure, ischemic stroke, and rheumatic disorders. The expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely immobilized for at least 24 hours. The efficacy of betrixaban was based on the composite outcome up to the Day 35 visit of the occurrence of asymptomatic proximal deep vein thrombosis (DVT), symptomatic proximal or distal DVT, nonfatal pulmonary embolism, or VTE-related death. Betrixaban was shown to reduce the composite outcome compared with those taking enoxaparin plus placebo (4.4% versus 6.0%).

As with other anticoagulants, bleeding is the most important concern with the use of betrixaban, and it's contraindicated in patients with pathologic bleeding. The incidence of major bleeding such as intracranial hemorrhage was 0.67% in patients treated with betrixaban

and 0.57% in patients treated with enoxaparin. Bleeding was the most frequent reason for treatment discontinuation, with an incidence of 2.4% for betrixaban versus 1.2% for enoxaparin.

The risk of bleeding is increased by the concurrent use of other medications that affect hemostasis, including aspirin and other antiplatelet agents, other anticoagulants such as heparin, fibrinolytic agents, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Concomitant use with other anticoagulants is best avoided.

The anticoagulant effect of betrixaban can be expected to persist for at least 72 hours after the last dose. As with rivaroxaban, apixaban, and edoxaban, betrixaban has no specific antidote that reverses an excessive anticoagulant action; this is a disadvantage for these drugs compared with most other anticoagulants.

Precautions: (1) Contraindicated in patients with active pathologic bleeding. (2) Contraindicated in patients with severe hypersensitivity reactions to betrixaban. (3) Epidural or spinal hematomas may develop in patients treated with anticoagulants, including betrixaban, who are receiving neuraxial anesthesia or undergoing spinal puncture; this is the subject of a boxed warning in the labeling. These hematomas may result in paralysis and clinicians must take appropriate precautions. (4) Dosages should be reduced in patients with severe renal impairment. Betrixaban isn't recommended for use in patients with hepatic impairment. (5) Betrixaban is a substrate of P-glycoprotein (P-gp), and its action and risk of bleeding may be increased by the concurrent use of a P-gp inhibitor such as amiodarone, azithromycin, verapamil, ketoconazole, or clarithromycin. The dosage of betrixaban should be reduced in patients being treated concurrently with one of these drugs.

Adverse reactions: nonmajor bleeding events, urinary tract infection, constipation, hypokalemia

Supplied as: 40 mg and 80 mg capsules

Dosage: initially, a single dose of 160 mg, followed by 80 mg once a day with food. The recommended duration of treatment is 35 to 42 days.

Nursing considerations: (1) Discuss bleeding risks with patients and teach them to recognize and report signs and symptoms of occult bleeding, such as dark tarry stools, and any unusual, unexpected, or excessively prolonged bleeding. (2) Inform patients that aspirin, NSAIDs, and many other common drugs can increase the bleeding risk. Advise them to check with the healthcare provider before taking other medications, including over-the-counter products, and to inform all providers, including dentists, that they're taking an anticoagulant. (3) Tell patients to take each dose with food and to complete the course of treatment as directed. If they miss a dose, they should take it as soon as possible on the same day, but warn them not to double doses to make up for a missed dose.

REFERENCES

1. FDA approved betrixaban (Bevyxxa, Portola) for the prophylaxis of venous thromboembolism (VTE) in adult patients. Food and Drug Administration. News release. June 23, 2017. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm564422.htm.

2. Bevyxxa (betrixaban) capsules, for oral use. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208383s000lbl.pdf.

3. Amin AN, Varker H, Princic N, Lin J, Thompson S, Johnston S. Duration of venous thromboembolism risk across a continuum in medically ill hospitalized patients. *J Hosp Med*. 2012;7(3):231-238.

DRUGS FOR CONSTIPATION

Plecanatide

Indicated for chronic idiopathic constipation

Patients who experience persistent constipation for more than 6 months for which there is no apparent explanation (such as intestinal pseudoobstruction or the use of opioids) are diagnosed as having chronic idiopathic constipation (CIC). Typically unresponsive to standard treatments such as laxatives, CIC is more common in women and in those over age 65.[1] Medications with a labeled indication for CIC include lubiprostone and linaclotide.

Plecanatide (*Trulance*, Synergy), a 16 amino acid peptide, is indicated to treat CIC in adults.[2,3] Like linaclotide, plecanatide acts as a guanylate cyclase-C (GC-C) agonist. These drugs and their active metabolites bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C increases both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, resulting in increased intestinal fluid and accelerated transit. A change in stool consistency occurs, and intestinal pain may be reduced.

