

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

Pr **VIBERZI**<sup>®</sup>

eluxadoline

75 mg and 100 mg tablets

ATC Code: A07DA06

$\mu$  opioid receptor agonist /  $\delta$  opioid receptor antagonist

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**PrVIBERZI®**

(eluxadoline)

75 mg and 100 mg tablets

**PART I: HEALTH PROFESSIONAL INFORMATION**

**SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Oral	Tablet 75 mg and 100 mg	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

**INDICATIONS AND CLINICAL USE**

VIBERZI (eluxadoline) is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

In clinical trials VIBERZI improved abnormal stool consistency more prominently than abdominal pain.

**Geriatrics (> 65 years of age):**

VIBERZI was not studied in patients 65 years and older in a specifically dedicated study. In the pivotal trials, 8% of patients were 65 years and older, and a higher proportion of elderly patients than younger patients experienced adverse reactions (see WARNINGS AND PRECAUTIONS, Special Populations, and DOSAGE AND ADMINISTRATION, Recommended Dose and Dose Adjustment).

**Pediatrics (< 18 years of age):**

Safety and effectiveness of VIBERZI in pediatric patients have not been established therefore use in children is not recommended.

## CONTRAINDICATIONS

VIBERZI is contraindicated in patients with:

- Hypersensitivity to eluxadoline or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.
- Known or suspected biliary duct obstruction; or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm.
- Patients without a Gallbladder. These patients are at increased risk for pancreatitis and/or sphincter of Oddi spasm.
- Alcoholism, alcohol abuse or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day. These patients are at increased risk for acute pancreatitis.
- A history of pancreatitis; or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis.
- Hepatic impairment (Child-Pugh Class A, B, and C). These patients are at risk for significantly increased plasma concentrations of eluxadoline
- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.
- Patients on concomitant treatment with potent inhibitors of OATP1B1 (e.g. cyclosporine) (See Drug-drug Interactions).

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

**Pancreatitis – Serious cases of pancreatitis have been reported in patients taking VIBERZI, primarily in patients without a gallbladder (See WARNINGS AND PRECAUTIONS – Pancreatitis).**

**VIBERZI is contraindicated in patients without a gallbladder (See CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).**

## **Hepatic/Biliary/Pancreatic**

### **Pancreatitis**

Pancreatitis, with or without sphincter of Oddi spasm, including serious cases resulting in hospitalization, have been reported in patients taking either the 75 mg or 100 mg dosage of VIBERZI, primarily in patients without a gallbladder. Fatal cases have also been reported in patients without a gallbladder. VIBERZI is contraindicated in patients without a gallbladder (see CONTRAINDICATIONS). Most of the reported cases of serious pancreatitis occurred within a week of starting treatment with VIBERZI and some developed symptoms after one or two doses.

In patients with a gallbladder, evaluate a patient's alcohol intake prior to starting VIBERZI. Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for signs and symptoms of pancreatitis. Instruct patients to stop VIBERZI immediately and seek medical attention if they experience symptoms suggestive of pancreatitis such as new or worsening acute abdominal or epigastric pain radiating to the back or shoulder, with or without nausea and vomiting (see CONTRAINDICATIONS).

### **Sphincter of Oddi Spasm**

There is a risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (e.g., biliary-type pain) in patients taking VIBERZI, especially in patients without a gallbladder.

Postmarketing serious adverse reactions of sphincter of Oddi spasm with or without pancreatitis resulting in hospitalization have been reported, primarily in patients without a gallbladder. Most of the reported cases of sphincter of Oddi spasm occurred within a week of starting treatment with VIBERZI and some developed symptoms after one or two doses. VIBERZI is contraindicated in patients without a gallbladder. Patients with known or suspected sphincter of Oddi disease or dysfunction and/or biliary tract or pancreatic disease, including a history of pancreatitis, must not receive VIBERZI (see CONTRAINDICATIONS).

Instruct patients to stop VIBERZI immediately and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain, (e.g. acute epigastric or biliary [i.e., right upper quadrant] pain), that may radiate to the back or shoulder with or without nausea and vomiting. Do not restart VIBERZI in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking VIBERZI (see CONTRAINDICATIONS).

### **Constipation**

Constipation, sometimes requiring hospitalization, has been reported following VIBERZI administration, sometimes after one or two doses. In postmarketing experience, severe cases with development of intestinal obstruction, ileus, fecal impaction and ischemic colitis, including rectal hemorrhage, requiring intervention, have also been reported. Instruct patients to stop VIBERZI and immediately contact their healthcare provider if they experience symptoms suggestive of severe constipation, which may present with an abrupt onset of abdominal pain, nausea,

vomiting, and abdominal distention. Avoid use with other drugs that may cause constipation [see DRUG INTERACTIONS].

### **Hepatic Impaired Subjects:**

Compared to subjects with normal liver function, hepatic impaired subjects (Child-Pugh Class A, B or C) have a marked increase in eluxadoline systemic exposure and in terminal elimination half-life ( $t_{1/2}$ ) (from 4.4 hours up to 22 hours) after oral administration of VIBERZI. The risk of adverse reactions may be significantly increased (see Specific Populations in DETAILED PHARMACOLOGY). Therefore, VIBERZI is contraindicated in hepatic impaired subjects (see CONTRAINDICATIONS).

### **Drug Abuse**

In the two human abuse potential studies, euphoria was reported to be 3- to 5-fold higher than placebo in non-dependent, recreational opioid users treated with single oral doses of 100 mg to 1000 mg; and was higher than placebo (0%) with intranasal doses of 100 mg (21.9%) and 200 mg (18.8%). Therefore, eluxadoline can produce psychological dependence (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics).

### **Dependence/Tolerance**

In a 52-week clinical study, no evidence of physical dependence or withdrawal from VIBERZI was detected based on adverse event reporting or administration of the subjective opiate withdrawal scale (SOWS). Animal data suggest that potential for intravenous abuse in humans cannot be ruled out (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacodynamics).

### **Hypersensitivity Reactions**

In post-marketing experience, serious hypersensitivity reactions (including anaphylaxis) have been reported following VIBERZI administration. Some of these reactions occurred after the first one or two doses of VIBERZI (see ADVERSE REACTIONS). Instruct patients to immediately stop VIBERZI and seek medical attention if they experience symptoms suggestive of a hypersensitivity reaction (see CONTRAINDICATIONS).

## **Special Populations**

**Pregnant Women:** Eluxadoline was not studied in pregnant women, therefore, VIBERZI should not be used during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see TOXICOLOGY).

**Nursing Women:** Eluxadoline was not studied in nursing women; therefore, VIBERZI should not be used in nursing women. It is not known whether eluxadoline is excreted in human milk; however, in animal studies eluxadoline was excreted in the milk of lactating rats after oral administration (See TOXICOLOGY - Reproductive and Developmental Toxicity).

