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Eluxadoline (Viberzi®): A Novel Agent for the Treatment of Irritable Bowel Syndrome with Diarrhea (IBS-D)

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Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by abdominal pain or discomfort and is associated with defecation or a change in bowel habits. According to a systematic review done in 2011, the pooled global prevalence of IBS is 11.2%.[1] Women are affected more often than men, with pooled prevalences of 14% and 8.9%, respectively, for women and men. According to Rome III Diagnostic Criteria for Functional Gastrointestinal Disorders, IBS is defined as recurrent abdominal pain or discomfort for at least 3 days per month for the past 3 months, and associated with two or more of the following: improvement with defecation; onset associated with a change in frequency of stool; and onset associated with a change in form (appearance) of stool.[2] IBS can be a chronic disorder and may significantly reduce a patient's quality of life. IBS places a large financial load on society, due to decreased work productivity and increased use of healthcare resources.[4,5] Patients with IBS experience chronic pain syndromes, anxiety, and depression at a higher rate than patients without IBS.[6]

IBS is categorized as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and mixed IBS (IBS-M). The treatment of IBS-D in the past has mainly consisted of nonpharmacologic (diet and lifestyle modifications) and pharmacologic (loperamide, alosetron, peppermint oil, antidepressants, pro/prebiotics, and various antibiotics) approaches with varying degrees of success.[3] **Table 1** summarizes the available treatment options, their current place in therapy, and relative costs to patients. In May 2015, a new agent, eluxadoline (Viberzi™), was granted an FDA-approved indication for the treatment of IBS-D.[7] The purpose of this article is to review the use of eluxadoline for the treatment of IBS-D, including a review of the pharmacology, clinical trials, adverse effects, dosing, interactions, costs, and abuse potential of eluxadoline.

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Mechanism of Action

Eluxadoline is a mu-opioid receptor agonist, delta-opioid receptor antagonist, and kappa-opioid receptor agonist.[7] Mu-, delta-, and kappa- opioid receptors are expressed throughout the gastrointestinal (GI) tract and are important for the regulation of motility and secretion.[8] Activation of the mu opioid receptor reduces GI motility, visceral sensation, and secretions.[9] Inhibition of the delta opioid receptor, theoretically, will counteract the inhibitory effects of unopposed mu-opioid agonism on the GI tract. Eluxadoline varies from traditional opioids as it is not absorbed systemically to a clinically significant extent, therefore its actions are mainly limited to the GI tract.

Pharmacokinetics

Eluxadoline follows approximately linear pharmacokinetics with no accumulation upon repeated twice daily dosing.[7] The absolute bioavailability of eluxadoline has not been determined. High fat meals (50% of calories coming from fat content) decrease the peak serum concentration by 50% and AUC (area under the curve, in a plot of drug plasma concentration versus time) by 60%. The median time to peak concentration is 1.5 hours under fed conditions, and 2 hours under fasting conditions. Eluxadoline is 81% protein plasma bound. The metabolism of eluxadoline has not been clearly established. Evidence suggests that glucuronidation can occur to form an acyl glucuronide metabolite. The mean plasma elimination half-life of eluxadoline ranges from 3.7 hours to 6 hours. In healthy male subjects given a single 300-mg oral dose of eluxadoline, 82.2% of the total radioactivity was recovered in feces within 336 hours and <1% was recovered in urine within 192 hours.

