# Eluxadoline (VIBERZI) Tablets, C-IV

**National Drug Monograph**
**July 2016**
**VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives**

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

## FDA Approval Information

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| **Description/Mechanism of Action** | Eluxadoline is a locally active, mixed mu-opioid receptor agonist with delta-opioid receptor antagonist and kappa opioid receptor agonist effects. Eluxadoline has low oral bioavailability. The DEA classified it as a schedule IV substance. |
| **Indication(s) Under Review in This Document** | Treatment of irritable bowel syndrome with diarrhea (IBS-D) in adults |
| **Dosage Form(s) Under Review** | 75-mg and 100-mg tablets |
| **REMS** | ☐ **REMS** ☐ **No REMS** ☐ **Postmarketing Requirements** |
| **Pregnancy Risk Summary** | There are no studies with eluxadoline in pregnant women that inform any drug-associated risks. |

## Executive Summary

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| **Efficacy** | • In IBS-D adults with or without prior exposure or inadequate response to loperamide, eluxadoline 100 mg twice daily (ELX100) had a statistically significant, small to negligible beneficial effect (NNT 8.7), and eluxadoline 75 mg twice daily (ELX75) had a statistically significant, negligible and inconsistent beneficial effect (NNT 13.9) relative to placebo in terms of composite responder rates (a measure reflecting simultaneous improvements in both abdominal pain and stool consistency) over 26 weeks.<br>• Secondary efficacy measures generally favored eluxadoline, including stool consistency responder rate, IBS-D global symptom responder rate, IBS-Adequate Relief (AR) responder rate, and symptom scores for urgency, and bloating.<br>• There is no evidence to support off-label use of eluxadoline. |
| **Safety** | • Contraindications: Patients with biliary duct obstruction, sphincter of Oddi disease or dysfunction, alcohol use disorder, history of pancreatitis, structural diseases of the pancreas, severe hepatic impairment, history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction.<br>• Warnings and Precautions: Sphincter of Oddi spasm, pancreatitis.<br>• Eluxadoline is a Schedule IV controlled substance because of a potential for drug abuse and dependence.<br>• Common Adverse Reactions: Constipation, nausea, abdominal pain.<br>• Potential Drug Interactions: OATP1B1 inhibitors, strong CYP inhibitors, drugs that cause constipation, OATP1B1 and BCRP substrates, and CYP3A. |
| **Other Considerations** | • Eluxadoline has low oral bioavailability (1.02%) in humans mainly due to poor gastrointestinal permeability and moderate first-pass hepatic extraction<br>• Doses should be taken with food. Systemic exposure decreases when eluxadoline is administered with food. |
| **Projected Place in Therapy** | • Eluxadoline is a Schedule IV mixed mu- and kappa-opioid receptor agonist and delta-opioid receptor antagonist with low oral bioavailability that offers another treatment option to patients with IBS-D who have an inadequate response or intolerance to conventional treatments including loperamide. |

- Potential advantages of eluxadoline over other agents used for IBS-D include better quality evidence of efficacy (in contrast to loperamide), no risk of development of bacterial resistance (as opposed to rifaximin), and efficacy for moderate to severe IBS-D in both men and women (whereas alosetron is approved for severe IBS-D in women).

## Background

**Purpose for Review**

Recent FDA approval

Issues to be determined:

✓ Does eluxadoline offer efficacy advantages to alternative drug therapies?

✓ Does eluxadoline offer safety or tolerability advantages over alternatives?

✓ Are there subgroup response predictors for eluxadoline?

**Other Therapeutic Options**

**Nonpharmacologic options** include dietary modification, probiotics and physical activity. Gluten avoidance is a dietary modification suggested for IBS-D.

**Pharmacologic options** are often used complementarily rather than as alternatives.

| Formulary Options | Other Considerations | Clinical Guidance |
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| *Antibiotics* | | |
| Neomycin tab | Improved global IBS symptoms in one placebo-controlled RCT (NNT = 5 at 7 days; N = 111)[1] Use is limited by significant adverse effects. This agent is the only evidence-supported antibiotic *alternative* to rifaximin. | Lower quality evidence than with eluxadoline. Need further, long-term studies before neomycin can be recommended for continuous or intermittent use.[6] |
| *Antidepressants* | | |
| Tricyclics<br>Amitriptyline tab<br>Clomipramine cap<br>Desipramine tab<br>Doxepin cap, oral liquid<br>Imipramine tab<br>Nortriptyline cap, soln | Slows intestinal transit. TCAs improve pain and global symptoms of IBS (NNT = 4), based on a 2011 Cochrane review.[2]<br>NNT from a 2012 systematic review / meta-analysis was 8 (3.7–71.9).[3] | For persistent abdominal pain despite antispasmodics.[4] Start at low doses for IBS. If intolerant to one TCA, patient may be tried on a second TCA. |
| Selective Serotonin Reuptake Inhibitors (SSRIs)<br>Citalopram tab, soln<br>Escitalopram tab<br>Fluoxetine cap, soln<br>Paroxetine tab<br>Sertraline tab, soln | Inconsistent efficacy results among trials; however, meta-analytic subgroup analyses showed SSRIs improve global assessment scores.[2] Treatment effects may be similar to those of TCAs.[5] | For co-morbid anxiety or depression. May be used to relieve abdominal pain in patients intolerant or not responding to TCAs. |
| *Antidiarrheals* | | |
| Loperamide cap, oral liquid | Improves stool frequency and consistency, but is not beneficial for bloating, abdominal discomfort, or global IBS symptoms, and lacks safety and tolerability data.[6] Associated with ileus, megacolon and toxic megacolon.<br>Shown to have extremely low abuse potential in clinical abuse potential studies using high doses. There have been recent reports of OTC loperamide abuse and overdose deaths associated with cardiotoxicity in people with opioid use disorder, who primarily used the drug to prevent opioid withdrawal.[7,8,9] | Primarily used for diarrhea, urgency or incontinence. |
| *Antispasmodics* | | |