**Pediatrics (<18 years of age):** VIBERZI is not recommended for use in children under 18 years of age as safety and effectiveness of VIBERZI in pediatric patients have not been established.

**Geriatrics (> 65 years of age):** Of 1795 IBS-D patients in clinical studies of VIBERZI who received 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old. There were no overall differences in the types of adverse reactions observed between elderly and younger patients; however, a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs 59%), serious adverse reactions (9% vs 4%), and gastrointestinal adverse reactions (39% vs 28%). Therefore, for patients 65 years or older, the VIBERZI dose should be 75 mg twice daily (see DOSAGE & ADMINISTRATION - Recommended Dose and Dosage Adjustment).

### **Monitoring and Laboratory Tests**

No initial testing or routine monitoring is required.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Exposure in placebo-controlled clinical trials in adult patients with IBS-D included 1032 patients exposed to 100 mg BID (505 for 6 months, and 243 for 1 year), and 807 patients exposed to 75 mg BID (496 for 6 months, and 245 for 1 year). In the Phase 3 trials, the proportion of patients treated with 100 mg VIBERZI who reported mild, moderate, and severe adverse events were 24%, 25% and 10%, respectively.

The most common adverse reactions (incidence of >5%) reported were constipation, nausea and abdominal pain.

Serious adverse events were reported, in 4.2% of patients treated with 75 mg, 4.0% of patients treated with 100 mg VIBERZI, and 2.6% of patients treated with placebo. There were no serious adverse events of constipation. Serious adverse reactions of pancreatitis and sphincter of Oddi spasm may occur uncommonly (less than 1% of patients).

Approximately 8.3% of patients treated with 75 mg, 7.8% of patients treated with 100 mg VIBERZI and 4.3% of patients treated with placebo discontinued prematurely due to adverse reactions. In the VIBERZI treatment groups, the most common reasons for discontinuation due to adverse reactions were constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg). In comparison, less than 1% of patients in the placebo group withdrew due to constipation or abdominal pain.

### Clinical Trial Adverse Drug Reactions

*Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The data below describes adverse events that occurred in the 3 double-blind, placebo-controlled clinical trials involving over 1700 adult patients with IBS-D treated with 75 mg or 100 mg of VIBERZI twice daily for up to 52 weeks in one phase 3 study, up to 26 weeks in another phase 3 study, and up to 12 weeks in a phase 2 study (See Table 1).

**Table 1 - Adverse Reactions Occurring in  $\geq 1\%$  of VIBERZI-Treated Patients and at an incidence greater in Placebo-treated patients in Pooled Placebo-Controlled Studies in IBS-D**

	VIBERZI 75 mg BID n=807 (%)	VIBERZI 100 mg BID n = 1032 (%)	Placebo BID n = 975 (%)
<b>Number of Subjects With at Least One Adverse Event</b>	486 (60.2)	575 (55.7)	533 (54.7)
<b>Gastrointestinal disorders</b>			
Constipation	60 (7.4)	84 (8.1)	24 (2.5)
Nausea	65 (8.1)	73 (7.1)	49 (5.0)
Abdominal Pain*	45 (5.6)	68 (6.6)	38 (3.9)
Vomiting	32 (4.0)	43 (4.2)	12 (1.2)
Gastroesophageal reflux disease**	24 (3.0)	33 (3.2)	21 (2.2)
Abdominal distension	21 (2.6)	28 (2.7)	15 (1.5)
Flatulence	21 (2.6)	33 (3.2)	17 (1.7)
Dry mouth	15 (1.9)	13 (1.3)	15 (1.5)
Diarrhea	14 (1.7)	13 (1.3)	10 (1.0)
<b>Infections and Infestations</b>			
Upper respiratory tract infection	27 (3.3)	53 (5.1)	38 (3.9)
Nasopharyngitis	33 (4.1)	31 (3.0)	33 (3.4)
Bronchitis	26 (3.2)	30 (2.9)	21 (2.2)
Urinary tract infection	17 (2.1)	18 (1.7)	17 (1.7)
Gastroenteritis viral	22 (2.7)	14 (1.4)	18 (1.8)
Gastroenteritis	14 (1.7)	10 (1.0)	13 (1.3)



**Table 1 - Adverse Reactions Occurring in  $\geq 1\%$  of VIBERZI-Treated Patients and at an incidence greater in Placebo-treated patients in Pooled Placebo-Controlled Studies in IBS-D**

	<b>VIBERZI 75 mg BID n=807 (%)</b>	<b>VIBERZI 100 mg BID n = 1032 (%)</b>	<b>Placebo BID n = 975 (%)</b>
<b>Nervous System Disorders</b>			
Dizziness	21 (2.6)	33 (3.2)	21 (2.2)
Somnolence	1 (0.1)	11 (1.1)	3 (0.3)
Migraine	10 (1.2)	1 (0.1)	11 (1.1)
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Arthralgia	12 (1.5)	14 (1.4)	13 (1.3)
<b>Investigations</b>			
Alanine aminotransferase (ALT) increased	17 (2.1)	26 (2.5)	14 (1.4)
Aspartate aminotransferase (AST) increased	13 (1.6)	15 (1.5)	9 (0.9)
<b>General Disorders</b>			
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
<b>Injury, Poisoning and Procedural Complications</b>			
Contusion	11 (1.4)	9 (0.9)	8 (0.8)
Fall	13 (1.6)	9 (0.9)	4 (0.4)
Joint sprain	7 (0.9)	11 (1.1)	6 (0.6)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			
Pharyngolaryngeal Pain	12 (1.5)	11 (1.1)	10 (1.0)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Rash***	22 (2.7)	28 (2.7)	15 (1.5)
<b>Psychiatric Disorders</b>			
Anxiety	10 (1.2)	20 (1.9)	17 (1.7)
Depression	9 (1.1)	12 (1.2)	11 (1.1)
<b>Vascular Disorders</b>			
Hypertension	20 (2.5)	14 (1.4)	16 (1.6)

\* Abdominal pain term includes: abdominal pain, abdominal pain lower and abdominal pain upper

\*\* Gastroesophageal reflux disease term includes: gastroesophageal reflux disease, dyspepsia, and gastritis. AE incidence for gastritis was 0.1%, 1.0% and 0.1% for 75 mg, 100 mg and placebo respectively.

\*\*\* Rash term includes: dermatitis, dermatitis allergic, rash, rash erythematous, rash generalized, rash maculopapular, rash papular, rash pruritic, urticaria and idiopathic urticaria

Constipation was the most commonly reported adverse reaction in VIBERZI -treated patients. The majority of constipation events occurred within the first 3 months of therapy with approximately 50% of occurring within the first 2 weeks of treatment. Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg VIBERZI. A total of

1.5% of patients with 100 mg BID, 1.1% with 75 mg BID, and 0.3% with placebo discontinued the study/treatment due to constipation.

