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# Eluxadoline

Updated: April 20, 2017.

# OVERVIEW

## Introduction

Eluxadoline is a mixed opioid receptor agonist (mu) and antagonist (delta) that is used to treat diarrhea-predominant irritable bowel disease. Eluxadoline is associated with a low rate of serum aminotransferase elevations that appear to be due to isolated instances of sphincter of Oddi spasm and/or pancreatitis that occurs most frequently in persons without a gallbladder.

## Background

Eluxadoline (el" ux ad' oh leen) is mixed opioid receptor agonist and antagonist, having agonist activity for the mu (μ) receptor and antagonist activity for the delta (δ) receptor. This combination of activities leads to its activity in reducing bowel transit and decreasing pain without the side effects that occur with mu receptor agonism alone. Eluxadoline is also minimally absorbed and thus does not have the central nervous system effects of typical opiates and does not require DEA restrictions. Several prospective controlled trials have shown that eluxadoline decreases gastrointestinal discomfort and symptoms in patients with diarrhea-predominant irritable bowel syndrome and it was approved for this use in the United States in 2015. Eluxadoline is available in tablets of 75 and 100 mg under the brand name Viberzi. The recommended dose is 100 mg twice daily with dose reduction based upon tolerance. Side effects include constipation, nausea, and abdominal pain. Uncommon, but potentially severe adverse reactions include severe abdominal pain due to spasm of the sphincter of Oddi or pancreatitis, complications that occur mostly in patients without a gallbladder or with preexisting pancreatic or hepatobiliary disease.

## Hepatotoxicity

In preregistration clinical trials, serum aminotransferase elevations were uncommon during eluxadoline therapy and in pooled analyses ALT elevations above 3 times the upper limit of normal occurred in 2% to 3% of eluxadoline- vs 1% of placebo-treated subjects. More detailed analysis found rare instances of marked ALT and AST elevations with eluxadoline therapy, not seen with placebo treatment. These more marked elevations were sometimes accompanied by abdominal pain and signs of sphincter of Oddi spasm (as can occur with opioid therapy) or pancreatitis. The abnormalities also arose largely in patients without a gallbladder or with a history of pancreatitis or hepato-biliary disease. Subsequent to the approval of eluxadoline and its more widescale use, over a hundred reports of pancreatitis (including 2 deaths) were reported to the Food and Drug Administration and eluxadoline was given a “black box” warning regarding its use in persons without a gallbladder. The clinical features of these reactions have not been well described, but they typically arise within the first few weeks of treatment with severe abdominal pain and vomiting sometimes accompanied by marked ALT and AST

elevations with or without increases in amylase and lipase. Jaundice is rare and the liver test abnormalities are most likely due to partial bile duct obstruction. There have been no reports of severe acute hepatitis or acute liver failure attributed to eluxadoline therapy.

Likelihood score: C (probable cause of acute liver injury, likely due to bile duct spasm or obstruction).

## Mechanism of Injury

Eluxadoline is minimally absorbed and unlikely to have direct hepatotoxic effects. Most instances of serum aminotransferase elevations attributed to eluxadoline therapy have been accompanied by evidence of acute pancreatitis or sphincter of Oddi spasm or both.

## Outcome and Management

Eluxadoline has been shown to cause sphincter of Oddi spasm and pancreatitis and its use should be limited to patients with a gallbladder and without known preexisting pancreatitis, hepatobiliary disease or advanced cirrhosis. It should also be avoided in persons who drink alcohol to excess.

