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Tenapanor

Updated: April 30, 2023.

OVERVIEW

Introduction

Tenapanor is a small molecular inhibitor of the sodium/hydrogen ion exchanger-3 (NHE3) used to treat constipation predominant irritable bowel syndrome (IBS). Tenapanor has minimal systemic absorption and has not been associated with serum enzyme elevation during therapy nor has it been linked to cases of clinically apparent liver injury.

Background

Tenapanor (ten a' pan or) is a small molecule inhibitor of the sodium-hydrogen exchanger isoform 3 (NHE3) which is responsible for sodium absorption in the intestine with resultant passive uptake of water. Inhibition of the transporter results in an increase in osmotic secretion of water, shortening of intestinal transit time and softening of stool consistency. On the other hand, inhibition of the exchanger can also result in diarrhea and possibly dehydration. Tenapanor acts locally and has minimal absorption. Tenapanor was found to improve frequency ~~numbers~~ and completeness of bowel movements and symptoms of bloating and distension in patients with constipation-predominant IBS and was approved for this indication in adults in 2019. Tenapanor has also been evaluated as a means of reducing hyperphosphatemia in patients with chronic renal failure on dialysis, but has yet to be given approval for that indication. Tenapanor is available in tablets of 50 mg under the brand name Ibsrela, the recommended dose being 50 mg twice daily taken before breakfast and before dinner. Tenapanor has not been approved for treatment of children and is contraindicated in children below the age of 6 because of the risk of dehydration. Common side effects include diarrhea, abdominal distension, flatulence, and dizziness. Rare, but potentially severe adverse events include severe diarrhea and dehydration. Tenapanor has embryo-fetal toxicity in animals and should not be used in pregnancy.

Hepatotoxicity

When given orally, tenapanor has minimal systemic absorption and has not been associated with elevations in serum enzymes or bilirubin or with instances of clinically apparent liver injury. Since approval and general availability of tenapanor, there have been no published reports of liver injury attributed to its use.

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

Mechanism of Injury

Tenapanor has minimal systemic absorption and has not been linked to instances of liver injury.

Drug Class: Gastrointestinal Agents, Irritable Bowel Syndrome Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tenapanor – Ibsrela®

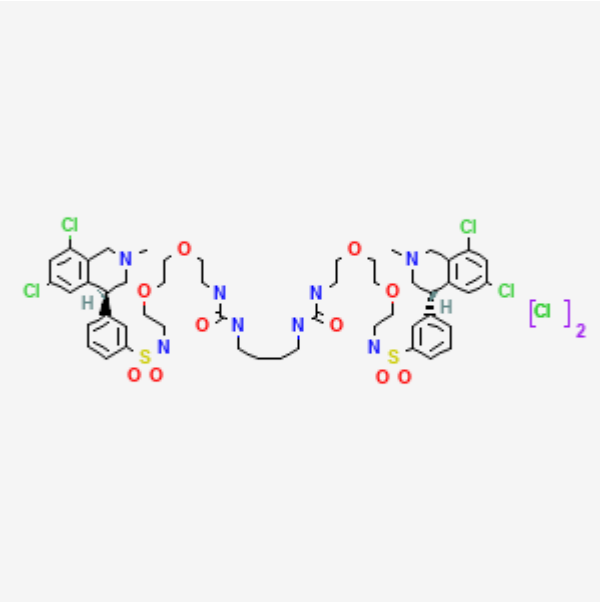
DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tenapanor	1234365-97-9	C50-H66-Cl4-N8-O10-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 30 April 2023

Abbreviations: IBS, irritable bowel syndrome; NHE3, sodium-hydrogen exchanger isoform 3.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999 before the availability of tenapanor).

Sharkey KA, MacNaughton WK. Gastrointestinal motility and water flux, emesis, and 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).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/211801Orig1s003.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; provides results from pharmacokinetic studies that demonstrated minimal or no detectable serum tenapanor levels after oral administration even in patients with significant hepatic and renal dysfunction or when given with strong inhibitors and inducers of cytochrome P450 [CYP] enzymes).

Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol. 2017;112:763–774. PubMed PMID: 28244495.

(Among 356 adults with constipation-predominant irritable bowel syndrome treated with tenapanor [5, 20 or 50 mg] twice daily for 12 weeks, response rates were highest with the 50 mg dose [61% vs 34% with placebo] while diarrhea arose in 11% of subjects, "There were no clinically meaningful changes from baseline in laboratory parameters").

Block GA, Rosenbaum DP, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: a randomized phase 3 trial. J Am Soc Nephrol. 2019;30:641–652. PubMed PMID: 30846557.

(Among 219 adults with chronic renal failure on maintenance hemodialysis treated with 3, 10 or 30 mg of tenapanor twice daily for 8 weeks, serum phosphate levels fell in all three groups, but diarrhea was a frequent side effect [30%-50%]; no mention of ALT elevations or hepatotoxicity).

Markham A. Tenapanor: first approval. Drugs. 2019;79:1897–1903. PubMed PMID: 31677150.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy, and safety of tenapanor shortly after its approval for use in the US, discusses the gastrointestinal side effects but does not mention ALT elevations or hepatotoxicity).

Chey WD, Lembo AJ. Rosenbaum aDP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 12-week, placebo-controlled phase 3 trial (T3MPO-1). Am J Gastroenterol. 2020;115:281–293. PubMed PMID: 31934897.

(Among 606 adults with constipation-predominant IBS treated with tenapanor [50 mg] or placebo twice daily for 12 weeks, tenapanor treated patients had greater increases in complete spontaneous bowel movements and more reductions in abdominal symptoms, while adverse events included diarrhea [15% vs 2%] and nausea [2.6% vs 1.7%], discontinuation rates were 7.4% vs <1%, and there were no drug related deaths or serious adverse events and "no notable changes from baseline were observed in laboratory parameters").

Block GA, Bleyer AJ, Silva AL, Weiner DE, Lynn RI, Yang Y, Rosenbaum DP, et al. Safety and efficacy of tenapanor for long-term serum phosphate control in maintenance dialysis: a 52-week randomized phase 3 trial (PHREEDOM). Kidney360. 2021;2:1600-1610.

(Among 564 patients with chronic renal failure on maintenance dialysis with hyperphosphatemia treated with either tenapanor or sevelamer carbonate for 26 weeks, those on tenapanor with improvements in serum phosphate levels being later re-randomized to continue therapy or stop tenapanor, side effects during therapy were predominantly gastrointestinal with diarrhea arising in 52% taking tenapanor, being severe in 6% and resulting in withdrawal in 16%; no mention of ALT levels or hepatotoxicity).

Chey WD, Lembo AJ, Yang Y, Rosenbaum DP. Efficacy of tenapanor in treating patients with irritable bowel syndrome with constipation: a 26-week, placebo-controlled phase 3 trial (T3MPO-2). Am J Gastroenterol. 2021;116:1294–1303. PubMed PMID: 33337659.

(Among 593 adults with constipation-predominant IBS treated with tenapanor [50 mg] or placebo twice daily for 26 weeks, response rates were higher for tenapanor [37% vs 24%] and the main side effect was diarrhea [16% vs 4%], which led to early discontinuation in 6.5% vs 0.7%, and "Generally, there was no evidence of clinically significant differences between treatment groups in electrolytes and other laboratory parameters").

Tenapanor (Ibsrela) for irritable bowel syndrome with constipation. Med Lett Drugs Ther. 2022;64(1652):91–94. PubMed PMID: 35657365.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of tenapanor shortly after its approval for use in adults with constipation-predominant IBS, discusses the side effects of diarrhea, abdominal distension, flatulence, and dehydration, but does not mention ALT elevations or hepatotoxicity).