#### *Sphincter of Oddi Spasm*

In clinical trials, sphincter of Oddi spasm occurred in 0.2% (2/807) of patients receiving 75 mg and 0.8% (8/1032) of patients receiving 100 mg VIBERZI twice daily vs 0% in patients receiving placebo.

- Among patients receiving 75 mg, 1/807 (0.1%) patient experienced sphincter of Oddi spasm presenting with abdominal pain but with lipase elevation less than 3 times the upper limit of normal (ULN) and 1/ 807 (0.1%) patient experienced sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain
- Among patients receiving 100 mg, 1/1032 (0.1%) patient experienced sphincter of Oddi spasm manifested as pancreatitis and 7/1032 (0.7%) patients experienced sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain

Of those patients who experienced sphincter of Oddi spasm, 80% (8/10) reported their initial onset of symptoms within the first week of treatment. The case of sphincter of Oddi spasm-induced pancreatitis occurred within minutes of taking the first dose of VIBERZI and resolved within 24 hours of discontinuation. No cases of sphincter of Oddi spasm occurred greater than 1 month after treatment onset. All events resolved upon discontinuation of VIBERZI, with symptoms typically improved the following day.

#### *Pancreatitis*

Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in 2/807 (0.2%) of patients receiving 75 mg and 3/1032 (0.3%) of patients receiving 100 mg VIBERZI twice daily in clinical trials vs 0% in patients receiving placebo. Of these 5 cases, 3 were associated with excessive alcohol intake, one was associated with biliary sludge, and in one case the patient discontinued VIBERZI 2 weeks prior to onset of symptoms. All pancreatic events resolved with lipase normalization upon discontinuation of VIBERZI, with 80% (4/5) resolving within 1 week of treatment discontinuation.

#### **Less Common Clinical Trial Adverse Drug Reactions (<1%)**

Adverse reactions that were reported in less than 1% of patients with IBS-D are listed below by body system.

**General Disorders and administration site conditions:** Feeling drunk

**Nervous System:** Sedation

**Psychiatric Disorders:** Euphoric mood

**Respiratory:** Asthma, bronchospasm, respiratory failure, wheezing

#### **Abnormal Hematologic and Clinical Chemistry Findings**

In clinical trials of VIBERZI, sporadic elevations of liver enzymes were seen in both the eluxadoline and placebo arms.

In a placebo- and positive-controlled study in healthy adult subjects, eluxadoline administered in single doses of 100 and 1000 mg did not have significant effects on cardiac repolarization.

### **Postmarketing Experience**

The following adverse reactions have been identified during post-marketing use of VIBERZI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Gastrointestinal disorders:* Fecal impaction, ileus, intestinal obstruction, ischemic colitis, rectal hemorrhage

*Hypersensitivity:* Anaphylaxis, angioedema (e.g. swollen face and throat), dyspnea, throat tightening and chest pain/tightness

### **Abuse Potential**

In the two human abuse potential studies, euphoria was reported to be 3- to 5-fold higher than placebo in non-dependent, recreational opioid users treated with single oral doses of 100 mg to 1000 mg; and was higher than placebo (0%) with intranasal doses of 100 mg (21.9%) and 200 mg (18.8%). Therefore, eluxadoline can produce psychological dependence (See WARNINGS AND PRECAUTIONS and ACTION AND CLINICAL PHARMACOLOGY -

Pharmacodynamics). Among adverse reactions in clinical trials of IBS-D, euphoria was reported in 2/1032 patients with Viberzi 100 mg, and feeling drunk was reported in 1/1032 patient treated with Viberzi 100 mg and 1/807 patient treated with Viberzi 75mg.

## **DRUG INTERACTIONS**

### **Overview**

Coadministration of VIBERZI with cyclosporine significantly increased the systemic exposure of eluxadoline (see Drug Interactions in DETAILED PHARMACOLOGY). This interaction appears at least in part due to inhibition of OATP1B1 (see Drug Interactions in DETAILED PHARMACOLOGY).

Coadministration of VIBERZI with rosuvastatin resulted in mild increase in exposure to rosuvastatin and its metabolite (see Drug Interactions in DETAILED PHARMACOLOGY). This interaction appears at least in part due to inhibition of OATP1B1 (see Drug Interactions in DETAILED PHARMACOLOGY and Product Monograph for Rosuvastatin).

Coadministration of VIBERZI with probenecid resulted in mild increase in systemic exposure of eluxadoline (see Drug Interactions in DETAILED PHARMACOLOGY).

The potential impact of interaction of eluxadoline with other drugs at a CYP enzyme level is unknown due to lack of information (see Drug Interactions in DETAILED PHARMACOLOGY). Caution should be exercised when strong CYP inhibitors are co-administrated (Table 2).

## **Drug-Drug Interactions**

Tables 2 provides information on drugs which demonstrated clinically important drug interaction or potentially result in clinically relevant interactions with VIBERZI and the recommended approach for risk management.

**Table 2      Established or Potential Drug-Drug Interactions**

Drug class	Interacting Drug	Level of evidence	Clinical Effect	Clinical Recommendation
OATP1B1 inhibitors	cyclosporine, gemfibrozil, atazanavir, lopinavir, ritonavir, saquinavir, tipranavir rifampin, eltrombopag	Clinical trial or theoretical	Cyclosporine significantly increased systemic exposure to eluxadoline (see Drug Interactions in DETAILED PHARMACOLOGY)	VIBERZI should not be used in patients treated with potent OATP1B1 inhibitors (see Contraindications)
OATP1B1 Substrate	rosuvastatin	Clinical trial or theoretical	Increased exposure to rosuvastatin (see Drug Interactions in DETAILED PHARMACOLOGY)	The risk of myopathy/rhabdomyolysis due to rosuvastatin may be increased. Monitor patients for related reactions and use lowest effective dose of rosuvastatin (see Product Monograph for Rosuvastatin).
	probenecid	Clinical trial	Mild increase in systemic exposure of eluxadoline (see Drug Interactions in DETAILED PHARMACOLOGY)	

Drugs that Cause Constipation	alosetron*, anticholinergics, opioids	Theoretical	Increased risk of constipation and related adverse reactions.	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.
Strong CYP inhibitors	ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6)	Theoretical	Potential for increased exposure to eluxadoline.	Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions (see Adverse Reactions).