Drug Classes: Gastrointestinal Agents, Irritable Bowel Syndrome Agents

# PRODUCT INFORMATION

**REPRESENTATIVE TRADE NAMES**

Eluxadoline – Viberzi®

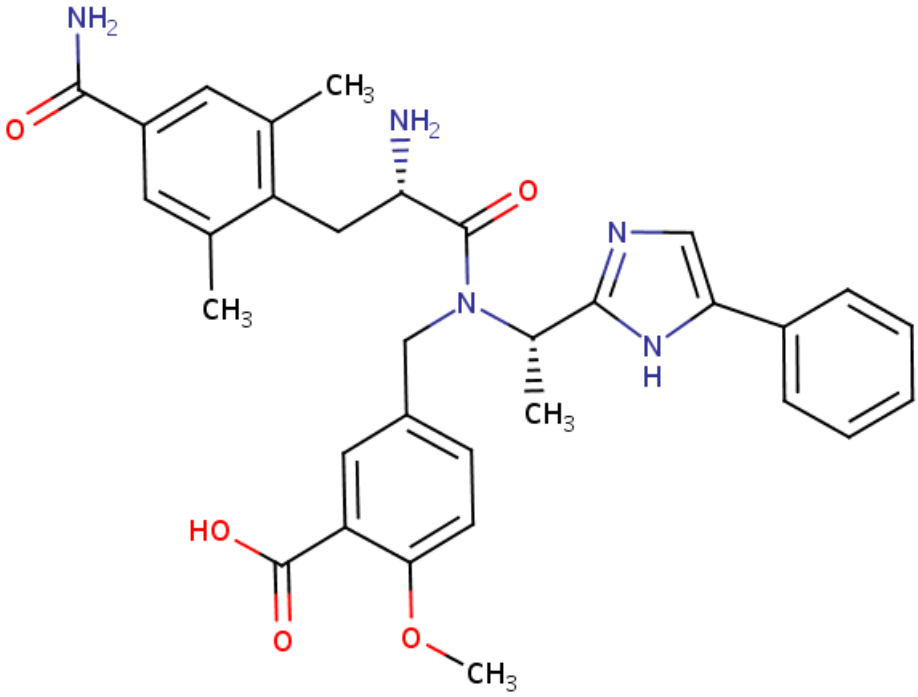
**DRUG CLASS**

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULA AND STRUCTURE

| DRUG | CAS REGISTRY NUMBER | MOLECULAR FORMULA | STRUCTURE |
|---|---|---|---|
| Eluxadoline | 864821-90-9 | C32-H35-N5-O5 |  |

## ANNOTATED BIBLIOGRAPHY

References updated: 20 April 2017

Zimmerman HJ. Laxatives. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 721-3.

*(Expert review of hepatotoxicity published in 1999 before the availability of eluxadoline).*

Pasricha PJ. Treatment of disorders of bowel motility and water flux; antiemetics; agents used in biliary and pancreatic disease. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 983-1008.

*(Textbook of pharmacology and therapeutics; eluxadoline not discussed).*

Shah E, Kim S, Chong K, Lembo A, Pimentel M. Evaluation of harm in the pharmacotherapy of irritable bowel syndrome. Am J Med 2012; 125: 381-93. PubMed PMID: 22444104.

*(Systematic review of adverse side effects of drugs used to treat irritable bowel syndrome, before the availability of eluxadoline).*

Lembo AJ, Lacy BE, Zuckerman MJ, Schey R, Dove LS, Andrae DA, Davenport JM, et al. Eluxadoline for irritable bowel syndrome with diarrhea. N Engl J Med 2016; 374: 242-53. PubMed PMID: 26789872.

*(Among 2427 adults with irritable bowel syndrome with diarrhea who were treated with eluxadoline [75 or 100 mg] or placebo twice daily for 26 or 52 weeks, symptoms improved with drug therapy and adverse events more frequent with eluxadoline included nausea [8% vs 5%], constipation [7% to 9% vs 2.5%] and abdominal pain [6% to 7% vs 4%], and 8 eluxadoline treated patients [0.3%], but no placebo recipient developed pancreatitis; severe adverse events were more frequent in patients with prior cholecystectomy [6.1-12.6% vs 2.7-3.7%], a difference also seen in placebo recipients [8.2% vs 1.7%]).*

Dove LS, Lembo A, Randall CW, Fogel R, Andrae D, Davenport JM, McIntyre G, et al. Eluxadoline benefits patients with irritable bowel syndrome with diarrhea in a phase 2 study. Gastroenterology 2013; 145: 329-38. PubMed PMID: 23583433.

*(Among 807 patients with irritable bowel disease with diarrhea treated with eluxadoline [5, 25, 100 or 200 mg] or placebo twice daily for 12 weeks, symptoms improved with the higher drug doses while overall adverse event rates were similar across groups, although 4 eluxadoline treated patients developed pancreatitis; nevertheless, "results from routine laboratory evaluations…were unremarkable").*

Traynor K. Eluxadoline approved for irritable bowel syndrome with diarrhea. Am J Health Syst Pharm 2015; 72: 1078. PubMed PMID: 26092951.

*(News report on approval of eluxadoline for irritable bowel disease with diarrhea; mentions its association with occasional cases of pancreatitis).*

Eluxadoline (Viberzi) for irritable bowel syndrome with diarrhea. Med Lett Drugs Ther 2016; 58 (1485): 4-5. PubMed PMID: 26714241.

*(Concise review of the mechanism of action, clinical efficacy, safety and costs of eluxadoline therapy of irritable bowel disease with diarrhea; mentions adverse events of sphincter of Oddi spasm and pancreatitis in patients without a gallbladder or with preexisting hepato-biliary and pancreatic disease).*

Cash BD, Lacy BE, Schoenfeld PS, Dove LS, Covington PS. Safety of eluxadoline in patients with irritable bowel syndrome with diarrhea. Am J Gastroenterol 2017; 112: 365-74. PubMed PMID: 27922029.

*(Safety analysis of pooled data from 2814 patients in 3 placebo controlled clinical trials in irritable bowel syndrome, found side effects more frequent with eluxadoline than placebo to include constipation [7.4% to 8.1% vs 2.4%], nausea [7.1% to 8.1% vs 5%] and 10 episodes [0.6%] of severe abdominal pain suggestive of Sphincter of Oddi spasm usually accompanied by marked elevations in aminotransferase levels, all of which occurred in patients without a gallbladder).*

In brief: Pancreatitis with eluxadoline (Viberzi) in patients without a gallbladder. Med Lett Drugs Ther 2017; 59 (1519): 70. PubMed PMID: 28419076.

*(Brief review of an FDA communication on reports of 118 cases of serious pancreatitis and two fatal instances in patients without a gallbladder who received eluxadoline, stressing the contraindications to its use in patients with preexisting hepatobiliary and pancreatic disease).*