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| Dicyclomine tab, cap, soln | Approved for functional bowel / IBS. The only antispasmodic shown to be effective for IBS in a Cochrane review.[2] Used at higher doses in IBS-D and may cause dose-related adverse effects. | Primarily used to relieve pain or postprandial urgency. |
| *Bile Acid Sequestrants (BASs)* | | |
| Cholestyramine oral powder<br>Colestipol oral granules for reconstitution | Gastrointestinal adverse effects (bloating, flatulence, abdominal discomfort, constipation) limit use of these agents. | For patients with persistent diarrhea despite antidiarrheals.[4] |
| *5-Hydroxytryptamine-3-receptor Antagonists* | | |
| Ondansetron inj, tab | Off-label use. One RCT (N = 120) showed ondansetron (titrated up to 8 mg 3 times daily for 5 weeks) significantly improved stool consistency, frequency and urgency but did not improve abdominal pain.[10] | |

| **Nonformulary Options** | **Other Considerations** | **Clinical Guidance** |
|---|---|---|
| *Antibiotics* | | |
| Rifaximin | Development of bacterial resistance is a concern. | Monograph on Rifaximin (XIFAXAN) for IBS-D |
| *Antidepressants* | | |
| Tricyclics<br>Amoxapine<br>Protriptyline<br>Trimipramine<br>SSRIs<br>Fluvoxamine | | |
| *Antispasmodics* | | |
| Chlordiazepoxide / Clidinium cap | Unapproved, marketed, Drug Efficacy Study Initiative (DESI) drug classified by FDA as *possibly* effective as adjunctive therapy in the treatment of IBS (irritable colon, spastic colon, mucous colitis). Final classification of the less-than-effective indication requires further investigation.[11] | Used for IBS associated with anxiety. |
| Hyoscyamine inj, tab, tab ER 12 h, tab dispersible, tab sublingual, elixir | Differs from products studied in trials.[6] Antispasmodics effective as a class. | |
| Phenobarbital / Hyoscyamine / Atropine / Scopolamine (DONNATAL) elixir tab, tab ER, elixir | Unapproved, marketed, DESI drug classified by FDA as *possibly* effective as adjunctive therapy in the treatment of irritable bowel syndrome (irritable colon, spastic colon, mucous colitis).[12] A 1978 article reported phenobarbital / belladonna to be effective in IBS (N = 16).[13] | Use on an as-needed basis for patients with abdominal pain due to IBS that persists despite treatment for constipation.[4] |
| *Bile Acid Sequestrants (BASs)* | | |
| Colesevelam cap, oral susp, tab | Insufficient evidence to support off-label use for IBS-D (one small, proof-of-concept RCT; N = 24).[14] | |
| *5-Hydroxytryptamine-3-receptor Antagonists* | | |
| Alosetron | Used for pain, urgency or diarrhea. Had been withdrawn from US market because of serious risks (ischemic colitis, complications of severe constipation). Now available via the Alosetron Prescribing Program at doses lower than those previously approved. Improves global IBS response (NNT 8)[15] and abdominal pain. | Approved for treatment of severe IBS-D in females with symptoms that have lasted for 6 months and who have not responded to all other conventional treatments. |

## Efficacy (FDA Approved Indications)

### Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to May 2016) using the search term *eluxadoline*. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials and long-term (≥ 1 year) observational studies published in peer-reviewed journals were included. Study results were also obtained from the FDA Medical Review(s).

### Review of Efficacy

- The FDA approval of eluxadoline was primarily based on two high- to moderate-quality phase III multicenter, multinational, double-blind, placebo-controlled randomized clinical trials (RCTs) and one phase II RCT, all sponsored by the manufacturer (Table 1).[16] The two phase III trials were identically designed through Week 26.

