U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Linaclotide. [Updated 2019 May 13].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Linaclotide

Updated: May 13, 2019.

OVERVIEW

Introduction

Linaclotide is small peptide agonist of guanylate cyclase C receptors in the intestine and is used orally as treatment of chronic constipation and irritable bowel syndrome. Linaclotide has not been linked to serum enzyme elevations during treatment or to episodes of clinically apparent liver injury.

Background

Linaclotide (lin ak' loe tide) is 14 amino acid peptide that acts as an agonist of the guanylate cyclase C receptors in the intestine. Activation of this receptor by linaclotide increases cyclic guanosine monophosphate levels which lead to an increase in secretion of chloride and bicarbonate into the intestinal lumen, thus increasing fluid secretion and promoting intestinal transit. Linaclotide acts locally on the luminal side of enterocytes in the upper intestine and is minimally absorbed. Several clinical trials have shown that linaclotide increases the number of spontaneous bowel movements, improves stool consistency and can alleviate symptoms of chronic constipation including the constipation of irritable bowel syndrome. Linaclotide was approved for use in the United States in 2012 for irritable bowel syndrome with constipation as well as idiopathic chronic constipation. Linaclotide is available in capsules of 72, 145 and 290 mcg under the brand name Linzess. The recommended dose for chronic idiopathic constipation is 72 or 145 mcg once daily and for irritable bowel syndrome with constipation is 290 mcg once daily. It is contraindicated in children below the age of 6 years and is not recommended for use in children below the age of 18 years. Side effects include diarrhea (~20%), abdominal pain, bloating, flatulence and headache. Rare but potentially severe adverse events include severe dehydration particularly in children.

Hepatotoxicity

In clinical trials, linaclotide therapy was not associated with significant changes in serum enzyme levels or episodes of clinically apparent liver injury. Minor transient ALT elevations arose in <1% of persons receiving long-term linaclotide therapy for constipation. Since its approval and marketing, there have been no reports of symptomatic serum aminotransferase elevations or clinically apparent liver injury with jaundice attributable to linaclotide. Thus, liver injury from linaclotide must be rare if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

Linaclotide is largely active on the epithelial cells in the intestinal tract and has minimal absorption. The lack of systemic absorption and the low doses used (in microgram amounts) may account for its lack of liver injury.

Drug Class: Gastrointestinal Agents, Drugs for Constipation, Irritable Bowel Syndrome Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Linaclotide – Generic, Linzess®