\*Not approved in Canada

### **Drug-Food Interactions**

The absorption of eluxadoline is rapid under fasting conditions, with a median  $T_{max}$  value of 2 hours. Results from a food-effect study of single 100 mg doses of VIBERZI in the fed and fasted state indicate that food significantly reduces eluxadoline exposure, both  $C_{max}$  (50%) and AUC (60%). In the Phase 3 safety and efficacy trials patients took VIBERZI with food to enhance eluxadoline concentration in the gastrointestinal tract (GIT), its intended local site of action. Based on these results, VIBERZI should be taken with food to achieve therapeutic eluxadoline levels in the GIT.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Interactions with laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

Physicians should periodically assess the need for continued treatment with VIBERZI.

Patients on treatment who develop severe constipation should stop taking VIBERZI and contact their physician.

### Recommended Dose and Dosage Adjustment

The recommended dosage of VIBERZI is 100 mg taken orally twice daily with food.

For patients who are unable to tolerate the 100 mg dose, the recommended dosage of VIBERZI is 75 mg taken orally twice daily with food.

For patients 65 years or older, the starting dose should be 75 mg twice daily with food. If the 75 mg BID dose is well tolerated but not efficacious, the dose could be increased to 100 mg twice daily (see WARNINGS AND PRECAUTIONS).

### Missed Dose

In the event that a dose is missed (delay of > 4 hours), the patient should skip that dose. Do not take two tablets to account for the missed dose. Wait until it is time for the next dose and then take the usual dose with food.

## OVERDOSAGE

No reports of overdose with VIBERZI have been received.

The patient should be carefully observed and given standard supportive treatment as required. Given eluxadoline's action at opioid receptors, administration of a narcotic mu opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, subjects should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection.

For management of a suspected drug overdose, contact your regional Poison Control Centre.
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## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Eluxadoline is a mixed mu opioid receptor ( $\mu$ OR) agonist and delta opioid receptor ( $\delta$ OR) antagonist with a binding affinity ( $K_i$ ) to human  $\mu$ OR and  $\delta$ OR is 1.8 nM and 430 nM, respectively.

The binding affinity of eluxadoline for the human kappa opioid receptor has not been

determined; however, the  $K_i$  for guinea pig cerebellum kappa opioid receptor is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut. (See Animal Pharmacology in DETAILED PHARMACOLOGY section)

## Pharmacodynamics

### *Drug Abuse and Dependence/Tolerance:*

Two cross-over human abuse potential studies were conducted in healthy, non-dependent, recreational opioid users, 23-55 years of age.

In one study, single oral doses of eluxadoline, 100 mg, 300 mg, 1000 mg, oxycodone hydrochloride 30 and 60 mg (positive control), and placebo were administered to 33 subjects who completed the study. Although eluxadoline was not significantly different from placebo on *Overall Drug Liking*, the 1000 mg dose did show statistically significantly higher scores vs placebo on the *Take Drug Again* VAS at the 24-hour time point. Also, the 300 mg and 1000 mg eluxadoline doses had significantly higher scores vs placebo on *Subjective Drug Value* at both 12 and 24 hour time-points but remained significantly lower vs oxycodone hydrochloride scores. For eluxadoline doses 100, 300, and 1000 mg, the most common adverse events included *somnolence* (31%, 42%, and 19%; oxycodone: 39%; placebo: 5%), and *euphoric mood* (14%, 19%, and 28%; oxycodone: 76%; placebo: 5%).

In another study, 31 subjects self-administered crushed tablets of eluxadoline 100 and 200 mg, oxycodone 15 and 30 mg, and placebo intranasally. Both eluxadoline 100 and 200 mg doses showed significantly lower scores compared to oxycodone on *Overall Drug Liking* VAS and *Take Drug Again* VAS. On end-points such as *Good Effects* VAS, and *ARCI* (Addiction Research Centre Inventory), eluxadoline 100 and 200 mg doses did score significantly higher than placebo. Both eluxadoline doses led to decreased *pupil diameter* by nearly two-fold vs placebo but the decrease was much less than that observed following oxycodone hydrochloride administration (4-fold vs placebo).

In both studies, as compared to placebo, eluxadoline oral and intranasal doses 300 and 1000 mg produced small but significant increases on both positive subjective measures (e.g., *Drug Liking* and *High*) and negative subjective measures (e.g., *Drug Disliking* and *Dysphoria*).

In rats, a single intravenous dose of eluxadoline hydrochloride salt (5 mg/kg) caused respiratory depression. In a drug discrimination study in monkeys, intravenous administration of eluxadoline hydrochloride salt (10 mg/kg) substituted for morphine discriminative stimuli. In another study, monkeys self-administered eluxadoline hydrochloride salt (3.2 mg/kg) to a degree that was less than that of heroin but greater than that of saline. Viberzi tablets can be easily crushed and the potential for intravenous abuse of eluxadoline from crushed tablets in humans cannot be ruled out.

In a 52-week clinical study, no evidence of significant physical dependence or withdrawal from VIBERZI was detected. However, in the two human abuse potential studies, euphoria was reported to be 3-to 5-fold higher than placebo in non-dependent, recreational opioid users treated with single oral doses of 100 mg to 1000 mg; and was higher than placebo (0%) with intranasal

doses of 100 mg (21.9%) and 200 mg (18.8%). Therefore, eluxadoline can produce psychological dependence.

#### *Cardiac Electrophysiology*

At a dose 10 times the maximum recommended dose, VIBERZI does not prolong the QT interval to any clinically relevant extent.

#### **Pharmacokinetics**

**Absorption:** Orally administered eluxadoline is rapidly absorbed into the systemic circulation (T<sub>max</sub>: 1.5 to 2 hours [range: 1 to 8 hours], with low plasma eluxadoline levels (C<sub>max</sub> approximately 3 ng/ml and AUC of approximately 24 ng.h/ml). A high fat meal significantly decreases the plasma level of eluxadoline. Multiple oral doses (twice) daily in healthy subjects did not result in accumulation of the drug (see Human Pharmacology in DETAILED PHARMACOLOGY section). The absolute bioavailability of eluxadoline has not been determined.

**Distribution:** In humans, eluxadoline was moderately (81%) bound to plasma proteins.

**Metabolism:** Eluxadoline exists predominantly as the (S,S)-diastereomer (>99%) and undergoes little or no chiral conversion in vivo. Metabolism of eluxadoline is not clearly established in human. There is evidence of formation of an acyl glucuronide metabolite (M11) of eluxadoline in in vitro human hepatocytes and human body (see Human Pharmacology in DETAILED PHARMACOLOGY section).

**Excretion:** Eluxadoline is primarily cleared via the biliary system with the kidney playing a minimal role in elimination. The observed mean plasma terminal elimination half-life (t<sub>1/2</sub>) of eluxadoline was from 3.7 hours to 6 hours (see Human Pharmacology in DETAILED PHARMACOLOGY section).

#### ***Special Populations and Conditions***

**Pediatrics:** Safety and effectiveness of VIBERZI in pediatric patients have not been established therefore use in children is not recommended.