**Table 1 Overview of Clinical Trials**

| TRIAL | PURPOSE / INTERVENTIONS | POPULATION, N RANDOMIZED / COMPLETED | DESIGN |
|---|---|---|---|
| IBS-2001, Dove (2013)[17] | Dose-ranging, efficacy-safety proof-of-concept trial<br><br>ELX 5 mg b.i.d.<br>ELX 25 mg b.i.d.<br>ELX 100 mg b.i.d.<br>ELX 200 mg b.i.d.<br>PBO b.i.d.<br><br>Allowed rescue loperamide and acetaminophen | Adults 18–65 years old with IBS-D (Rome III criteria) and met the following criteria over the week prior to randomization: average worst abdominal pain score in past 24 h > 3.0 (0–10 scale), average stool consistency (Bristol Stool Scale) score ≥ 5.5<br><br>807 / 525 (34.9% Discontinued, mainly due to noncompliance with daily interactive voice reporting system, voluntary withdrawal, adverse events and lack of efficacy with the 5-mg dose) | 12-wk 263-center DB PC RCT (US)<br>**Clinical Response** defined as meeting BOTH IBS-D improvement from baseline criteria:<br>1) Average daily pain score over the past week improved by ≥30% and at least 2 points; and<br>2) BSS consistency score of 3 or 4 on >66% of reported days in past week |
| IBS-3001, Lembo (2016)[18] | Major efficacy-safety trial to demonstrate that ELX is superior to PBO in reducing abdominal pain and improving stool consistency<br><br>ELX 75 mg b.i.d.<br>ELX 100 mg b.i.d.<br>PBO b.i.d.<br><br>Allowed loperamide rescue medication with total dose restrictions over continuous time periods (not more than 8 mg/24 h, 14 mg/48 h, and 22 mg/7d). | Adults 18–80 years old with IBS-D (Rome III criteria) and met the following criteria over the week prior to randomization: average worst abdominal pain score in past 24 h > 3.0 (0–10 scale), average stool consistency (Bristol Stool Scale) score ≥ 5.5 and at least 5 days with a BSS score ≥ 5; and average daily IBS-D global symptom score ≥ 2.0 (0– 4 scale).<br><br>36% used loperamide in the past year and 64.8% of them were inadequate responders.<br>Baseline mean worst abdominal pain score 6.2; mean stool consistency (BSS) score 6.3.<br><br>1281 / 783 (38.8% Discontinued, mainly for voluntary reasons (21.0%) with rates similar across treatment groups) | 52-wk 295-center DB PC Phase III RCT including 26-wk double-blind safety assessment (269 US, 9 CA, 17 UK sites)<br>**Composite Response** defined as simultaneous improvement in abdominal pain and BSS scores for more than 50% of the days with diary entries through Week 12 |
| IBS-3002 | Same as for IBS-3001 | Same as for IBS-3001<br><br>35.6% used loperamide in the past year and 58.1% of them were inadequate responders.<br>Baseline mean worst abdominal pain score 6.0; mean stool consistency (BSS) score 6.2.<br><br>1146 / 787 (31.3% Discontinued, mainly for voluntary reasons (18.3%) with rates similar across treatment groups) | 26-wk 261-center DB PC Phase III RCT with additional 4-wk, single-blind withdrawal period (total 30 wks)(241 US, 10 CA, 10 UK sites)<br>Composite Response defined as for IBS-3001. |

BSS, Bristol Stool Scale; DB, Double-blind; ELX, Eluxadoline; IBS-D, Irritable bowel syndrome with diarrhea; MC, Multicenter; PBO, Placebo; PC, Placebo-controlled; RCT, Randomized clinical trial.

- The phase II dose-ranging study showed that eluxadoline 100 mg twice daily was efficacious and seemed to be associated with a slightly lower rate of gastrointestinal adverse events than 200 mg twice daily: 35/165 (21.2%) vs. 48/172 (28.0%). The 200-mg dose did not seem to improve post hoc response rates over the 100-mg dose. The 75-mg dose showed some efficacy and a favorable safety profile.

*Phase III Clinical Trials*

- The primary efficacy measure was the proportion of **composite responders** over the initial 12-week double-blind period for the US Food and Drug Administration (FDA) and through 26 weeks for the European Medicines Agency (EMA).
    - A **composite responder** was a patient who met the daily response criteria, which required simultaneous improvement in both abdominal pain and stool consistency for at least 50% of the days with diary entries during Weeks 1–12.
        - Daily pain response – worse abdominal pain scores in the past 24 hours improved by ≥30% compared with baseline, where baseline was the average of daily worst abdominal pain score the week prior to randomization.
        - Daily stool consistency response – Bristol Stool Scale (BSS) score <5 or the absence of a bowel movement if accompanied by ≥30% improvement in worst abdominal pain compared with baseline pain. BSS scale: 1 / Hard Stool to 7 / Watery Diarrhea.
- Secondary efficacy measures included the following responder definitions:
    - A pain responder was a patient who met the daily pain response criteria described above for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval.
    - A stool consistency responder was a patient who met the daily stool consistency response criteria described above for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval.
    - An IBS-D global symptom responder was a patient who met the daily IBS-D global symptom response criteria for at least 50% of days with diary entries during each interval over the 12-week interval, 26-week interval, and each 4-week interval. The daily IBS-D global symptom response criteria were IBS-D global symptom score of 0 / None or 1 / Mild (on a 0 to 4 / Very Severe scale) or a daily symptom score improvement by ≥2.0 compared with the baseline average.
    - An IBS-Quality of Life (QOL) responder was a patient who achieved at least a 14-point improvement in IBS-QOL total score from baseline to applicable visit.
    - An IBS-Adequate Relief (AR) responder was a patient who had a weekly response of "yes" to adequate relief of their IBS symptoms for at least 50% of the total weeks during the 12-week and 26-week intervals. A patient must have had a positive response for ≥6 weeks for the 12-week interval and ≥13 weeks for the 26-week interval.
- Other secondary measures included discomfort, bloating, daily bowel frequency, incontinence, incontinence-free days, urgency, and IBS-QOL total score and scores compared with baseline.
- The study populations for both phase III trials consisted of patients with mean age of about 45 years (range, 18 to 80 years). About 34% of the study patients were male, 86% were white, and 95% were from the US.
- Main Results
    - Eluxadoline 100 mg twice daily (ELX100) had a statistically significant, small to negligible beneficial effect and eluxadoline 75 mg twice daily (ELX75) had a statistically significant, negligible and inconsistent beneficial effect relative to placebo in terms of composite responder rates (Table 2).