The effectiveness of plecanatide was demonstrated in two 12-week placebo-controlled studies. The primary endpoint was defined as a patient who had at least three complete spontaneous bowel movements (CSBMs) in a given week and an increase of at least one CSBM from baseline in the same week for at least 9 weeks out of the 12-week treatment period and at least three of the last 4 weeks of the study. In both studies, the responder rate for patients treated with the new drug was 21%, compared with 10% and

13% of the patients receiving placebo. Improvements in the frequency of CSBMs/week were experienced as early as week 1. Patients also experienced improvements in stool frequency and consistency and straining.

As with linaclotide, the labeling for plecanatide includes both a contraindication and a boxed warning regarding the risk of serious dehydration in pediatric patients. Both drugs are contraindicated in patients under age 6 years and should be avoided in patients age 6 through 17 years.

Diarrhea, the most commonly experienced adverse reaction, usually occurred within 4 weeks of initiation of treatment. Severe diarrhea was reported in 0.6% of patients and occurred within the first 3 days of treatment.

Precautions: (1) Contraindicated in children under age 6 and not recommended for patients under age 18 due to risk of severe dehydration. (2) Contraindicated in patients with known or suspected mechanical gastrointestinal obstruction. (3) Treatment should be suspended in patients who experience severe diarrhea and rehydration therapy should be provided as indicated.

Adverse reaction: diarrhea

Supplied as: 3 mg tablets

Dosage: 3 mg once a day

Nursing considerations: (1) Tell patients that plecanatide may be taken without regard to food. (2) Teach patients to swallow tablets whole. For patients with swallowing difficulties, the tablets may be crushed and administered orally either in applesauce or with water, or administered with water via nasogastric or gastric feeding tube. Consult the labeling for specific preparation and administration instructions. (3) Tell patients to stop taking the medication and call their healthcare provider if they develop severe diarrhea. (4) Tablets packaged in bottles of 30 should be dispensed in the original bottle and not repackaged or subdivided. Tell patients not to remove the desiccant from the bottle; however, they should dispose of the polyester coil that was placed in the bottle to protect the medication during shipping. The tablets are also available in unit dose blister packs of 30. The drug should be stored in the original container or package until use and protected from moisture.

REFERENCES

1. Definition & facts for constipation. National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/digestive-diseases/constipation/definition-facts.

2. FDA approves Trulance for chronic idiopathic constipation. Food and Drug Administration. News release. January 19, 2017.

3. Trulance (plecanatide) tablets, for oral use. Prescribing information. https://www.trulancehcp.com.

Naldemedine tosylate

Indicated to treat OIC in adults taking opioids for chronic noncancer pain

Use of opioid analgesics to manage chronic pain often results in opioid-induced constipation (OIC). In some patients, laxatives and stool softeners don't provide an adequate response.

Naldemedine tosylate (*Symproic*, Purdue; Shionogi) is indicated to treat OIC in adults with chronic noncancer pain.[1] A derivative of naltrexone, naldemedine is a peripherally acting mu-opioid receptor antagonist in tissues such as the gastrointestinal (GI) tract. It differs structurally from naltrexone by the addition of a side chain that reduces the ability of the new drug to cross the blood-brain barrier. It's also a substrate of the P-glycoprotein (P-gp) efflux transporter. Based on these properties, the central nervous system penetration of naldemedine is expected to be negligible when it's used in the recommended dosage. This limits its potential for interference with centrally mediated opioid analgesia.

The effectiveness of naldemedine was demonstrated in two placebo-controlled studies in patients with OIC and noncancer-related pain (such as back pain) who'd been treated with an opioid for at least 4 weeks. A responder was defined as a patient who had at least three spontaneous bowel movements (SBMs) per week and a change from baseline of at least one SBM per week for at least 9 out of the 12 study weeks and three out of the last 4 weeks. In the two studies, 48% and 53% of the patients treated with naldemedine experienced an increase in the number of SBMs per week, compared with 35% and 34% of those receiving placebo.

Although naldemedine isn't considered to carry a risk of abuse or dependency, it was initially classified as a Schedule II controlled substance because it's structurally related to agents that do have such a risk. However, the FDA has since descheduled it as a controlled substance.