**Geriatrics:** Clinical studies specifically designed to determine the impact of age on the pharmacokinetics of VIBERZI have not been conducted (See WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics). A daily dose of 75 mg BID should be used (see DOSAGE & ADMINISTRATION - Recommended Dose and Dosage Adjustment).

#### **Hepatic Insufficiency:**

Compared to subjects with normal liver function, hepatic impaired subjects (Child Pugh Class A, B, C) may have significant increase in eluxadoline systemic exposure and, especially, terminal elimination half-life (t<sub>1/2</sub>, 14 to 22 hours compared to 3.7 to 6 hours in subjects with normal liver function) after oral administration of eluxadoline (see Specific Populations in DETAILED



PHARMACOLOGY). Significant accumulation of eluxadoline is expected in hepatic impaired subjects administrated with a therapeutic dose of VIBERZI twice daily.

**Renal Insufficiency:** Eluxadoline has not been specifically studied in patients who have renal impairment. Given the limited renal elimination, renal impairment is not expected to affect clearance of eluxadoline in subjects with normal liver function.

### **STORAGE AND STABILITY**

Store VIBERZI tablets at room temperature (15 - 30 °C).

### **DOSAGE FORMS, COMPOSITION AND PACKAGING**

VIBERZI is available as 75 mg and 100 mg eluxadoline tablets for oral administration.

75 mg tablets: Each 75 mg capsule-shaped tablet is coated in pale-yellow to light tan color, debossed with “FX75” on one side. Available in bottles of 60 tablets and sample blister packs of 8 tablets.

100 mg tablets: Each 100 mg capsule-shaped tablet is coated in pink-orange to peach color, debossed with “FX100” on one side. Available in bottles of 60 tablets and sample blister packs of 8 tablets.

#### **Composition:**

The inactive ingredients in VIBERZI tablets include: colloidal silica, crospovidone, mannitol, magnesium stearate, silicified microcrystalline cellulose and Opadry II (iron oxide red, iron oxide yellow, polyethylene glycol, partially hydrolyzed polyvinyl alcohol, talc and titanium dioxide).

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

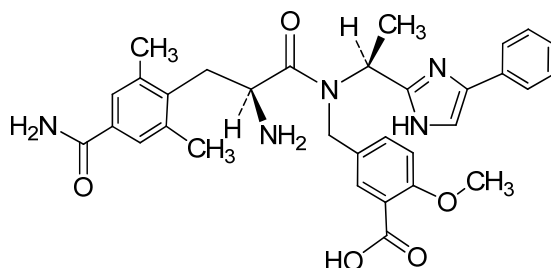
Proper name: Eluxadoline

Chemical name: 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid

Molecular formula: C<sub>32</sub>H<sub>35</sub>N<sub>5</sub>O<sub>5</sub>

Molecular weight: 569.65

Structural formula:



Physicochemical properties: Eluxadoline is a white to off-white crystalline powder. It is slightly soluble in water.

## CLINICAL TRIALS

### Study demographics and trial design

The efficacy and safety of VIBERZI in IBS-D patients was established in two randomized, multi-center double-blind, placebo-controlled trials (Trials 1 and 2).

Study 1 and Study 2 included identical 26-week double-blind, placebo-controlled treatment periods. Study 1 continued double-blinded treatment for an additional 26 weeks for long-term safety (total of 52 weeks of treatment), followed by a 2-week follow-up. Study 2 included a 4-week single-blinded, placebo-withdrawal period after the 26-week treatment period.

All patients met Rome III criteria for IBS-D (loose [mushy] or watery stools  $\geq 25\%$  and hard or lumpy stools  $< 25\%$  of bowel movements) and were required to have both an average of worst abdominal pain scores in the past 24 hours of  $> 3.0$  on a 0 to 10 scale over the week prior to randomization, AND an average daily stool consistency score of  $\geq 5.5$  and at least 5 days with a score  $\geq 5$  on a 1 to 7 Bristol Stool Scale (BSS) over the week prior to randomization.

Exclusion criteria included: prior pancreatitis, alcohol abuse, cholecystitis in the prior 6 months, sphincter of Oddi dysfunction, inflammatory bowel disease, intestinal obstruction, gastrointestinal infection or diverticulitis within prior 3 months, lipase greater than 2 x ULN, ALT or AST greater than 3 x ULN, or total bilirubin  $> 3$  mg/dL ( $> 51.3$  mmol/L). Patients with history of cholecystectomy with any history of post cholecystectomy biliary tract pain were also excluded (successful cholecystectomy with no biliary pain were acceptable).

During the study, patients were allowed to take only loperamide rescue medication for diarrhea, and aspirin or nonsteroidal anti-inflammatory drugs for abdominal pain, but not narcotic or opioid agents.

A total of 806 patients were treated with Viberzi 100 mg BID, 808 with Viberzi BID, and 809 with placebo. Two thirds of the patients were female. Fifty two percent were 41 to 64 years old, 37% were 18 to 40 years old, and 10% were  $\geq 65$  years old. Demographic characteristics were not significantly different across treatment groups.

### Study results

#### Primary Endpoint

An overall composite responder was defined by the simultaneous improvement in the daily worst abdominal pain score by  $\geq 30\%$  as compared to the baseline weekly average AND a reduction in the BSS to  $< 5$  on at least 50% of the days within a 12-week time interval. The composite responder endpoint was also evaluated over a 26-week time interval. Improvement in daily worst abdominal pain in the absence of a concurrent bowel movement was also considered a response day.

The proportion of composite responders over 12 weeks and 26 weeks is shown in **Table 3**.

In both trials, the proportion of patients who were composite responders to VIBERZI was statistically significantly higher than placebo for both doses. No significant difference in the proportion of responders was detected between male and female patients.

**Table 3- Primary Efficacy of VIBERZI in Patients with IBS-D (ITT Population)**

	Study 1			Study 2		
	VIBERZI 100mg twice daily n=426	VIBERZI 75mg twice daily n=427	Placebo n=427	VIBERZI 100mg twice daily n=382	VIBERZI 75mg twice daily n=381	Placebo n=382
<b>Composite<sup>1</sup> Response over 12 weeks</b>						
Responder rates	25.1%	23.9%	17.1%	29.6%	28.9%	16.2%
Treatment difference vs placebo	8.0% <sup>2</sup>	6.8% <sup>4</sup>		13.4% <sup>3</sup>	12.7% <sup>3</sup>	
<b>Composite Response over 26 weeks</b>						
Responder rates	29.3%	23.4%	19.0%	32.7%	30.4%	20.2%
Treatment difference vs placebo	10.3% <sup>3</sup>	4.4%		12.5% <sup>3</sup>	10.2% <sup>2</sup>	

<sup>1</sup>Composite= Simultaneous improvement of Worst Abdominal Pain (WAP) by  $\geq 30\%$  and Bristol Stool Score (BSS)  $< 5$  on the same day, for  $\geq 50\%$  of days over the interval

<sup>2</sup>  $P < 0.01$

<sup>3</sup>  $P < 0.001$

<sup>4</sup>  $P < 0.05$

The individual components of the primary responder endpoints for stool consistency (BSS score  $< 5$  on at least 50% of days) and daily abdominal pain (improvement in daily abdominal pain  $\geq 30\%$  compared to baseline on at least 50% of days) were assessed separately, and showed that statistically significantly more patients receiving VIBERZI were responders for stool consistency versus placebo, but the treatment benefit on the individual pain component was not statistically significant.