Clinical Trials

To date, two phase III randomized controlled trials have been conducted on eluxadoline.[10] The IBS-3002 trial lasted for 26 weeks, whereas the IBS-3001 trial lasted for 52 weeks. The results of these trials were published as a pooled analysis. Inclusion criteria were identical for both trials, which included patients aged 18 to 80 years, who had a diagnosis of IBS with diarrhea (as per Rome III diagnostic criteria for IBS). Moreover, during the first week before randomization, patients had to score an average of 3 (on a scale of 0-10, with 0 being no pain and 10 being the worst imaginable pain) for their worst abdominal pain. Additionally, patients had to score an average of 5.5 or more on the Bristol Stool Form scale (which ranges from 1 indicating hard stool and 7 indicating watery diarrhea), a score of 5 or more on the Bristol Stool Form scale for at least 5 days, and an average IBS-D global symptom score of 2.0 or more (on a scale of 0 to 4, with 0 indicating no symptoms of IBS with diarrhea). Exclusion criteria includ-

Table 1 | Available treatments for IBS-D.[3]

Treatment	Pros	Cons	Cost
Dietary interventions	Certain dietary factors may play a role with symptoms	Diets are very stringent and difficult to follow	Variable
Probiotics	May improve diarrhea, bloating, and pain	Many OTC probiotics have not been tested	High
Rifaximin	Minimally absorbed antibiotic approved by FDA for IBS-D	Antibiotic resistance of GI flora, long-term efficacy uncertain.	High
Peppermint oil	Superior to placebo in reducing IBS-D symptoms	Dyspepsia is a common side effect	Low
Loperamide	Improvement in diarrhea symptoms	Does not improve abdominal pain or bloating	Low
Antidepressants (TCA's and SSRI's)	May improve symptoms in some IBS-D patients	Both TCA and SSRI associated with adverse events with a NNH of 9	SSRIs can be costly, TCAs relatively inexpensive
Alosetron (females only)	Improvement in diarrhea, abdominal pain, and urgency	Only approved for women who have failed standard therapy; concerns regarding ischemic colitis	Expensive and not freely available

OTC = Over-the-counter; **IBS-D =** Irritable bowel syndrome with diarrhea; **FDA =** Food drug and administration; **TCA =** Tricyclic antidepressant; **SSRI =** Selective serotonin reuptake inhibitor; **NNH =** Number needed to harm

ed a history of inflammatory bowel disease or celiac disease, abnormal thyroid function, a history of abuse or binge drinking, pancreatitis, sphincter of Oddi dysfunction, post-cholecystectomy biliary pain, cholecystitis within the past 6 months, a known allergy to opioids, ongoing pregnancy or breast-feeding, or current use of antidiarrheal, antispasmodic, or narcotic drugs. Patients currently on antidepressants were eligible to be participants if they had been stable for ≥12 weeks prior to enrollment.

In both trials combined, 2425 patients were randomly assigned in equal portions to receive eluxadoline 75 mg, eluxadoline 100 mg, or placebo, each administered twice daily. Patients completed daily assessments during treatment on the following: symptoms (on a scale of 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms), stool consistency score, the number of bowel movements and whether they were associated with urgency or fecal incontinence, and the IBS-D global symptom score. Loperamide, administered at a 2-mg dose every 6 hours (maximum 4 doses in 24 hours) was allowed as rescue medication as needed.

The primary efficacy end point was the proportion of patients who had a composite response, which was defined as a reduction ≥30% from baseline in the daily average score for their worst abdominal pain for ≥50% of the days assessed and, on those same days, a stool-consistency score of <5. Secondary end points included pain relief (≥30% from baseline on ≥50% of the days), improvement in stool consistency, improvement in global symptom score, and adequate relief of IBS symptoms, as well as a change from baseline in the IBS-QOL questionnaire score.

At baseline, participants were an average age of 46 years and had a BMI of 30 kg/m^2. About 65% of participants were women and 86% were White. The proportion of patients in the IBS-3002 trial who were considered to have a response from weeks 1 through 26 was significantly greater at a dose of eluxadoline 75 mg (30.4%) or 100 mg (32.7%) twice daily than among those who received placebo (20.2%, p≤0.001 for both comparisons). The number needed to treat for weeks 1 to 26 was 14 for the 75-mg arm and 9 for the 100-mg arm. The effect of treatment with eluxadoline was observed within the first week and maintained throughout the 26-week assessment period. When the results from IBS-3001 and IBS-3002 were pooled together, both doses of eluxadoline (75 mg and 100 mg) were significantly better than placebo in raw scores at week 12 for stool consistency, frequency, bloating (100 mg dose only), global symptoms and IBS-QOL questionnaire (Table 2).