**Table 2 Percentage of Composite Responders in Phase III Trials**

| Outcome Measure | ELX100 | ELX75 | PBO | Diff, % (NNT) – ELX100 | Diff, % (NNT) – ELX75 |
|---|---|---|---|---|---|
| IBS-3001 Trial | | | | | |
| Composite Responders, n/N (%), Wk 1–12, PEM | 107/428 (25.1) | 102/427 (23.9) | 73/427 (17.1) | 8.0* (12.5) | 6.8* (14.7) |
| Composite Responders, n/N (%), Wk 1–26, PEM | 125/426 (29.3) | 100/427 (23.4) | 81/427 (19.0%) | 10.3* (9.7) | 3.6 (NSD) |
| IBS-3002 Trial | | | | | |
| Composite Responders, n/N (%), Wk 1–12, PEM | 113/382 (29.6) | 110/381 (28.9) | 62/382 (16.2) | 13.4* (7.5) | 12.7* (7.9) |
| Composite Responders, n/N (%), Wk 1–26, PEM | 125/382 (32.7) | 116/381 (30.4) | 77/382 (20.2) | 12.5* (8.0) | 10.2* (9.8) |
| Pooled Data | | | | | |
| Composite Responders, n/N (%), Wk 1–12 | 220/810 (27.2) | 212/808 (26.2) | 135/809 (16.7) | 10.5 (9.5) | 9.5 (10.5) |
| Composite Responders, n/N (%), Wk 1–26 | 250/808 (30.9) | 216/808 (26.7) | 158/809 (19.5) | 11.4 (8.7) | 7.2 (13.9) |

* $P \leq 0.014$

- The treatment efficacy was seen within the first week of therapy.
- Interval analyses of composite responders showed that the effects of eluxadoline were durable for a period of up to 26 weeks.
- Rescue loperamide use was highest in the placebo group: 22.2% ELX100, 26.9% ELX75, 28.3% PBO in the IBS-3001 trial and 29.3%, 26.5% and 34.6%, respectively, in the IBS-3002 trial. Imputing nonresponse when rescue loperamide was used still showed significant superiority of both doses of eluxadoline over placebo in terms of the composite responder results.
- Secondary efficacy measures generally favored eluxadoline. The manufacturer reported p-values; however, the FDA cautioned that statistical significance should not be claimed because there was no prespecified hierarchy for evaluation of the secondary efficacy measures and no adjustment for multiplicity.[16] In addition, the patient-reported outcomes IBS-QOL, IBS-AR and IBS-D global symptom responder are only exploratory. As reported in data tables, the secondary efficacy results showed the following:
  - ELX100 and ELX75 were not significantly different from placebo in terms of abdominal pain responder rates.
  - ELX100 was significantly better than placebo in stool consistency responder rate, IBS-D global symptom responder rate, and IBS-AR responder rate over Weeks 1–12 and Weeks 1–26 in both trials; however, ELX75 was significantly better than placebo in terms of each of these rates only for Weeks 1–12 in the IBS-3001 trial and for both treatment intervals in IBS-3002.
  - ELX100 was significantly better than placebo in IBS-QOL responder rate at Weeks 4 and 8 only, whereas ELX75 showed no significant differences from placebo in the IBS-3001 trial. Neither dose showed significant differences from placebo in IBS-QOL responder rate in the IBS-3002 trial.
  - Other patient-reported secondary efficacy outcomes also favored eluxadoline.
    - ELX100, but not ELX75, was significantly better than placebo in abdominal pain 40% and 50% responder rates (43.2% vs. 35.8% and 36.0% vs. 30.0%, respectively).[18]
    - Both doses of eluxadoline showed significantly greater improvements relative to placebo in ≥ 50% urgency-free days and ≥ 75% urgency-free days.
    - Pooled trial data also showed that ELX100 and ELX75 produced significantly greater improvements over placebo in scores for abdominal pain, stool consistency, frequency, bloating, and IBS-D global symptom score, except there were no significant differences between ELX75 and placebo for abdominal pain and bloating scores. The efficacy of ELX100 was inconsistent and the effects of ELX75 were nonsignificant in terms of IBS-QOL questionnaire scores.
- Subgroup analyses suggested that eluxadoline was effective across a variety of subgroups, including by sex and patients with or without inadequate response to loperamide, history of gastroesophageal reflux disease, history of depression and prior cholecystectomy.

- No symptoms suggestive of rebound were observed in the 4-week treatment withdrawal period (Weeks 26–30) of the IBS-3002 trial.

## Potential Off-Label Use

No published reports of off-label use were found. The following potential off-label uses for eluxadoline are based on indications for loperamide and clinical judgment:

- Acute nonspecific diarrhea
- Chronic diarrhea associated with inflammatory bowel disease
- Reducing the volume of discharge from ileostomies
- Infectious / traveler's diarrhea
- Diarrhea due to opioid withdrawal.

## Safety

For more detailed information, refer to the prescribing information.

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| **Boxed Warning** | • None |
| **Contraindications** | • Known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction. (Increased risk of sphincter of Oddi spasm.)<br>• Alcoholism, alcohol abuse, alcohol addiction or patients who drink more than 3 alcoholic beverages per day. (Increased risk for acute pancreatitis.)<br>• History of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. (Increased risk for acute pancreatitis.)<br>• Severe hepatic impairment (Child-Pugh Class C). (At risk for significantly increased plasma concentrations of eluxadoline.)<br>• History of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. (At risk for severe complications of bowel obstruction.) |
| **Warnings / Precautions** | • Sphincter of Oddi spasm<br>• Pancreatitis |