The proportion of patients who were composite responders to VIBERZI at each 4-week interval was numerically higher than placebo for both doses as early as 1 month through month 6 demonstrating that efficacy is maintained throughout the course of treatment.

During the 4-week single-blind withdrawal period of the 26-week pivotal Study 2, there was no evidence of significant or abrupt rebound worsening of diarrhea or abdominal pain compared to baseline.

Various secondary endpoints on the multiple symptoms of IBS-D were assessed which tended to be in line with the primary efficacy results.

## DETAILED PHARMACOLOGY

### Human Pharmacology:

#### Cardiac Electrophysiology

At an oral dose 10 times the maximum single recommended dose (100 mg), eluxadoline does not prolong the QT interval to any clinically relevant extent.

#### Pharmacokinetics

##### *Absorption*

The absolute bioavailability of eluxadoline has not been determined. Following an oral dose of 100 mg eluxadoline in healthy subjects, eluxadoline was rapidly absorbed with a median T<sub>max</sub> value of 1.5 hours (range: 1 to 8 hours), a C<sub>max</sub> of approximately 3 ng/mL and AUC of 24 ng.h/mL. In another study, a high fat meal significantly decreased the C<sub>max</sub> of eluxadoline by 50% and AUC by 60%. Upon administration of multiple oral doses twice daily in healthy subjects, there was no accumulation of the drug

##### *Distribution*

Plasma protein binding of eluxadoline was 81%.

##### *Metabolism*

The metabolism of eluxadoline is not clearly established in human. One *in vitro* study identified acyl glucuronides of eluxadoline (M11) as a major metabolite in cultured human hepatocytes.

##### *Elimination / Excretion*

Following a single oral dose of 300 mg [<sup>14</sup>C] eluxadoline in healthy male subjects, 82.2% of the total radioactivity was recovered in feces within 336 hours, and less than 1% was recovered in urine within 192 hours. Eluxadoline is primarily eliminated via feces. The mean plasma elimination half-life of eluxadoline ranged from 3.7 hours to 6 hours. Biliary excretion may be the dominant route of excretion of eluxadoline in human as suggested by the significant increase of systemic exposure to eluxadoline in patients with hepatic impairment compared to those with normal liver function (see DETAILED PHARMACOLOGY - Specific Populations).

#### Specific Populations

##### *Hepatic Impairment*

Following a single oral 100 mg dose of eluxadoline, mean eluxadoline plasma levels (C<sub>max</sub> and AUC<sub>0-t</sub>) increased on average about 6-fold, 4-fold, and 16-fold in mild, moderate, and severe hepatic impaired subjects (Child Pugh Class A, B or C), respectively, compared to the subjects with normal liver function. The mean terminal t<sub>1/2</sub> increased to 14 and 22 hours in mild and moderate hepatic impaired subjects, respectively, from 4.4 hours (range 3.7 to 6 hours) in subjects with normal liver function. This marked increase in terminal t<sub>1/2</sub> of eluxadoline may result in significant accumulation of eluxadoline in hepatic impaired patients treated with a BID dosing schedule. Clinical studies suggest that, in terms of the level of systemic exposure to

eluxadoline, oral 100 mg eluxadoline BID in hepatic impaired patients may be equivalent to an oral BID dosage of eluxadoline that is possibly higher than 1000 mg eluxadoline BID in subjects with normal liver functions. At such exposure level, the risk of adverse reactions, may be significantly increased.

## **Drug Interactions**

### **In Vitro Assessment of Drug Interactions**

The metabolism of eluxadoline through CYP pathways has not been established. *In vitro* study did not show induction of expression of CYP1A2, CYP2C9, CYP2C19, and CYP3A4 by eluxadoline. Eluxadoline was not an inhibitor for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19 and CYP2D6 but mildly inhibited the activity of CYP2E1 and CYP3A4 in an *in vitro* system. (See DRUG INTERACTIONS section).

Eluxadoline was not a substrate or an inhibitor for OAT1, OCT1, OCT2, OATP1B3, P-gp and BCRP in *in vitro* studies. There is some evidence suggesting that eluxadoline is a substrate for OAT3, OATP1B1, BSEP and MRP2 with a weak affinity and an inhibitor for OATP1B1 in *in vitro* conditions tested (See DRUG INTERACTIONS section).

### **In Vivo Assessment of Drug Interactions**

Interaction of eluxadoline with other drugs at a CYP metabolising enzyme level was not investigated in clinical studies.

The following drug interactions were studied in healthy subjects:

#### *Cyclosporine*

Coadministration of a single dose of 100 mg eluxadoline with a single dose of 600 mg cyclosporine resulted in 4.4-fold and 6.2-fold increase in AUC and  $C_{max}$  of eluxadoline, respectively, compared to administration of eluxadoline alone. As a multi-transporter inhibitor, cyclosporine inhibits OATP1B1 which was shown to be a transport for eluxadoline in *in vitro* human hepatocytes. Therefore, this interaction may be at least in part due to the inhibition of OATP1B1.

#### *Probenecid*

Coadministration of a single dose of 100 mg eluxadoline with a single dose of 500 mg probenecid resulted in a 35% and 31% increase in eluxadoline AUC and  $C_{max}$ , respectively, compared to administration of eluxadoline alone.

#### *Rosuvastatin*

Coadministration of a single oral dose of 20 mg rosuvastatin at Day 1 and oral 100 mg VIBERZI twice daily from Day 1 to Day 3 resulted in an increase in the AUC (40%) and  $C_{max}$  (18%) of rosuvastatin compared to administration of rosuvastatin alone. Similar results were observed with the active, major metabolite, n-desmethyl rosuvastatin. Since OATP1B1 was shown as a transporter for both rosuvastatin and eluxadoline in *in vitro* human hepatocytes, this interaction may be due at least in part to the inhibition of OATP1B1 by eluxadoline

### *Midazolam*

Coadministration of multiple doses of 100 mg eluxadoline twice daily with a single dose of 4 mg midazolam resulted in no change in  $C_{max}$  and only a slight decrease in AUC (~10%) of midazolam in humans, suggesting that eluxadoline will not affect the exposure of concomitantly administered CYP3A4 substrates.