Adverse Effects

The most frequently occurring adverse effects were constipation, nausea, and abdominal pain (Table 3).[10] Additional concerning adverse effects included sphincter of Oddi spasm, which occurred in 0.2% of individuals receiving eluxadoline 75 mg twice daily and in 0.8% of individuals receiving eluxadoline 100 mg twice daily, and pancreatitis, which occurred in 0.2% of individuals receiving eluxadoline 75 mg twice daily and 0.3% of individuals receiving 100 mg eluxadoline twice daily.[10] Of note, sphincter of Oddi spasms occurred within the first week of treatment in most cases. Patients without a gallbladder are at an increased risk of sphincter of Oddi spasm, therefore clinicians should consider alternative therapies before using eluxadoline in patients without a gallbladder. The majority of cases of pancreatitis were associated with excessive alcohol intake. It may be prudent for clinicians to counsel patients to avoid chronic or excessive acute alcohol consumption while taking eluxadoline.

Dosing and Administration

The standard dose of eluxadoline is 100 mg twice daily, administered with food.[7] An adjusted dose of 75 mg twice daily, taken with food, is recommended for patients who do not have a gallbladder, are unable to tolerate the 100 mg twice daily dose, are receiving concomitant OATP1B1 inhibitors (e.g., cyclosporine, gemfibrozil, antiretrovirals, rifampin), or have mild or moderate (Child-Pugh Class A or B) hepatic impairment. In the event of a missed dose of eluxadoline, patients should be counseled to take

Table 2 | Raw scores for secondary efficacy parameters at week 12 from the IBS-3001 and 3002 trials.[10]

End Point	Placebo (N=809)	Eluxadoline 100 mg twice daily (N=806)	p-value[a]	Eluxadoline 75 mg twice daily (N=808)	p-value[a]
Abdominal pain	3.53	3.23	P<0.001	3.01	P=0.06
Stool consistency	4.99	4.62	P<0.001	4.68	P<0.001
Frequency	3.30	2.96	P<0.001	3.01	P=0.002
Bloating	3.21	3.25	P=0.003	3.47	P=0.10
Global symptoms	1.69	1.46	P<0.001	1.52	P=0.008
IBS-QOL questionnaire	63.9	70.0	P<0.001	70.1	P<0.001

[a]For the comparison to placebo

the next dose at their regular time. Eluxadoline should be discontinued in patients who develop severe constipation for more than 4 days.

Eluxadoline has not been studied in pregnant women; however, animal studies on rats, using doses approximately 51 and 115 times the respective human exposure, demonstrated no teratogenic effects.[7] Eluxadoline is present in rat milk, but data are lacking on eluxadoline excretion in human milk. Safety and effectiveness in pediatric populations have not been established. Only a small percentage of patients (7.7%) studied in clinical trials were aged >65 years; however, no overall differences were observed in the types of adverse reactions observed between elderly and younger patients. Eluxadoline is contraindicated in severe hepatic impairment (Child-Pugh Class C), as plasma concentrations of eluxadoline are increased 16-fold.

Drug Interactions

The metabolism of eluxadoline via CYP pathways has not been clearly established.[7] Additionally, the potential inhibition of CYP3A4 in the gut due to eluxadoline has not been evaluated. Clinically important drug interactions with eluxadoline are summarized in Table 4.

DEA Scheduling & Abuse Potential

The Drug Enforcement Administration (DEA) placed eluxadoline as a Schedule IV medication, in part because of concerns over the relative potential for abusing eluxadoline.[11] Eluxadoline may be related to pentazocine and butorphanol as they are pharmacologically all kappa opioid agonists. Both pentazocine and butorphanol are listed as Schedule IV medications, and have potential for abuse.