**Safety Considerations**

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| **Pancreatitis** | • Adverse reactions of pancreatitis were reported for 5 (0.3%) of 1666 eluxadoline-treated patients (pooled doses) and none of the 808 placebo patients in the two phase III clinical trials.[18]<br>• Five patients (0.3%; 2 ELX75, 3 ELX100) had serious adverse events (SAEs) of pancreatitis in the two phase III clinical trials.[18]<br>• All cases of pancreatitis resolved upon discontinuation of eluxadoline. |
| **Spasm of the Sphincter of Oddi and Abdominal Pain** | • In the two phase III clinical trials, adverse events of spasm of the sphincter of Oddi (SSO) were reported by 7 (0.8%) of ELX100 patients, 1 (0.1%) of ELX75 patients, and none of the placebo patients.[18]<br>• In addition, 8 cases of abdominal pain with increased hepatic enzyme concentrations (0.5%) occurred.<br>• Of the 5 pancreatitis patients and the 8 cases of abdominal pain with increased hepatic enzymes (13 total), 9 were determined by an adjudication committee to be associated with SSO.<br>• SSO occurred only in eluxadoline-treated patients who did not have a gallbladder, and did not occur in the 1318 patients with a gallbladder.<br>• Most adverse events of abdominal pain resembled adverse events reported as sphincter of Oddi spasm and occurred at a higher incidence in patients with prior cholecystectomy.[16] |

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| | • Although sphincter of Oddi spasm was not confirmed with laboratory workup, the FDA agreed that the 75-mg dose may be used for patients who had a prior cholecystectomy or who couldn't tolerate the 100-mg dose.[18] |
| **Drug Abuse and Dependence** | • Schedule IV controlled substance.<br>• The results of human abuse potential studies using oral and intranasal eluxadoline suggest that the abuse potential of eluxadoline is lower than that of oxycodone. In the phase II and III trials, there were no data suggesting that eluxadoline increased the risk of abuse.<br>• Animal studies showed no behavioral signs of withdrawal, a measure of physical dependence; however, eluxadoline is rewarding and may produce reinforcement. There were no cases of drug withdrawal in clinical trials.<br>• Human studies suggest that eluxadoline may produce psychological dependence.<br>• In the phase III trials, adverse reactions of euphoria were reported by 2 (0.2%) of 859 ELX100 patients and by none of the 807 ELX75 patients, and adverse reactions of feeling drunk were reported by 0.1% of ELX100 patients and 0.1% of ELX75 patients. None of the 808 placebo patients reported either of these adverse reactions. |
| **Events of Falls, Syncope, and Road Traffic Accidents** | • Insufficient data to assess whether eluxadoline is associated with these events. |
| **Extent of Study Drug Exposure** | • Among 1835 eluxadoline-treated patients, 1061 received treatment for ≥ 26 weeks and 346 received treatment for ≥ 52 weeks. |

**Adverse Reactions**

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| **Common Adverse Reactions** | • Incidence > 5%: Constipation, nausea, abdominal pain |
| **Deaths / Serious Adverse Reactions** | • No deaths occurred during the Phase III trials. One death occurred after discontinuation from trial IBS-3001 and was considered to be related to arteriosclerotic cardiovascular disease and unrelated to study drug (ELX75).<br>• SAEs for any dose of eluxadoline vs. placebo in phase II and III trials: 82/2292 (3.6%) vs. 25/975 (2.6%).[16] SAE rates were 4.8% for ELX100, 4.2% for ELX75 and 3.0% for placebo in the two phase III trials.[18]<br>• Pancreatitis was the most commonly reported SAE (11 cases).[16] There were no SAEs of constipation. |
| **Discontinuations Due to Adverse Reactions** | • Incidence on 100 mg, 75 mg and placebo in phase II and III trials, respectively: 8.3%, 7.8%, 4.3%.<br>• Most common reasons: abdominal pain (1.5%) and constipation (1.4%)<br>• NNH: 23.3 for ELX100 and 25.2 for ELX75.[18] |

**Drug Interactions**

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| **Drug-Drug Interactions Affecting Eluxadoline[19]** | • *OATP1B1 Inhibitors*: Inhibitors of OATP1B1, an organic anion-transporting polypeptide, may increase systemic exposure to eluxadoline by decreasing first-pass extraction and biliary clearance of the drug.[20] Exposure to eluxadoline increased about 5-fold when co-administered with cyclosporine.[16] Dose eluxadoline at 75 mg twice daily and monitor patients for mental impairment or other adverse reactions. Examples: Cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag.<br>• *Strong CYP Inhibitors*: Potential for increased exposure to eluxadoline. Monitor patients. Examples: Ciprofloxacin (CYP1A2), gemfibrozil (CYP2C8), fluconazole (CYP2c19), clarithromycin (CYP3A4), paroxetine and bupropion (CYP2D6). This potential interaction is listed as a |

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| | precautionary measure because of incomplete information on eluxadoline metabolism.<br>• Drugs that Cause Constipation: Increased risk for constipation-related adverse reaction and potential for constipation related serious adverse reactions. Avoid concomitant use. Loperamide may be used occasionally but avoid chronic use, and discontinue loperamide immediately if constipation occurs. Examples: Alosetron, anticholinergics, opioids. |
| **Drug-Drug Interactions Affecting Drugs Co-administered with Eluxadoline[19]** | • *OATP1B1 and BCRP Substrate:* Eluxadoline may increase exposure of co-administered OATP1B1 and BCRP substrates. Rosuvastatin exposure may be increased with a potential for increased risk of myopathy and rhabdomyolysis. Use lowest effective dose of rosuvastatin.<br>• *CYP3A Substrates with Narrow Therapeutic Index:* Potential for increased exposure of co-administered drug. Monitor drug concentrations or pharmacodynamics markers of drug effect when concomitant use with eluxadoline is initiated or discontinued. Examples: Alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus. |