### *Oral Contraceptives*

Coadministration of multiple doses of 100 mg eluxadoline with multiple dose administration of an oral contraceptive (norethindrone 0.5 mg/ethinyl estradiol 0.035 mg) does not change the exposure of either drug.

### **Animal Pharmacology:**

**In vitro studies** In vitro studies demonstrated that eluxadoline is a potent agonist at human  $\mu$ OR ( $K_i = 1.8$  nM) and antagonist at human  $\delta$ OR ( $K_i = 430$  nM). Eluxadoline's affinity for human  $\kappa$ OR was not determined, but it exhibited high binding affinity at guinea pig  $\kappa$ OR ( $K_i = 55$  nM).

### **In vivo Studies**

Eluxadoline inhibited GI motility in dose-dependent manner in stressed mice (a model of diarrhea) over an oral dose range of 5-100 mg/kg.

Eluxadoline (50 mg/kg, oral) reversed hyperalgesic responses to colorectal distention in a rat model of acute zymosan-induced colitis.

After a single SC dose (5, 15, and 30 mg/kg) of eluxadoline in female rats, the tidal volumes were reduced while all other measured respiratory parameters increased. The magnitude of the effect was maximal at 5 mg/kg and above. Following IV administration rats demonstrated depressive changes in breathing at all dose levels (5, 10 and 20 mg/kg) of eluxadoline consistent with the activity of eluxadoline at  $\mu$ OR.

Eluxadoline did not exhibit any significant CNS effects in rats ( $\leq 500$  mg/kg), mice ( $\leq 1000$  mg/kg), or in nonhuman primates ( $\leq 200$  mg/kg) following oral administration.

### **Animal pharmacokinetics:**

**Absorption:** Absorption after a single oral dose of eluxadoline was moderate to rapid ( $T_{max}$  0.5 to 7.75 h) and the systemic bioavailability was low ( $\leq 0.83\%$ ) in mice, rats, and cynomolgus monkeys, primarily due to limited GI absorption and a significant first-pass effect.

**Distribution:** Eluxadoline was moderately bound to plasma proteins of all species (range 68.5% in dog to 87.8% in mice).

After an oral or SC  $^{14}C$  eluxadoline administration to rats, highest radioactivity, and unchanged eluxadoline was observed in the gastrointestinal tract (range 16 to 525  $\mu$ g eq.h/g). Radioactive components were rapidly excreted primarily in feces ( $>90\%$ ) and to some extent in urine ( $<8\%$ ).

Following oral dosing in male pigmented rats, eluxadoline was poorly absorbed and distributed with concentrations below the LLOQ in most tissues. In tissues with measurable concentrations, most declined to below the LLOQ by 24 hours. Only pigmented tissues of the eye showed measurable concentrations up to 168 hours.

Upon SC administration to pregnant rats, high radioactivity was observed in kidney cortex, kidney medulla and liver with exposure levels 2 to 4 times higher than in blood. In procreative tissues, the highest tissue-to-blood AUC ratios were observed in the uterine epithelium and lumen at about 1.6. Concentrations in whole fetus and fetal liver were below the LLOQ levels. Exposures to brain and fetal tissues were very limited.

**Metabolism:** Eluxadoline was not extensively metabolized in dog (11%) hepatocytes, but was moderate to extensively metabolized in hepatocytes from cynomolgus monkey (31%) and rat (76%). The major in vitro metabolic pathway in all non-rodent species was direct glucuronidation of the methoxy-benzoic acid moiety to form the acyl glucuronide, M11. Following administration by oral and SC routes, unchanged drug was the major drug-related component in the plasma of rats (99%) and cynomolgus monkeys (95-97%) as well as in urine (94-99%) and fecal samples (95-98%) of rats and monkeys.

**Excretion:** Following an oral/SC <sup>14</sup>C eluxadoline administration to rats, radioactive components were rapidly excreted primarily in feces (>90%) and to some extent in urine (<8%).

Following oral administration in lactating rats, eluxadoline was secreted in the milk in a less than 1:1 ratio compared to plasma.

## **TOXICOLOGY**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development. In a 26-week toxicology study in rodents, the NOAEL for male and female general toxicity was 2000 mg/kg/day, the highest dose tested (yielding a safety margin of approximately 11 based on systemic exposure compared to the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In a 39-week toxicology study in monkeys, the NOAEL for male and female general toxicity was 200 mg/kg/day, the highest dose tested (yielding a safety margin of approximately 13 based on systemic exposure).

### **Carcinogenicity**

Two-year oral carcinogenicity studies have been conducted with eluxadoline in CD-1 mice at doses up to 1500 mg/kg/day (about 14 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) and in Sprague Dawley rats at oral doses up to 1500 mg/kg/day (about 36 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Oral administration of eluxadoline for 104 weeks did not produce tumors in mice and rats.



### **Mutagenicity**

Eluxadoline was negative in the Ames test, chromosome aberration test in human lymphocytes, in the mouse lymphoma cell (L5178Y/TK<sup>+/+</sup>) forward mutation test and in the in vivo rat bone marrow micronucleus test.

### **Reproductive and Developmental Toxicity**

Non-clinical studies with eluxadoline demonstrated no effects on fertility, reproductive performance, pregnancy parameters, developing fetus, or growth and development of offspring.

Eluxadoline administered as combined oral (1000 mg/kg/day) and subcutaneous (5 mg/kg/day) doses during the period of organogenesis to rats and rabbits (exposures about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (with exposures about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg).

In the same study, eluxadoline was detected in the milk of lactating rats administered oral doses of 100, 300 and 1000 mg/kg/day (with exposures about 1.8, 3 and 10 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Milk samples were collected from six lactating females per group on lactation day 12. Mean concentrations of eluxadoline in the milk of lactating rats on lactation day 12 were 2.78, 5.49 and 44.02 ng/mL at 100, 300 and 1000 mg/kg/day, respectively.

### *Juvenile Toxicology Data*

Eluxadoline was orally administered to juvenile rats at 500, 750, and 1500 mg/kg/day (about 16, 54 and 30 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) for 4 weeks. There were no adverse physiological effects related to eluxadoline. Based on these results, the NOAEL for male and female juvenile rats was 1500 mg/kg/day (about 30 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg).

## REFERENCES

1. Dove LS, Lembo A, Randall CW, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. *Gastroenterology*. Aug 2013;145(2):329-338 e321.
2. Lembo, A, Lacy BE, Zuckerman MJ et al. Eluxadoline treatment for irritable bowel syndrome with diarrhea. *N Engl J Med* 2016;374:242-53.
3. Cash BD, Lacy BE, Schoenfeld PS et al. Safety of eluxadoline in patients with irritable bowel syndrome with diarrhea. *Am J Gastroenterol* 2016.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE  
PATIENT MEDICATION INFORMATION**

**PrVIBERZI®  
(eluxadoline tablets)**

Read this carefully before you start taking Viberzi and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Viberzi.