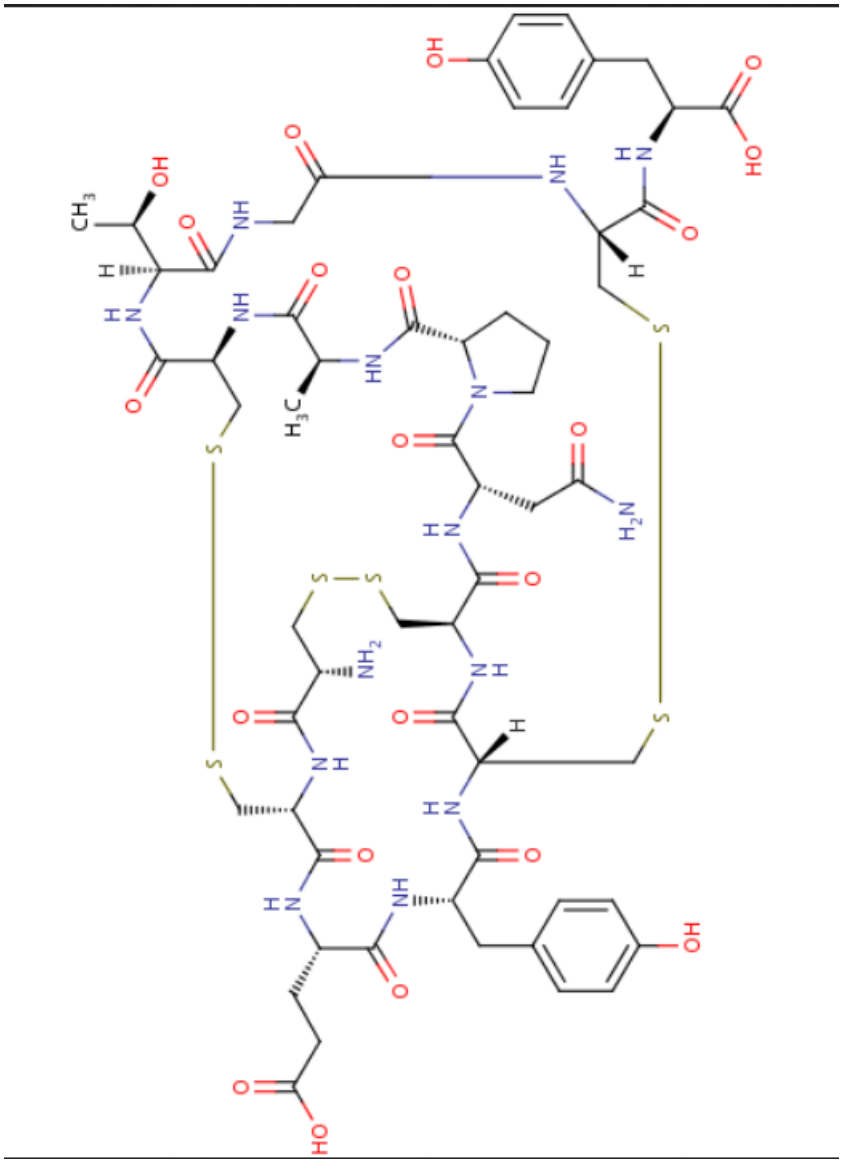
DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Linaclotide	851199-59-2	C59-H79-N15-O23-S6	

ANNOTATED BIBLIOGRAPHY

References updated: 13 May 2019

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 of laxatives published in 1999 with discussion of oxyphenisatin and other agents, but not linaclotide).

Sharkey KA, McNaughton WK. Treatment of disorders of bowel motility and water flux: anti-emetics; agents used in biliary and pancreatic disease. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 921-44.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202811Orig1s000MedR.pdf (

FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that ALT elevations above 3 times ULN occurred in 0.5% of 3173 patients in long-term safety trials of linaclotide, but that no cases of ALT elevations with jaundice were reported).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network(DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 19132805.

(Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, none were attributed to agents used for constipation or irritable bowel syndrome [IBS]).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to gastrointestinal agents, laxatives or drugs for IBS).

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 including lubiprostone, but not linaclotide).

Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, Shao JZ, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med 2011; 365: 527-36. PubMed PMID: 21830967.

(Among 1276 patients with chronic constipation treated with linaclotide or placebo for 12 weeks, diarrhea was the most common side effect [14-16% vs 4.7% in controls] and "there were no clinically significant differences in...blood chemistry values" between the two groups).

Rao S, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, Shi K, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol 2012; 107: 1714-24. PubMed PMID: 22986440.

(Among 800 patients with constipation predominant IBS treated with linaclotide or placebo for 12 weeks, the most common side effect was diarrhea [20% vs 3.5% with placebo] and there were "no clinically significant differences between the linaclotide and placebo groups in the incidence of abnormal laboratory parameters").

Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, MacDougall JE, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol 2012; 107: 1702-12. PubMed PMID: 22986437.

(Among 804 patients with IBS and constipation treated for 12 weeks, pain, bloating and bowel symptoms were improved with linaclotide compared to placebo therapy and side effects were similar except for diarrhea with linaclotide, and "there were no clinically meaningful differences...in the incidence of abnormal laboratory parameters").

Linaclotide (Linzess) for constipation. Med Lett Drugs Ther 2012; 54 (1403): 91-2. PubMed PMID: 23183319.

(Concise summary of the mechanism of action, efficacy and safety of linaclotide for constipation shortly after its approval in the United States; no mention of ALT elevations or hepatotoxicity).

Quigley EM, Tack J, Chey WD, Rao SS, Fortea J, Falques M, Diaz C, et al. Randomised clinical trials: linaclotide phase 3 studies in IBS-C - a prespecified further analysis based on European Medicines Agency-specified endpoints. Aliment Pharmacol Ther 2013; 37: 49-61. PubMed PMID: 23116208.