## Risk Evaluation

As of 17 May 2016

**Sentinel Event Advisories**

- None
- Sources: ISMP, FDA, TJC

**Look-alike / Sound-alike Error Potential**

| NME Drug Name | Lexi-Comp | First DataBank | ISMP | Clinical Judgment |
|---|---|---|---|---|
| Eluxadoline 75, 100mg tab | None | None | None | Effexor<br>Fluoxetine<br>Duloxetine |
| VIBERZI | None | None | None | VARIZIG<br>VARUBI<br>VIBATIV |

- Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

## Other Considerations

**Pharmacokinetics**

- There is wide (51% to 98%) variability in eluxadoline pharmacokinetic parameters.
- Eluxadoline has low oral bioavailability (1.02%) in humans mainly due to poor gastrointestinal permeability and moderate first-pass hepatic extraction (involving OATP1B1-mediated hepatic uptake of drug).[16,21] The absolute bioavailability of eluxadoline has not been determined. Following oral administration of a 100-mg dose to healthy volunteers, the Cmax was 2–4 ng/ml and AUC 12–22 ng·h/ml.[22] Following oral administration of a 300-mg dose of radiolabeled eluxadoline, 0.12% (0.00%–0.42%, n = 6) of the dose was recovered in urine after 192 hours.[21]
- Systemic exposure decreases when eluxadoline is administered with food. A high-fat meal (800–1000 total calories, 50% of calories from fat) decreased eluxadoline Cmax by 50% and AUC by 60%.
- Eluxadoline is not metabolized except for slow glucuronide metabolite formation in the urine after a 1000-mg dose.[20]

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| | • Elimination is primarily (>80%) via biliary excretion. No accumulation occurs with repeated twice daily dosing.<br>• The drug has minimal renal elimination. |

**Dosing and Administration**

- The recommended dose of eluxadoline is 100 mg taken orally twice daily with food.
- The recommended dose of eluxadoline is 75 mg taken orally twice daily with food in patients who
  - Do not have a gallbladder.
  - Are unable to tolerate the 100-mg dose of eluxadoline.
  - Are receiving concomitant OATP1B1 inhibitors.
  - Have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment.
- Discontinue eluxadoline in patients who develop severe constipation for more than 4 days.
- Instruct patients that if they miss a dose, take the next dose at the regular time and not to take 2 doses at the same time to make up for a missed dose.

**Special Populations (Adults)**

| | |
|---|---|
| **Elderly** | • 139 (7.7%) of 1795 IBS-D patients who received eluxadoline in clinical trials were at least 65 years of age and 15 (0.8%) were at least 75 years old.<br>• No age-related differences in effectiveness was observed.<br>• A numerically higher percentage 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%). |
| **Pregnancy** | • No studies with eluxadoline in pregnant women. |
| **Lactation** | • No data in humans. |
| **Renal Impairment** | • No information in prescribing information.<br>• The FDA suggested that the manufacturer conduct a renal impairment study post-approval. |
| **Hepatic Impairment** | • Contraindicated in severe (Child-Pugh Class C) hepatic impairment.<br>• Use lower dose (75 mg twice daily) for moderate (Child-Pugh Class B) and mild (Child-Pugh Class A) hepatic impairment.<br>• Plasma concentrations of eluxadoline increased 16-fold, 6-fold and 4-fold in patients with severe (Child-Pugh Class C), moderate (Child-Pugh Class B) and mild (Child-Pugh Class A) hepatic impairment, respectively.19 |
| **Pharmacogenetics/genomics** | • No information. |

**Projected Place in Therapy**

- IBS-D is a subtype of IBS that represents about 40% of those suffering from IBS and has a prevalence of 5% of the general population.[23] IBS-D is defined as the presence of loose or watery stools with at least 25 percent of bowel movements and hard or lumpy stools with less than 25 percent of bowel movements (in the absence of laxatives). Women are about 1.5 to 2 times more likely to be diagnosed with IBS than men, and patients younger than 50 years of age are more likely than older patients to be affected.[6,24] The prevalence of IBS was estimated to be 2% to19% among 1991 Gulf War deployed Veterans,[25,26] and 3.5% among Operation Enduring Freedom / Operation Iraqi Freedom / Operation New Dawn (OEF / OIF / OND) female Veterans over a 10-year period from FY2002 to FY2012.[27] In female Veterans, IBS has been shown to be associated with trauma,[28] and the odds of having IBS are increased more than 3- to 16-fold in the presence of anxiety, depression or PTSD.[29] IBS is one of several conditions that overlap with the clinical spectrum of chronic multisystem illness in Veterans.[30]

