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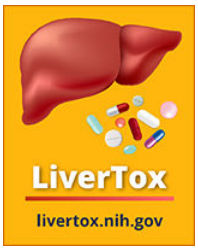


Rolapitant

Updated: March 1, 2024.

OVERVIEW

Introduction

Rolapitant is an orally available antiemetic agent that is used to prevent cancer chemotherapy related nausea and vomiting. Rolapitant therapy has not been associated with serum enzyme elevations or with instances of clinically apparent liver injury with jaundice.

Background

Rolapitant (roe la' pi tant) is a substance P/neurokinin 1 (NK-1) receptor antagonist which has potent and prolonged antiemetic activity. Rolapitant acts as a substance P antagonist blocking the neurokinin 1 (NK1) receptor, which is found in the central nervous system and induces the vomiting reflex when activated by substance P. Rolapitant has been shown to inhibit both acute and delayed nausea and vomiting associated with cancer chemotherapy and surgical procedures and appears to act synergistically with serotonin type 3 (5-HT3) receptor blockers. Because of its delayed half-life, rolapitant is particularly potent in preventing delayed (>24 hours after chemotherapy) nausea and vomiting. Rolapitant was approved for use in the United States in 2015 and current indications are in combination with other antiemetic agents in adults for prevention of delayed chemotherapy associated nausea and vomiting. