PDL DRUG REVIEW

Proprietary Name: Viberzi®
Common Name: eluxadoline
PDL Category: GI, Constipation-IBS-OIC

Comparable Products	Preferred Drug List Status
Lotronex	Non-Preferred

Summary

Pharmacology/Usage: Eluxadoline, the active ingredient of Viberzi®, is a mu-opioid receptor agonist. It is also a delta opioid receptor antagonist and a kappa opioid receptor agonist.

Viberzi® is listed as a Schedule IV of the Controlled Substances Act. Animal studies suggest that eluxadoline may produce psychological dependence. In addition, adverse reactions of euphoria (0%/0.2%) and feeling drunk (0.1%/0.1%) were reported in clinical trials with Viberzi® 75mg/100mg. In two human abuse-potential studies that included recreational opioid-experienced individuals, supra-therapeutic oral doses (300 and/or 1000mg) and intranasal doses (100-200mg) produced euphoria (rate range 14-28%) that was higher than placebo (0-5%) but less than oxycodone (44-76%). These Viberzi® doses also resulted in small but significant increases on positive subjective measures as compared to placebo, in addition to small but significant increases on negative subjective measures (i.e. Drug Disliking and Dysphoria).

Indications: For the treatment of irritable bowel syndrome with diarrhea (IBS-D).

There is no pregnancy category with this product; however, the risk summary indicates that there are no studies of use in pregnant women to inform any drug-associated risks. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Capsule-shaped Tablets: 75mg, 100mg

Recommended Dosage: Take 100mg BID with food. The recommended dosage of Viberzi® is 75mg BID with food in patients who: do not have a gallbladder; are unable to tolerate the 100mg dose; are receiving concomitant OATP1B1 inhibitors; or have mild or moderate hepatic impairment.

It is recommended to discontinue treatment in patients who develop severe constipation for more than 4 days.

As noted in the contraindications section, Viberzi® is contraindicated in those with severe hepatic impairment. It is recommended to administer Viberzi® 75mg BID in patients with mild or moderate hepatic impairment. Information regarding use in renal impairment was not found.

Drug Interactions: There may be an increased exposure to eluxadoline if given concomitantly with cyclosporine, an OATP1B1 inhibitor. Other OATP1B1 inhibitors include gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, or tipranavir), rifampin, and eltrombopag. It is recommended to reduce the Viberzi® dose to

75mg BID if use concomitantly and to monitor for impaired mental or physical abilities. There is a potential for increased exposure to eluxadoline if used concomitantly with strong CYP inhibitors (e.g. ciprofloxacin, gemfibrozil, fluconazole, clarithromycin, paroxetine, and bupropion). It is recommended to monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities. There is an increased risk for constipation related adverse events and potential for constipation related serious adverse events if eluxadoline is used concomitantly with drugs that cause constipation (such as alosetron, anticholinergics, opioids). It is recommended to avoid use with other drugs that may cause constipation. Loperamide may be used occasionally for acute management of severe diarrhea, but it is recommended to avoid chronic use and to discontinue loperamide if constipation occurs.

It is recommended to use the lowest effective dose of rosuvastatin with Viberzi®, as Viberzi® may increase exposure to rosuvastatin with concomitant use and with a potential for increased risk of myopathy/rhabdomyolysis. Last, there is a potential for increased exposure of CYP3A substrates with narrow therapeutic index (such as alfentanil, cyclosporine, ergotamine, dihydroergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) if used concomitantly with Viberzi®. It is recommended to monitor drug levels or other pharmacodynamic markers when used concomitantly with Viberzi.

Common Adverse Drug Reactions: *The listed % incidence for adverse drug reactions= reported % incidence for drug (Viberzi® 100mg BID) minus placebo.* The most frequently reported adverse events included constipation (6%), nausea (2%), abdominal pain (3%), upper respiratory tract infection (1%), vomiting (3%), nasopharyngitis (0%), abdominal distension (1%), bronchitis (1%), dizziness (1%), flatulence (1%), rash (1%), increased ALT (2%), fatigue (0%), and viral gastroenteritis (0%).

As Viberzi® is a mu opioid receptor agonist, there is potential for an increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain. In clinical trials, sphincter of Oddi spasm occurred in <1% of patients receiving Viberzi®. It is recommended to consider alternative therapies before using Viberzi® in patients without a gallbladder. Treatment should be discontinued if symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain. Treatment should not be restarted in patients who develop biliary duct obstruction or sphincter of Oddi spasm while taking Viberzi®.

There is a potential for an increased risk of pancreatitis, not associated with sphincter of Oddi spasm, when taking Viberzi®. In clinical trials, additional cases of pancreatitis not associated with sphincter of Oddi spasm were reported in 0.2% of Viberzi® 75mg treated patients and 0.3% of Viberzi® 100mg treated patients. It is recommended to avoid chronic or acute excessive alcohol while taking Viberzi®. Treatment should be discontinued if symptoms suggestive of pancreatitis occur.

Contraindications: With known or suspected biliary duct obstruction; Sphincter of Oddi disease or dysfunction; Alcoholism, alcohol abuse, or alcohol addiction, or in patients who drink >3 alcoholic beverages per day; A history of pancreatitis or structural disease of the pancreas, including known or suspected pancreatic duct obstruction; Severe hepatic impairment; A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction.

Manufacturer: Actavis Pharma

Analysis: The safety and efficacy of Viberzi® were assessed in two randomized, double-blind, placebo-controlled 26-week trials (Studies 1 and 2). Study 1 continued double-blind treatment for an additional 26 weeks for long-term safety (52 weeks total). Study 2 included a 4-week single-blinded, placebo-withdrawal period after completion of the 26 week period. During the double-blind period and the withdrawal phase, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea.

Study 1 (N=1281) and Study 2 (N=1145) patients were randomized to Viberzi® 100mg, Viberzi® 75mg or placebo. All patients in the studies met Rome III criteria for IBS-D and were required to meet both of the following criteria: an average of worst abdominal pain scores in the past 24 hours of >3.0 on a 1 to 10 scale over the week prior to randomization AND an average daily stool consistency score (Bristol Stool Scale or BSS)

of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization. An overall composite responder primary endpoint assessed the efficacy of Viberzi® in both trials. The primary endpoint 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 ≥50% of the days within a 12-week time interval. Improvement in daily worst abdominal pain in the absence of a concurrent bowel movement was also considered a response day.

Results suggested that in both studies, the proportions who were composite responders to Viberzi® was statistically significantly higher as compared with placebo for both doses. The table below, adapted from the prescribing information, illustrates the results.

	Study 1			Study 2		
Treatment group	Viberzi® 100mg	Viberzi® 75mg	Placebo	Viberzi® 100mg	Viberzi® 75mg	Placebo
Composite response over 12 weeks						
Responder Rates	25%	24%	17%	30%	29%	16%
Treatment difference	8%[1]	7%[3]	-	13%[2]	13%[2]	-
Composite response over 26 weeks						
Responder Rates	29%	23%	19%	33%	30%	20%
Treatment difference	10%	4%	-	13%	10%	-
Abdominal Pain response Improvement ≥30% over 12 weeks						
Responder Rates	43%	42%	40%	51%	48%	45%
Treatment difference	4%	3%	-	6%	3%	-
BSS <5 response over 12 weeks						
Responder Rates	34%	30%	22%	36%	37%	21%
Treatment difference	12%	8%	-	15%	16%	-

[1] p <0.01 [2] p<0.001 [3] p<0.05

During the 4-week single-blind withdrawal period in study 2, there was no evidence of worsening diarrhea or abdominal pain as compared to baseline with either dose. Information was not found in the prescribing information regarding results of long-term use (52 weeks).

Place in Therapy: Viberzi® is a new mu opioid receptor agonist indicated for the treatment of IBS-D that is listed as a Controlled Substance IV. Contraindications and drug interactions limits its use in certain patient populations. Comparator studies with other agents approved for IBS-D were not found.

There is no evidence at this time to support that Viberzi® is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Viberzi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or have failed on any preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Viberzi [package insert]. Parsippany, NJ: Actavis Pharma, Inc; 2016.