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NEW DRUGS

Eluxadoline, Lesinurad, and Idarucizumab

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Agent for irritable bowel syndrome with diarrhea

Irritable bowel syndrome (IBS) is estimated to affect 10% to 15% of adults in the United States. Some patients with IBS experience diarrhea as the most common manifestation (IBS-D), and others experience constipation as the most common manifestation (IBS-C). IBS-D is a functional bowel disorder that is characterized by chronic abdominal pain and frequent diarrhea (loose or watery stools at least 25% of the time). Although loperamide may help to control diarrhea, it does not provide adequate relief of symptoms in many patients. The serotonin subtype 3 receptor antagonist alosetron (e.g., Lotronex) is the only agent that has been available with a labeled indication for the treatment of patients with IBS-D. However, it is indicated only for the treatment of women with severe IBS-D and is available only under the provisions of a risk management program owing to its potential to cause serious gastrointestinal adverse events (e.g., ischemic colitis, serious complications of constipation).

Eluxadoline (Viberzi—Allergan) is a mu-opioid receptor agonist that also acts as an agonist at kappa-opioid receptors and as an antagonist at delta-opioid receptors. It is indicated for the treatment of adult patients with IBS-D. Unlike alosetron, which was evaluated in studies in which a large majority of the patients were women, eluxadoline is indicated for use in men as well as women.

The effectiveness of eluxadoline was demonstrated in 2 placebo-controlled studies that included almost 2500 patients. The new agent was more effective than placebo in simultaneously reducing abdominal pain and improving stool consistency over 26 weeks of treatment. The improvement in stool consistency was experienced by approximately one-third of the patients treated with eluxadoline, and in about 20% of the patients receiving placebo. Although abdominal pain was reduced in 40% to 50% of the patients treated with the new drug, the responder rate was only slightly higher than in the placebo group.

On the same date (May 27, 2015) that eluxadoline was approved, the FDA also approved rifaximin (Xifaxan) for the treatment of adult patients with IBS-D. Rifaximin was already available for the treatment of patients with travelers' diarrhea caused by noninvasive strains of *Escherichia coli* and to reduce the risk of overt hepatic encephalopathy recurrence.

The most frequently reported adverse events in the clinical studies of eluxadoline include constipation (8%), abdominal pain (7%), and nausea (7%). The mu-opioid receptor agonist action of eluxadoline may increase the risk of spasm in the sphincter of Oddi, the smooth muscle that surrounds the end portion of the common bile duct and pancreatic duct. Patients without a gallbladder are at increased risk of this response, and some patients also experienced pancreatitis. Fewer than 1% of the patients in the clinical trials experienced sphincter of Oddi spasm and fewer than 1% experienced pancreatitis. Patients without a gallbladder should be monitored for new or worsening abdominal pain or acute biliary pain with liver or pancreatic enzyme elevations. If such symptoms develop, the use of eluxadoline should be discontinued and medical attention sought.

Eluxadoline is contraindicated in patients with known or suspected biliary duct obstruction or sphincter of Oddi disease, a history of pancreatic disease, or severe hepatic impairment, or in patients who consume large quantities of alcoholic beverages (i.e., alcoholism, alcohol abuse or addiction, or those who drink more than 3 alcoholic beverages a day). The new drug is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction or a history of chronic or severe constipation or sequelae from constipation. Concurrent use with opioid analgesics, anticholinergic agents, or other drugs that may cause constipation should be avoided. Loperamide may be used occasionally for the acute management of severe diarrhea but it should not be used on a continuing basis. Loperamide should be immediately discontinued if constipation occurs.

In 2 abuse-potential studies of eluxadoline in recreational opioid-experienced individuals, euphoria was reported at a rate of 14% to 28%. These data suggest that the drug may produce psychologic dependence, and it is included in Schedule IV under the provisions of the Controlled Substances Act.

The **New Drugs** column informs readers about new chemical and biologic entities approved for marketing by the US Food and Drug Administration. The column is written by Contributing Editor Daniel A. Hussar, PhD, Remington Professor of Pharmacy, Philadelphia College of Pharmacy, University of the Sciences in Philadelphia.

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Eluxadoline has not been studied in pregnant women, and adverse effects on embryo and fetal development have not been observed in animal studies. The effectiveness and safety of eluxadoline in pediatric patients have not been established.

Following oral administration, eluxadoline is absorbed to only a limited extent. Almost all of a dose of the drug is eliminated in the feces. The new drug is a substrate for organic anion-transporter polypeptide (OATP)1B1. If an OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil) is used concurrently, the action of eluxadoline may be increased and the dosage should be reduced. Eluxadoline is an inhibitor of OATP1B1 and breast cancer resistance protein (BCRP), and it may increase the action of drugs such as rosuvastatin (Crestor) that are substrates of these transporters. If used concurrently with eluxadoline, the lowest effective dose of rosuvastatin should be used.