**Serious Warnings and Precautions**

Pancreatitis (inflammation of the pancreas) may occur with Viberzi. Stop using Viberzi and get immediate medical help if you have new or worsening pain in your belly, with or without nausea or vomiting. The pain may feel like it is moving to your back or shoulder. See “Serious side effects and what to do about them”, below.

**What is Viberzi used for?**

Viberzi is used to treat adults with irritable bowel syndrome with diarrhea (IBS-D)

**How does Viberzi work?**

IBS-D is a bowel disorder which causes stomach discomfort, bloating and pain, along with diarrhea.

Viberzi acts on local receptors in the gut and may reduce diarrhea and may help reduce pain.

Viberzi not a cure for IBS-D. If you stop taking Viberzi your symptoms may return in a week.

**What are the ingredients in Viberzi?**

Medicinal ingredients: eluxadoline

Non-medicinal ingredients: colloidal silica, crospovidone, mannitol, magnesium stearate, silicified microcrystalline cellulose, tablet coating (iron oxide red, iron oxide yellow, polyethylene glycol, partially hydrolyzed polyvinyl alcohol, talc, titanium dioxide)

**Viberzi comes in the following dosage forms:**

Viberzi is available in two tablet strengths, 75 mg and 100 mg.

**Do not use Viberzi if you:**

- Are allergic to any ingredient in Viberzi. Make sure to read “What are the ingredients in Viberzi?” above.
- have had a blockage in your bile duct (tube carrying bile from the liver and gallbladder to the intestine).
- have had a sphincter of Oddi problem (muscle that controls the flow of bile and pancreatic

fluid into the intestine).

- do not have a gallbladder
- have had problems with alcohol abuse, alcohol addiction, or drink more than 3 alcoholic drinks a day.
- have had pancreatitis (inflammation of the pancreas) or a blockage in your pancreas.
- have liver disease.
- have had long-lasting (chronic) or severe constipation.
- have had a bowel blockage (intestinal obstruction).
- are taking medicines which may increase the level of eluxadoline in your blood (e.g., OATP1B1 inhibitors such as cyclosporine).

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Viberzi. Talk about any health conditions or problems you may have, including if you:**

- are pregnant or plan to become pregnant. Viberzi should not be used during pregnancy.
- are breastfeeding or plan to breastfeed. Viberzi should not be used when breastfeeding.
- have a history of illicit or prescription drug or alcohol abuse.

#### **Other Warnings**

- **Constipation:** Stop taking Viberzi and contact your doctor if you develop severe constipation. See “Serious side effects and what to do about them”, below.
- **Drug Abuse and Dependence:** Viberzi is an opioid. It may lead to psychological dependence or abuse. Use Viberzi only as directed by your doctor.
- **Driving and Using machines:** Viberzi may make you feel sleepy, dizzy or tired. Do not drive or operate machinery until these symptoms have passed.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

#### **The following may interact with Viberzi:**

Some medicines may increase the level of eluxadoline in the blood for example:

- Cyclosporine (used to reduce inflammation).
- Gemfibrozil (used to lower lipid levels).
- Atazanavir, lopinavir, ritonavir or saquinavir (antiretrovirals used to treat HIV).
- Rifampin (antibiotic used to treat infections).

Do not take Viberzi with these medicines.

- Viberzi may increase the level of rosuvastatin (used to treat high cholesterol) in your blood. Talk to your doctor before taking Viberzi if you are taking rosuvastatin.
- Avoid taking Viberzi with drugs that cause constipation including opioids (e.g., fentanyl, oxycodone, hydrocodone, used to treat pain), anticholinergics (e.g., atropine used to treat heart disorders or oxybutynin or tolterodine, used to treat overactive bladder) or alosetron\* (\*not available in Canada).

Ask your doctor or pharmacist for a list of these medicines if you are not sure.

- You may take loperamide occasionally with Viberzi to treat severe diarrhea. Stop taking loperamide right away if you become constipated.
- Your risk of getting pancreatitis is increased if you drink more than 3 alcoholic drinks a day. Limit your use of alcoholic drinks while you are taking Viberzi.

**How to take Viberzi:**

Take Viberzi as prescribed by your healthcare professional.

**Usual adult dose:**

The usual adult dose is 100 mg (1 tablet) twice daily with food. Your healthcare professional may prescribe a lower dose of 75 mg twice daily with food, if you are 65 years of age or older or based on your medical history.

**Overdose:**

If you think you have taken too much Viberzi, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**Missed Dose:**

If you miss a dose of Viberzi (delay of > 4 hours), skip that dose and take the next dose at the usual time with food. Do not double your dose.

**What are possible side effects from using Viberzi?**

These are not all the possible side effects you may feel when taking Viberzi. If you experience any side effects not listed here, contact your healthcare professional.

The most common side effects reported with Viberzi are:

- Constipation.
- Nausea.
- Abdominal pain.
- Vomiting.
- Bloating.
- Gas.
- Sleepiness.
- Dizziness.
- Fatigue.

<b>Serious side effects and what to do about them</b>			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>UNKNOWN</b>			
<b>Severe constipation:</b> may present with a difficulty passing stool, sudden belly pain, nausea, vomiting, and abdominal distention (feeling bloated or full).			✓
<b>Allergic reactions:</b> swelling of the face, lips, mouth or throat, shortness of breath or other breathing problems, itching, rash or hives			✓
<b>RARE</b>			
<b>Sphincter of Oddi spasm:</b> new or worsening pain in the belly with or without nausea or vomiting. You may feel pain on the upper right side of your belly, just below the ribs. The pain may feel like it is moving to your back or shoulder.			✓
<b>Pancreatitis:</b> new or worsening pain in your belly, with or without nausea or vomiting. The pain may feel like it is moving to your back or shoulder.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p><b>Reporting Side Effects</b></p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p><b>3 ways to report:</b></p> <ul style="list-style-type: none"> <li>• Online at <a href="#">MedEffect</a>;</li> <li>• By calling 1-866-234-2345 (toll-free);</li> <li>• By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> <li>- Fax to 1-866-678-6789 (toll-free), or</li> <li>- Mail to: Canada Vigilance Program Health Canada, Postal Locator 1908C Ottawa, ON K1A 0K9</li> </ul> </li> </ul> <p>Postage paid labels and the Consumer Side Effect Reporting Form are available at <a href="#">MedEffect</a>.</p> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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**Storage:**

Store your bottle of pills at room temperature (15° to 30°C). Keep out of reach and sight of children.

**If you want more information about Viberzi:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website [www.allergan.ca](http://www.allergan.ca), or by calling 1-800-668-6424.

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