In two human abuse potential studies performed in recreational opioid-experienced individuals, supratherapeutic oral doses of eluxadoline (300 mg and 1000 mg) and intranasal doses (100 mg and 200mg) produced euphoria (rates of 14% to 28%) that was greater than placebo (rate of 0% to 5%) but less than that of oxycodone (rate of 44% to 76%).[7] Supratherapeutic oral and intranasal doses of eluxadoline also produced small, but potentially significant increases in positive subjective measures, such as "drug liking" and "feeling high" compared to placebo. Additionally, these doses of eluxadoline produces small, but potentially significant increases on negative subjective measures of "drug disliking" and "dysphoria" compared to placebo. In these same studies, oxycodone (30 mg and 60 mg oral, and 15 and 30 mg intranasal) produced significantly greater responses on the positive and negative subjective measures than those produced by eluxadoline and placebo. More data on eluxadoline are needed to fully assess the potential for abuse.

Costs

The cash price for a 30-day supply of eluxadoline is estimated to be $1127.47 on the basis of an average of 3 different pharmacy quotes. Eluxadoline is not on the formulary for any governmental programs, including Medicare or Medicaid, which may make it difficult for some patient populations to afford their medicine. The manufacturer of eluxadoline has offered a savings program in which certain individuals can register for. The savings program

Table 3 | Adverse effects of eluxadoline in phase 3 clinical trials.[10]

Adverse Reactions	Eluxadoline 100 mg twice daily (N=859)	Eluxadoline 75 mg twice daily (N=807)	Placebo (N=808)
Constipation	8.6	7.4	2.5
Nausea	7.5	8.1	5.1
Abdominal pain[a]	7.2	5.8	4.1
URTI	5.5	3.3	4.0
Vomiting	4.2	4.0	1.4
Dizziness	3.3	2.6	2.1
Nasopharyngitis	2.7	4.1	3.3
Abdominal Distention	2.6	2.6	1.6
Bronchitis	3.1	3.2	2.2
Flatulence	3.1	2.6	1.6
Increased ALT	3.0	2.1	1.5
Sinusitis	2.8	3.3	3.2
Viral gastroenteritis	2.2	4.5	3.3

[a]includes abdominal pain, abdominal pain lower, and abdominal pain upper.
Data are presented as %. **ALT =** alanine transaminase; **URTI =** upper respiratory tract infection.

Table 4 | Clinically relevant interactions affecting eluxadoline.[7]

OATP1B1 Inhibitors	
Clinical Impact	Increased exposure to eluxadoline when coadministered with OATP1B1 inhibitors
Intervention	Administer eluxadoline at a dose of 75 mg twice daily and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities and for other eluxadoline-related adverse reactions
Examples	Cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir,ritonavir, saquinavir, tipranavir), rifampin, eltrombopag
Strong CYP Inhibitors[a]	
Clinical Impact	Potential for increased exposure to eluxadoline
Intervention	Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities and for other eluxadoline-related adverse reactions
Examples	Ciprofloxacin (CYP1A2), gemfibrozil (CYP2C8), fluconazole (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion (CYP2D6)
Drugs that Cause Constipation	
Clinical Impact	Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions
Intervention	Avoid use with other drugs that may cause constipation; loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs
Examples	Alosetron, anticholinergics, opioids
OATP1B1 and BCRP Substrate	
Clinical Impact	Eluxadoline may increase the exposure of co-administered OATP1B1 and BCRP substrates. Increased exposure to rosuvastatin when co-administered with eluxadoline with a potential for increased risk of myopathy/rhabdomyolysis
Intervention	Use the lowest effective dose of rosuvastatin
Examples	Atorvastatin, ezetimibe, fexofenadine, fluvastatin, methotrexate, olmesartan, pitavastatin, pravastatin, rifampicin, valsartan
CYP3A4 Substrates with Narrow Therapeutic Index	
Clinical Impact	Potential for increased exposure of co-administered drug
Intervention	Monitor drug concentrations or other pharamcodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued.
Examples	Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

[a]As a precautionary measure due to incomplete information on the metabolism of eluxadoline.
CYP = cytochrome P450; **OATP =** organic anion-transporting polypeptide

allows eligible patients to pay $0 for their first 30-day prescription, and as little as $30 for each 30-day refill (up to 13 fills).