(Reanalysis of controlled trials of linaclotide for constipation predominant IBS [Rao 2012, Chey 2012] using different endpoints; no further discussion of side effects).

Berntgen M, Enzmann H, Schabel E, Prieto Yerro C, Gómez-Outes A, Salmonson T, Musaus J. Linaclotide for treatment of irritable bowel syndrome--the view of European regulators. Dig Liver Dis 2013; 45: 724-6. PubMed PMID: 23701993.

(Review of the efficacy and safety of linaclotide in IBS which led to the approval of its use by the European Medicines Agency).

Lacy BE, Schey R, Shiff SJ, Lavins BJ, Fox SM, Jia XD, Blakesley RE, et al. Linaclotide in chronic idiopathic constipation patients with moderate to severe abdominal bloating: a randomized, controlled trial. PLoS One 2015; 10: e0134349. PubMed PMID: 26222318.

(Among 483 patients with chronic idiopathic constipation and abdominal bloating treated with linaclotide [145 or 290 mcg] or placebo once daily for 12 weeks, abdominal symptoms improved more frequently while adverse event rates were slightly higher with linaclotide, diarrhea occurring in 6% and 17% vs 2.3% with placebo; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, one case was attributed to metoclopramide, but none to other prokinetic agents or drugs for chronic idiopathic constipation).

Black CJ, Ford AC. Chronic idiopathic constipation in adults: epidemiology, pathophysiology, diagnosis and clinical management. Med J Aust 2018; 209: 86-91. PubMed PMID: 29996755.

(Review of the role of guanylate cyclase C in gastrointestinal physiology and the biologic basis for the use of guanylate cyclase receptor agonists as therapy of gastrointestinal disorders).

Waldman SA, Camilleri M. Guanylate cyclase-C as a therapeutic target in gastrointestinal disorders. Gut 2018; 67: 1543-52. PubMed PMID: 29563144.

(Review of the definition, diagnosis, epidemiology, pathophysiology, clinical features and management and drug therapy of chronic idiopathic constipation).

Schoenfeld P, Lacy BE, Chey WD, Lembo AJ, Kurtz CB, Reasner DS, Bochenek W, et al. Low-dose linaclotide (72 μg) for chronic idiopathic constipation: a 12-week, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol 2018; 113: 105-14. PubMed PMID: 29091082.

(Among 1223 patients with chronic idiopathic constipation treated with linaclotide [72 or 145 mcg] or placebo once daily for 12 weeks, overall response rates were higher with linaclotide [13% vs 4.7%] and the major side effect was diarrhea [19% and 22% vs 7%] and there were no hepatic serious adverse events and no mention of ALT elevations).

Nee JW, Johnston JM, Shea EP, Walls CE, Tripp K, Shiff S, Fox SM, et al. Safety and tolerability of linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation: pooled phase 3 analysis. Expert Rev Gastroenterol Hepatol 2019; 13: 397-406. PubMed PMID: 30791771.

(Among 3853 adults evaluated in a pooled safety analysis of placebo-controlled trials of linaclotide therapy of chronic idiopathic constipation, adverse events occurring more frequently with linaclotide were diarrhea [17-20%] and abdominal pain [4-7%], and "laboratory values showed no consequential changes from baseline").

Fukudo S, Miwa H, Nakajima A, Kinoshita Y, Kosako M, Hayashi K, Akiho H, et al. High-dose linaclotide is effective and safe in patients with chronic constipation: A phase III randomized, double-blind, placebo-controlled study with a long-term open-label extension study in Japan. Neurogastroenterol Motil 2019; 31: e13487. PubMed PMID: 30353619.

(Among 186 Japanese adults with chronic constipation treated with linaclotide [500 mcg daily] in a 4 week placebo controlled trial followed by 52 weeks of open-label therapy, the most frequent adverse event was diarrhea [13% vs 1%], but there were no hepatic serious adverse events and "no clinically significant differences in hematologic or blood chemical results").