- Place in Therapy Based on Practice Guidelines and Reviews Published in the Past 5 Years:
    - The American Gastroenterological Association (AGA, 2014) gives no recommendations for eluxadoline, as the guideline preceded the FDA approval of eluxadoline.[31] Loperamide is suggested (over no drug treatment) in patients with IBS-D (conditional recommendation; very low quality evidence), based on a large body of indirect evidence showing that it reduces stool frequency.
    - The American College of Gastroenterology (ACG, 2014) recommendations for treatment of IBS also preceded approval of eluxadoline.[32] There was insufficient evidence to recommend loperamide (strong recommendation; very low quality evidence) and no evidence to support its use for relieving global symptoms of IBS. Antispasmodics received a weak recommendation (low quality evidence).
    - UpToDate recommends the use of antidiarrheals (loperamide or eluxadoline) as initial treatment, and bile acid sequestrants as second-line therapy.[4] Antispasmodics may be used for abdominal pain due to IBS on an as-needed basis and/or prior to stressors known to exacerbate symptoms.
- High-quality evidence showed that eluxadoline simultaneously improved abdominal pain and diarrhea (composite responder rate) with small to negligible beneficial effects. Moderate-quality evidence (downgraded for suboptimal statistical methodology for secondary efficacy measures) suggested that eluxadoline improved global symptoms and quality of life as well as most of the specific symptoms of IBS-D, including frequency of bowel movements and urgency. Patients with and without prior exposure or inadequate response to loperamide benefited from eluxadoline therapy, although the majority of clinical trial patients had no prior loperamide exposure in the year prior to trial enrollment. The evidence of safety of eluxadoline in IBS-D for treatment up to 26 weeks is high to moderate in quality. Evidence of efficacy and safety beyond 26 weeks is low quality due to small number of patients. The clinical trial populations reflected the usual female-predominant demographics of IBS; however, there is some uncertainty about whether the benefits and favorable safety profile of eluxadoline will be seen in actual clinical practice in the US Veteran patient population.
- Additional data are needed to assess factors that may reduce the risk of pancreatitis (e.g., restricting treatment to patients with gallbladders or who abstain from alcohol), the incidence and severity of pancreatitis in actual clinical use, and subgroup response predictors for improved benefit-to-harm treatment profiles. Furthermore, head-to-head trials comparing eluxadoline with loperamide and further experience are needed to assess whether eluxadoline, a mixed mu-opioid receptor agonist / delta-opioid receptor agonist, has advantages (such as lower risk of constipation and ileus) over the full mu-opioid receptor agonist loperamide.
- In summary, eluxadoline is a Schedule IV mixed mu- and kappa-opioid receptor agonist and delta-opioid receptor antagonist with low oral bioavailability that offers another treatment option to patients with IBS-D who have an inadequate response or intolerance to conventional treatments including loperamide. Potential advantages of eluxadoline over other agents used for IBS-D include better quality evidence of efficacy (in contrast to loperamide), no risk of development of bacterial resistance (as opposed to rifaximin), and efficacy for moderate to severe IBS-D in both men and women (whereas alosetron is approved for severe IBS-D in women). The 100-mg dose of eluxadoline was more consistently efficacious and had a small increase in the risk of adverse reactions relative to the 75-mg dose. The lower dose should be used in patients with prior cholecystectomy, intolerance to the 100-mg dose, concomitant OATPB1 inhibitor treatment, or mild to moderate hepatic impairment. Before starting treatment with eluxadoline, providers should evaluate patients for risk factors for acute pancreatitis (e.g., history of pancreatitis, biliary duct disease, sphincter of Oddi dysfunction, increased serum lipase, cholecystectomy and excessive alcohol use) and opioid use disorder. Patients should be screened and monitored for potential drug interactions. Adverse reactions of abdominal pain may be due to spasm of the sphincter of Oddi, which may increase the risk of acute pancreatitis. Although the 75-mg dose was approved for use in patients with a history of cholecystectomy, the risks and benefits of any dose of eluxadoline need to be carefully weighed in patients with risk factors for pancreatitis.

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## References


1 Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. Am J Gastroenterol. 2003 Feb;98(2):412-9

2 Ruepert L, Quartero AO, de Wit NJ, van der Heijden GJ, Rubin G, Muris JW. Bulking agents, antispasmodics and antidepressants for the treatment of irritable bowel syndrome. Cochrane Database Syst Rev. 2011

3 Shah E, Kim S, Chong K, Lembo A, Pimentel M. Evaluation of harm in the pharmacotherapy of irritable bowel syndrome. Am J Med. 2012 Apr;125(4):381-93

4 Wald A. Treatment of irritable bowel syndrome in adults. In: UpToDate, Talley NJ, Grover S (Eds), UpToDate, Waltham, MA. Accessed: 20 May 2016

5 Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. Gut. 2009;58(3):367

6 American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol. 2009 Jan;104 Suppl 1:S1-35

7 Eggleston W, Clark KH, Marraffa JM. Loperamide Abuse Associated With Cardiac Dysrhythmia and Death. Ann Emerg Med. 2016 Apr 26. pii: S0196-0644(16)30052-X

8 Mukarram O, Hindi Y, Catalasan G, Ward J. Loperamide Induced Torsades de Pointes: A Case Report and Review of the Literature. Case Rep Med. 2016;2016:4061980

9 Wightman RS, Hoffman RS, Howland MA, Rice B, Biary R, Lugassy D. Not your regular high: cardiac dysrhythmias caused by loperamide. Clin Toxicol (Phila). 2016 Jun;54(5):454-8

10 Garsed K, Chernova J, Hastings M, Lam C, Marciani L, et al. A randomised trial of ondansetron for the treatment of irritable bowel syndrome with diarrhoea. Gut. 2014 Oct;63(10):1617-25. Epub 2013 Dec 12

11 LIBRAX (chlordiazepoxide HCl, clidinium bromide) capsules [Prescribing Information online]. Valeant Pharmaceuticals North America, Bridgewater, NJ, Jan 2014. Available at: http://www.valeant.com/Portals/25/Pdf/PI/Librax-PI.pdf . Accessed 20 May 2016.

