PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **VIBERZI®**

Eluxadoline tablets

Tablets, 75 mg eluxadoline, oral

Tablets, 100 mg eluxadoline, oral

μ opioid receptor agonist / δ opioid receptor antagonist

AbbVie Corporation

8401 Trans-Canada Highway
St-Laurent, Quebec, H4S 1Z1

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RECENT MAJOR LABEL CHANGES

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VIBERZI (eluxadoline tablets) is indicated for:

- treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults.

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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 7.1.4 Geriatrics and 4.2 Recommended Dose and Dosage Adjustment).

2 CONTRAINDICATIONS

Eluxadoline is contraindicated in patients with:

- Hypersensitivity to eluxadoline or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 9.4 Drug-drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Pancreatitis – Serious cases of pancreatitis have been reported in patients taking VIBERZI, primarily in patients without a gallbladder** (See Hepatic/Biliary/Pancreatic).
- **VIBERZI is contraindicated in patients without a gallbladder** (See 2 CONTRAINDICATIONS and Hepatic/Biliary/Pancreatic).

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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 7.1.4 Geriatrics).
- Health Canada has not authorized an indication for pediatric use.

4.4 Administration

VIBERZI should be taken orally twice daily with food.

4.5 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.

5 OVERDOSAGE

No reports of overdosage 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Tablet 75 mg and 100 mg	Colloidal silica, crospovidone, magnesium stearate, mannitol, Opadry II (iron oxide red, iron oxide yellow, polyethylene glycol, partially hydrolyzed polyvinyl alcohol, talc and titanium dioxide) and silicified microcrystalline cellulose

Description

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.

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.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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 10.2 Pharmacodynamics).

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 10.2 Pharmacodynamics).

Driving and Operating Machinery

Due to events of somnolence and sedation observed in clinical studies, caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Gastrointestinal

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 9.4 Drug-drug Interactions).

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 2 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 2 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 2 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 2 CONTRAINDICATIONS).

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 (t1/2) (from 4.4 hours up to 22 hours) after oral administration of VIBERZI. The risk of adverse reactions may be significantly increased (see 10.3 Pharmacokinetics, Special Populations and Conditions). Therefore, VIBERZI is contraindicated in hepatic impaired subjects (see 2 CONTRAINDICATIONS).

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 8 ADVERSE REACTIONS). Instruct patients to immediately stop VIBERZI and seek medical attention if they experience symptoms suggestive of a hypersensitivity reaction (see 2 CONTRAINDICATIONS).

7.1 Special Populations

7.1.1 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 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

Eluxadoline was not studied in nursing women; therefore, VIBERZI should not be used in nursing women. It is unknown if VIBERZI is excreted in human milk. Precaution should be exercised because many drugs can be excreted in human milk. In animal studies, eluxadoline was excreted in the milk of lactating rats after oral administration (See Reproductive and Developmental Toxicology).

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

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 4.2 Recommended Dose and Dosage Adjustment).

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 2).

Table 2 - Adverse Reactions Occurring in ≥ 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 (%)**
Number of subjects with at least one adverse event	486 (60.2)	575 (55.7)	533 (54.7)
Gastrointestinal disorders			
Constipation	60 (7.4)	84 (8.1)	24. (2.5)
Nausea	65 (8.1)	73 (7.1)	49 (5.0)

	VIBERZI 75 mg BID n = 807 (%)	VIBERZI 100 mg BID n = 1032 (%)	Placebo BID n = 975 (%)
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)
Infections and Infestations			
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)
Nervous System Disorders			
Dizzinesss	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)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	12 (1.5)	14 (1.4)	13 (1.3)
Investigations			
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)
General Disorders			
Fatigue	21 (2.6)	20 (1.9)	23 (2.4)
Injury, Poisoning and Procedural Complications			
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)

	VIBERZI 75 mg BID n = 807 (%)	VIBERZI 100 mg BID n = 1032 (%)	Placebo BID n = 975 (%)
Respiratory, Thoracic and Mediastinal Disorders			
Pharyngolaryngeal Pain	12 (1.5)	11 (1.1)	10 (1.0)
Skin and Subcutaneous Tissue Disorders			
Rash***	22 (2.7)	28 (2.7)	15 (1.5)
Psychiatric Disorders			
Anxiety	10 (1.2)	20 (1.9)	17 (1.7)
Depression	9 (1.1)	12 (1.2)	11 (1.1)
Vascular Disorders			
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.

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 10.2 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.

8.3 Less Common Clinical Trial Adverse Reactions

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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial 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.

8.5 Post-Market Adverse Reactions

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

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Coadministration of VIBERZI with cyclosporine significantly increased the systemic exposure of eluxadoline. This interaction appears at least in part due to inhibition of OATP1B1.

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

Coadministration of VIBERZI with probenecid resulted in mild increase in systemic exposure of eluxadoline.

The potential impact of interaction of eluxadoline with other drugs at a CYP enzyme level is unknown due to lack of information. Caution should be exercised when strong CYP inhibitors are co-administrated (See Table 3).

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been studied.

9.4 Drug-Drug Interactions

The drugs listed in Table 3 are based on either drug interaction studies, or potential interactions due to the expected magnitude and seriousness of the interaction.

Table 3 - Established or Potential Drug-Drug Interactions

Drug class Proper/Common name	Source of Evidence	Effect	Clinical comment
OATP1B1 Inhibitors Example Compounds: cyclosporine, gemfibrozil, atazanavir, lopinavir, ritonavir, saquinavir, tipranavir, rifampin, eltrombopag	CT / T	Cyclosporine significantly increased systemic exposure to eluxadoline.	VIBERZI should not be used in patients treated with potent OATP1B1 inhibitors (see 2 CONTRAINDICATIONS)
OATP1B1 Substrate rosuvastatin	CT / T	Increased exposure to rosuvastatin.	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	CT	Mild increase in systemic exposure of eluxadoline.	

Drugs that Cause Constipation alosetron*, anticholinergics, opioids	T	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 Example compounds ciprofloxacin (CYP1A2), gemfibrozil (CYP2C8), fluconazole (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion (CYP2D6)	T	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 8 ADVERSE REACTIONS).

Legend: CT = Clinical Trial; T = Theoretical; *Not approved in Canada

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.

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.

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 Cmax 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 Cmax, 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 Cmax (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 Cmax 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 Contraceptive

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.

9.5 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.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Eluxadoline is a mixed mu opioid receptor (μOR) agonist and delta opioid receptor (δOR) antagonist with a binding affinity (Ki) to human μOR and δOR 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 Ki for guinea pig cerebellum kappa opioid receptor is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut.

10.2 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.

Animal Pharmacodynamics

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.

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

10.3 Pharmacokinetics

Table 4- Summary of Eluxadoline Pharmacokinetic Parameters in Healthy Subjects

	C_{max}	T_{max}	$t_{½}$ (h)	$AUC_{0-\infty}$
Single dose mean	3 ng/mL	1.5 – 2 h	3.7 – 6 h	24 ng.h/mL

Absorption

Orally administrated eluxadoline is rapidly absorbed into the systemic circulation (T_{max}: 1.5 to 2 hours [range: 1 to 8 hours], with low plasma eluxadoline levels (C_{max} approximately 3 ng/ml and AUC of approximately 24 ng.h/ml). A high fat meal significantly decreases the plasma level of eluxadoline (C_{max} decreased by 50% and AUC decreased by 60%). Multiple oral doses (twice) daily in healthy subjects did not result in accumulation of the drug. 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. Eluxadoline was not extensively metabolized in dog (11%) hepatocytes, but was moderate to extensively metabolized in hepatocytes from cynomolgus monkey (31%) and rat (76%) via direct glucuronidation of the methoxy-benzoic acid moiety to form the acyl glucuronide, M11. However, unchanged drug was the major drug-related component in the plasma, urine and feces of rats and monkeys (≥94%).

Elimination

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. The kidney plays a minimal role in elimination. The observed mean plasma terminal elimination half-life ($t_{1/2}$) of eluxadoline was from 3.7 hours to 6 hours. Following a single oral dose of 300 mg [^{14}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.

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 7.1.4 Geriatrics). A daily dose of 75 mg BID should be used (See 4.2 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 a significant increase in eluxadoline systemic

exposure (C_{max} and AUC_{0-t} increased an average of about 6-fold, 4-fold and 16-fold for Child Pugh Class A, B, and C respectively) and, especially, terminal elimination half-life ($t_{1/2}$, 14 to 22 hours in mild and moderate hepatic impaired subjects compared to 4.4 hours (range 3.7 to 6 hours) in subjects with normal liver function) after a single oral administration of eluxadoline 100 mg. Significant accumulation of eluxadoline is expected in hepatic impaired subjects administrated with a therapeutic dose of VIBERZI twice daily. 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.

- **Renal Insufficiency:** In a small open-label pharmacokinetic study, patients with end-stage renal disease (ESRD, but not on dialysis) and healthy subjects were administered a single oral dose of eluxadoline. A significant increase in exposure of eluxadoline (C_{max} and AUC_{0-t} was approximately 2.2- and 4.2-fold higher) was observed in ESRD patients compared to healthy subjects. However, due to the negligible role of renal elimination of eluxadoline (less than 1%), the clinical relevance of this study is limited.

11 STORAGE, STABILITY AND DISPOSAL

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

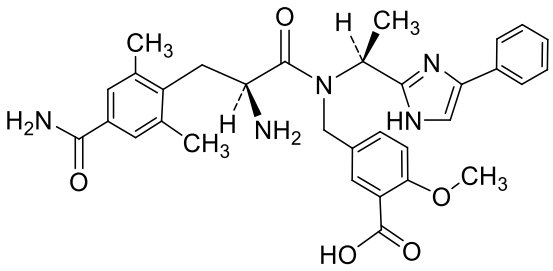
Drug Substance

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 and molecular mass: $C_{32}H_{35}N_5O_5$ 569.65

Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Irritable Bowel Syndrome with Diarrhea (IBS-D)