The relationship of eluxadoline and the CYP metabolic pathways has not been clearly established. The concurrent use of a strong CYP inhibitor (e.g., clarithromycin, paroxetine, fluconazole, gemfibrozil, ciprofloxacin) may increase the action of the new drug, and patients should be monitored for possible impairment of mental or physical abilities needed to perform potentially hazardous activities, such as driving. Eluxadoline may increase the action of drugs that are CYP3A substrates and have a narrow therapeutic index (e.g., cyclosporine, fentanyl), and concurrent use should be closely monitored.

The recommended dosage of eluxadoline is 100 mg twice a day with food. The dosage should be reduced to 75 mg twice a day with food in patients who do not have a gallbladder, have mild or moderate hepatic impairment, are concurrently taking an OATP1B1 inhibitor, or who are not able to tolerate the 100 mg dose. Treatment should be discontinued in patients who develop severe constipation for more than 4 days. If a patient misses a dose, the next dose should be taken at the regular time.

Eluxadoline tablets are supplied in 75 mg and 100 mg potencies.

Agent for gout

Hyperuricemia is characterized by elevated concentrations of uric acid in the blood. Uric acid is produced by the breakdown of purines that are found in all tissues in the body. Elevated concentrations of uric acid can occur when there is an increase in the amount of uric acid that is formed, when the kidneys do not excrete enough uric acid, and/or when an individual eats larger quantities of foods that are high in purines. Although most individuals with hyperuricemia do not experience gout, some experience concentrations of uric acid that exceed its solubility, resulting in the precipitation of crystals in the joints and other tissues, inflammation, and acute pain.

Allopurinol has been the standard maintenance treatment for several decades for patients with gout. It acts by inhibiting xanthine oxidase enzymes that catalyze the breakdown of purines to form uric acid. The newer agent febuxostat (Uloric) is also a xanthine oxidase inhibitor that reduces the formation of uric acid. Probenecid is a uricosuric agent that increases the excretion of uric acid in the urine; however, it is seldom used in current therapy for gout, partly owing to the increased possibility of formation of kidney stones. Colchicine and nonsteroidal antiinflammatory drugs (NSAIDs) are used for the treatment of gout flares and for prophylaxis to reduce the frequency of their occurrence.

Lesinurad (Zurampic—AstraZeneca) has been approved for the treatment of patients with gout and has a unique mechanism of action in inhibiting the function of transporter proteins involved in uric acid reabsorption in the kidneys. Uric acid transporter 1 (URAT1) is responsible for the majority of the reabsorption of filtered uric acid from the renal tubular lumen, and organic anion transporter 4 (OAT4) is a uric acid transporter associated with diuretic-induced hyperuricemia. Lesinurad inhibits the action of URAT1 and OAT4, thereby increasing renal clearance and excretion of uric acid, and reducing serum uric acid concentrations.

Lesinurad is specifically indicated in combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid concentrations with a xanthine oxidase inhibitor alone. The new drug was evaluated in combination with a xanthine oxidase inhibitor in 3 placebo-controlled studies involving more than 1500 participants. The studies were of 12 months' duration and patients received prophylaxis for gout flares with colchicine or an NSAID during the first 5 months of lesinurad treatment. Studies 1 and 2 included patients who were on a stable daily dose of allopurinol of at least 300 mg (or 200 mg in patients with moderate renal impairment), had a serum uric acid concentration greater than 6.5 mg/dL, and had reported at least 2 gout flares in the preceding 12 months. The combination of allopurinol and lesinurad (200 mg once a day) lowered serum uric acid to the target concentration of less than 6 mg/dL in approximately 55% of patients at 6 months, compared with approximately 25% of patients receiving allopurinol plus placebo. In study 3, lesinurad was used in combination with febuxostat, and the average decrease in serum uric acid concentrations was similar to that reported in studies 1 and 2.

Lesinurad is not recommended for the treatment of patients with asymptomatic hyperuricemia, or in patients taking daily doses of allopurinol of less that 300mg (or less than 200 mg in patients with an estimated creatinine clearance of less than 60 mL/min).

The adverse events that were reported most often in the clinical studies that can be considered to be attributable to the addition of lesinurad to the xanthine oxidase inhibitor include headache (5%), influenza (5%), and gastroesophageal reflux disease (3%). The use of lesinurad resulted in increased serum creatinine concentrations in 4% of patients, and a small number of patients experienced nephrolithiasis and renal failure. The risk of acute renal failure is the subject of a boxed warning in its labeling. A higher incidence of renal adverse events has been observed in patients who were treated with lesinurad as monotherapy and in patients treated with a daily dose of the drug of 400 mg. Accordingly, lesinurad should be used with a xanthine oxidase inhibitor and not as monotherapy, and the daily dosage should not exceed 200 mg. Treatment should not be initiated in patients with an estimated creatinine clearance of less than 45 mL/min. Renal function should be monitored periodically during treatment, and more frequently in patients with a creatinine clearance of less than 60 mL/min or with serum creatinine elevations 1.5 to 2