Precautions: (1) Contraindicated in patients with known or suspected GI obstruction and in patients at increased risk of recurrent obstruction, because of the potential for GI perforation. (2) Use caution in patients with conditions that may impair the integrity of the GI tract wall, such as peptic ulcer disease and Crohn disease; these patients should be monitored for development of severe, persistent, or worsening abdominal pain. (3) Although naldemedine isn't likely to cross the blood-brain barrier, patients with disruptions of this barrier may be at increased risk of opioid withdrawal or reduced analgesia. Monitor these

patients for signs and symptoms related to opioid withdrawal, such as hyperhidrosis, chills, and flushing, which have been experienced by approximately 1% of the patients treated with the new drug. (4) Not recommended for use in patients with severe hepatic impairment because naldemedine hasn't been studied in these patients. (5) Naldemedine is a substrate of P-gp as well as CYP3A, and the concurrent use of a moderate CYP3A inhibitor such as diltiazem or fluconazole, a strong CYP3A inhibitor such as clarithromycin or itraconazole, or a P-gp inhibitor such as amiodarone or cyclosporine, may increase the concentration and risk of adverse reactions; patients should be closely monitored. Conversely, a strong CYP3A inducer such as carbamazepine, rifampin, or St. John's wort, may significantly reduce the concentration and effectiveness of naldemedine and concurrent use should be avoided. (6) The concurrent use of another opioid antagonist should also be avoided because of the increased risk of opioid withdrawal.

Adverse reactions: abdominal pain, diarrhea, nausea, gastroenteritis

Supplied as: tablets in an amount equivalent to 0.2 mg of naldemedine

Dosage: 0.2 mg once a day

Nursing considerations: (1) Tell patients that naldemedine can be taken without regard to food. (2) Instruct patients to notify the healthcare provider if they experience severe or persistent abdominal pain or signs and symptoms of opioid withdrawal, such as flushing, chills, diarrhea, nausea, and vomiting. (3) If treatment with the opioid analgesic is discontinued, naldemedine should also be discontinued.

REFERENCE

1. Symproic (naldemedine) tablets, for oral use. Prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208854s000lbl.pdf.

DRUG FOR ALS

Edaravone

Second treatment approved for this devastating neurodegenerative disease

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig disease, is a progressive, neurodegenerative disease that affects 12,000 to 15,000 Americans, with approximately 5,000 patients diagnosed with the disease each year.[1] It's characterized by the destruction of nerve cells that control voluntary muscles involved in functions such as chewing, swallowing, talking, walking, and breathing. As nerve cell activity declines, the muscles become weaker and paralysis results. Most patients with ALS die from respiratory failure, usually within 3 to 5 years after symptoms first appear.[1]

The only other drug available to treat ALS is riluzole, an oral medication.[2] Although its exact mechanism of action is unknown, it's believed to act by reducing glutamate release and slowing the accumulation of this amino acid in nerve cell synapses.[3,4] It's been shown to prolong survival and/or time to tracheotomy, but it prolongs survival by only 3 months on average.[3]

Edaravone (*Radicava*, Mitsubishi Tanabe) is administered via I.V. infusion.[5] The placebo-controlled clinical trial on which its approval was based was conducted in Japan with 137 patients, of which 69 patients were in the edaravone arm of the study and 68 were in the placebo arm. More than 90% of the patients in each group were being treated with riluzole.

The ALS Functional Rating Scale—Revised (ALSFRS-R) was used to assess the patients in the study. It consists of 12 questions that evaluate the fine motor, gross motor, bulbar, and respiratory function of patients with ALS (speech, salivation, swallowing, handwriting, cutting food, dressing/hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, and respiratory insufficiency). The primary efficacy endpoint was a comparison of the change between treatment arms in the ALSFRS-R total scores from baseline to Week 24.

The decline in these scores from baseline was significantly less in the edaravone-treated patients compared with those in the placebo group. The drug's mechanism of action and whether it prolongs survival aren't yet known.

Precautions: (1) Contraindicated in patients with a history of hypersensitivity to either the medication or any of the inactive ingredients. Hypersensitivity reactions including anaphylaxis have been reported and patients should be monitored closely for such responses. (2) The formulation of edaravone contains sodium bisulfite that may cause serious allergic and asthmatic reactions in susceptible patients, particularly those with asthma.

Adverse reactions: contusion; gait disturbance; headache; dermatitis; eczema; respiratory failure, respiratory disorder, and/or hypoxia

Supplied as: a single-dose polypropylene bag containing 30 mg of the drug in 100 mL of aqueous solution

Dosage: an I.V. infusion of 60 mg as two consecutive 30 mg I.V. infusion bags over a total of 60 minutes (infusion rate approximately 1 mg per minute [3.33 mL per minute]). The initial treatment cycle is 60 mg once a day for 14 days,

followed by a 14-day drug-free period. In subsequent treatment cycles, a 60 mg dose is administered once a day for 10 days out of 14-day periods, followed by 14-day drug-free periods.

Nursing considerations: (1) Protect the drug from light and store it in its overwrapped packaging to protect it from oxygen degradation until the time of use. The oxygen indicator will turn blue or purple if oxygen has exceeded acceptable levels. (2) Administer the drug within 24 hours once the overwrap package is opened. ■

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