12 DONNATAL - phenobarbital hyoscyamine, atropine, scopolamine hydrobromide tablet [Patient Insert online]. AvKARE, Inc., Pulaski, TN. Dec 2013. Available at: https://www.avkare.com/img/products/NDIyOTEtMjQ1LTAx/4 . Accessed 20 May 2016.

13 Rhodes JB, Abrams JH, Manning RT. Controlled clinical trial of sedative-anticholinergic drugs in patients with the irritable bowel syndrome. J Clin Pharmacol. 1978 Jul;18(7):340-5

14 Odunsi-Shiyanbade ST, Camilleri M, McKinzie S, Burton D, Carlson P, Busciglio IA, Lamsam J, Singh R, Zinsmeister AR. Effects of chenodeoxycholate and a bile acid sequestrant, colesevelam, on intestinal transit and bowel function. Clin Gastroenterol Hepatol. 2010 Feb;8(2):159-65

15 Schey R, Rao SS. The role of rifaximin therapy in patients with irritable bowel syndrome without constipation. Expert Rev Gastroenterol Hepatol. 2011 Aug;5(4):461-4

16 Center for Drug Evaluation and Research. Medical Review of Eluxadoline (VIBERZI). Food and Drug Administration, 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206940Orig1s000MedR.pdf

17 Dove LS, Lembo A, Randall CW, Fogel R, Andrae D, Davenport JM, McIntyre G, Almenoff JS, Covington PS. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology. 2013 Aug;145(2):329-38

18 Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, Davenport JM, McIntyre G, Lopez R, Turner L, Covington PS. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. N Engl J Med. 2016 Jan 21;374(3):242-53. Supplementary appendix available at: http://www.nejm.org/doi/suppl/10.1056/NEJMoa1505180/suppl_file/nejmoa1505180_appendix.pdf .

19 Academy of Managed Care Pharmacy (AMCP) Formulary Dossier on VIBERZI (eluxadoline), version 3.1, 18 November 2015.

20 Davenport JM, Covington P, Bonifacio L, McIntyre G, Venitz J. Effect of uptake transporters OAT3 and OATP1B1 and efflux transporter MRP2 on the pharmacokinetics of eluxadoline. J Clin Pharmacol 2015;55:534–42.

21 Davenport JM, Covington P, Bonifacio L, McIntyre G, Venitz J. Effect of uptake transporters OAT3 and OATP1B1 and efflux transporter MRP2 on the pharmacokinetics of eluxadoline. J Clin Pharmacol. 2015 May;55(5):534-42

[22] VERBERZI (eluxadoline) tablets CIV prescribing information [online]. Actavis Pharma, Inc., Parsippany, NJ, May 2015. Available at: http://www.allergan.com/assets/pdf/viberzi_pi . Accessed 20 May 2016.
[23] Camilleri M. Current and future pharmacological treatments for diarrhea-predominant irritable bowel syndrome. Expert Opin Pharmacother. 2013 Jun;14(9):1151-60
[24] Wald A. Clinical manifestations and diagnosis of irritable bowel syndrome in adults. In: UpToDate, Talley NJ, Grover S (Eds), UpToDate, Waltham, MA. Accessed: 22 January 2016
[25] Gray GC, Reed RJ, Kaiser KS, et al.. Self-reported symptoms and medical conditions among 11,868 Gulf War-era veterans: the Seabee Health Study. Am J Epidemiol. 2002;155:1033–1044
[26] Kang HK, Li B, Mahan CM, et al.. Health of US veterans of 1991 Gulf War: a follow-up survey in 10 years. J Occup Environ Med/Am Coll Occup Environ Med. 2009;51:401–410
[27] Mohanty AF, Muthukutty A, Carter ME, Palmer MN, Judd J, Helmer D, McAndrew LM, Garvin JH, Samore MH, Gundlapalli AV. Chronic multisymptom illness among female Veterans deployed to Iraq and Afghanistan. Med Care. 2015 Apr;53(4 Suppl 1):S143-8
[28] White DL, Savas LS, Daci K, Elserag R, Graham DP, Fitzgerald SJ, Smith SL, Tan G, El-Serag HB. Trauma history and risk of the irritable bowel syndrome in women veterans. Aliment Pharmacol Ther. 2010 Aug;32(4):551-61
[29] Savas LS, White DL, Wieman M, Daci K, Fitzgerald S, Laday Smith S, Tan G, Graham DP, Cully JA, El-Serag HB. Irritable bowel syndrome and dyspepsia among women veterans: prevalence and association with psychological distress. Aliment Pharmacol Ther. 2009 Jan;29(1):115-25
[30] VA/DoD Clinical Practice Guideline for the Management of Chronic Multisystem Illness. Department of Veterans Affairs and Department of Defense. 2014. http://www.healthquality.va.gov/guidelines/MR/cmi/VADoDCMICPG.pdf .
[31] Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S; Amercian Gastroenterological Association. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014Nov;147(5):1146-8. Erratum in: Gastroenterology. 2015 Feb;148(2):455. multiple investigator names added.
[32] Ford AC, Moayyedi P, Lacy BE, Lembo AJ, Saito YA, Schiller LR, Soffer EE, Spiegel BM, Quigley EM; Task Force on the Management of Functional Bowel Disorders. American College of Gastroenterology monograph on the management of irritable bowel syndrome and chronic idiopathic constipation. Am J Gastroenterol. 2014 Aug;109 Suppl 1:S2-26; quiz S27.

## Appendix A: GRADEing the Evidence

| Quality of Evidence | Description |
|---|---|
| High | Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects). |
| Moderate | Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of theevidence. |
| Low | Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes. |

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.