Summary

Eluxadoline is a mu- and kappa-opioid receptor agonist, and delta-opioid antagonist indicated for the treatment of IBS-D. Eluxadoline is effective in improving symptoms of IBS-D, including decrease in stool frequency and urgency, as well as improvement in average abdominal pain. The recommended dosage in adults is 100 mg twice daily taken with food. Eluxadoline has low bioavailability following oral administration, resulting in the majority of its actions occurring in the digestive tract. The most common adverse effects of eluxadoline in phase 3 clinical trials were constipation, nausea, and abdominal pain. Eluxadoline carries absolute contraindications for alcoholism, biliary obstruction, constipation, GI obstruction, and pancreatitis. Patients should discontinue eluxadoline if severe constipation occurs for more than 4 days. Eluxadoline is a Schedule IV medication and may have a potential for abuse. The high cost of eluxadoline may prohibit patients from being able to obtain the medication. More studies are needed to fully assess the place in therapy for eluxadoline relative to other available IBS-D treatments.

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Editor's Corner

Liraglutide May Reduce Cardiovascular Outcomes in Type 2 Diabetes

A recent study published in the *New England Journal of Medicine* investigated the long-term effects of liraglutide, an analogue of human glucagon-like peptide 1 (GLP-1), on cardiovascular (CV) outcomes in patients with type 2 diabetes.[1]

The study included adult patients with type 2 diabetes with HbA1c ≥7% who were at high risk for CV disease. Patients aged between 50 and 59 years were required to have at least one CV coexisting condition, which included coronary heart disease, cerebrovascular disease, or chronic heart failure; while patients aged 60 year or older had to have at least one CV risk factor (i.e., hypertension and left ventricular hypertrophy, proteinuria, left ventricular systolic dysfunction). Nine-thousand three-hundred forty patients were randomized to receive either 1.8 mg of liraglutide or matching placebo once daily administered as a subcutaneous injection. Primary composite outcome was the first occurrence of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.

At study end, the incidence of the primary composite outcome occurred significantly less in the liraglutide group compared to the placebo group (13% vs 14.9%; HR 0.87, p=0.01 for superiority). Liraglutide also resulted in significantly lower rates of nephropathy, death from CV causes, and all-cause mortality. Serious adverse events occurred at similar rates in both groups; however, adverse events that led to the discontinuation of treatment drugs were more common with liraglutide, which was largely driven by gastrointestinal side effects.

The results of this study provides insight into the potential CV benefits of GLP-1 agonists in patients with type 2 diabetes at high risk for CV disease, and appear to be at odds with a previous trial investigating the CV outcomes of lixisenatide, another GLP-1 agonist. This trial failed to show any significant CV benefit in patients with diabetes and recent acute coronary syndrome,[2] however, between-group differences in baseline characteristics among study populations may have contributed to the contrasting results between the two trials.[3] Nevertheless, it remains to be seen whether the CV benefits pertain to a select individual drug or a class effect. Studies with exenatide (EXSCEL) and dulaglutide (REWIND) are currently underway and may offer additional information regarding the impact of GLP-1 agonists on CV outcomes.

This study also adds to the growing list of evidence showing positive benefits on CV outcomes with antihyperglycemic agents. Previously, empagliflozin, an SGLT-2 inhibitor, was found to decrease CV morbidity and mortality in patients with type 2 diabetes.[4] As additional trials with other antihyperglycemic agents begin to wrap up, the final results from these trials should help shed further light on the impact of antihyperglycemic agents on preventing macrovascular complications in patients with type 2 diabetes.

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