Table 5 - Summary of patient demographics for clinical trials in IBS-D

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
1	26-week, double-blind, placebo-controlled, multi-center study + 26-week double-blind long-term safety	75 mg VIBERZI BID 100 mg VIBERZI BID Placebo Oral 52 weeks	429 426 427	44.9 (18 – 80) years	M = 34.6 F = 65.4
2	26-week, double-blind, placebo-controlled, multi-center study + 4-week single-blind placebo withdrawal	75 mg VIBERZI BID 100 mg VIBERZI BID Placebo Oral 30 weeks	381 383 382	45.9 (18 – 77) years	M = 33.0 F = 67.0

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 ≥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 ≥5.5 and at least 5 days with a score ≥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 75 mg 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 ≥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 ≥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 6

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 6 – Results of Study 1 and 2 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**
Composite[1] Response over 12 weeks						
Responder rates	25.1%	23.9%	17.1%	29.6%	28.9%	16.2%
Treatment difference vs placebo	8.0%[2]	6.8%[4]		13.4%[3]	12.7%[3]	
Composite Response over 26 weeks						
Responder rates	29.3%	23.4%	19.0%	32.7%	30.4%	20.2%
Treatment difference vs placebo	10.3%[3]	4.4%		12.5%[3]	10.2%[2]	

[1]Composite= Simultaneous improvement of Worst Abdominal Pain (WAP) by ≥30% and Bristol Stool Score (BSS) < 5 on the same day, for ≥ 50% of days over the interval

[2] *P*<0. 01

[3] *P*<0.001

[4] *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 ≥ 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.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Genotoxicity: Eluxadoline was negative in the Ames test, chromosome aberration test in human lymphocytes, in the mouse lymphoma cell (L5178Y/$TK^{+/-}$) forward mutation test and in the in vivo rat bone marrow micronucleus test.

Reproductive and Developmental Toxicology: 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 Toxicity: 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).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

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 taking 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 the **Serious side effects and what to do about them** table, below, for more information on this and other serious side effects.
- Do not take VIBERZI if you do not have a gallbladder.

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 pain.

VIBERZI is 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, magnesium stearate, mannitol, Opadry II (iron oxide red, iron oxide yellow, polyethylene glycol, partially hydrolyzed polyvinyl alcohol, talc, titanium dioxide), silicified microcrystalline cellulose

VIBERZI comes in the following dosage forms:

Tablets: 75 mg or 100 mg

Do not use VIBERZI if:

- you are allergic to eluxadoline or any of the non-medicinal ingredients in VIBERZI (see **What are the ingredients in VIBERZI?**)

- you have had a blockage in your bile duct (tube carrying bile from the liver and gallbladder to the intestine)
- you have had a sphincter of Oddi problem (muscle that controls the flow of bile and pancreatic fluid into the intestine)
- you do not have a gallbladder
- you have had problems with alcohol abuse, alcohol addiction, or drink more than 3 alcoholic drinks a day
- you have had pancreatitis (inflammation of the pancreas) or a blockage in your pancreas
- you have liver problems
- you have had long-lasting (chronic) or severe constipation
- you have had a bowel blockage (intestinal obstruction)
- you are taking medicines which may increase the level of VIBERZI 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 you should know about:

- **Constipation**: Stop taking VIBERZI and talk to your healthcare professional if you develop severe constipation. See the **Serious side effects and what to do about them** table, below, for more information on this and other serious side effects.
- **Drug Abuse and Dependence**: VIBERZI is an opioid. It may lead to psychological dependence or abuse. Use VIBERZI only as directed by your healthcare professional.
- **Driving and Using Machines**: VIBERZI may make you feel sleepy, dizzy or tired. Give yourself time after taking VIBERZI to see how you feel before driving a vehicle or using machinery.

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

Do NOT take VIBERZI with the following:

- 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)
- eltrombopag (used to treat blood problems)

The following may interact with VIBERZI:

- probenecid (used to treat gout)
- ciprofloxacin, clarithromycin (antibiotics used to treat infections)
- fluconazole (used to treat fungal infections)
- paroxetine, bupropion (used to treat depression and other mental health problems)
- VIBERZI may increase the level of rosuvastatin (used to treat high cholesterol) in your blood. Talk to your healthcare professional 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 problems or oxybutynin or tolterodine, used to treat overactive bladder) or alosetron* (*not available in Canada). Ask your healthcare professional 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 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, or a person you are caring for, have taken too much VIBERZI, contact a 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 to make up for the missed dose.

What are possible side effects from using VIBERZI?

These are not all the possible side effects you may have when taking VIBERZI. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- constipation
- nausea
- abdominal pain

- vomiting
- bloating
- gas
- sleepiness
- dizziness
- fatigue

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Severe constipation: may present with a difficulty passing stool, sudden belly pain, nausea, vomiting, and abdominal distention (feeling bloated or full).			✓
Allergic reactions: swelling of the face, lips, mouth or throat, shortness of breath or other breathing problems, itching, rash or hives.			✓
RARE			
Sphincter of Oddi spasm: 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.			✓
Pancreatitis: 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, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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.

Storage:

Store VIBERZI 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's websitewww.abbvie.ca, or by calling 1-888-704-8271.

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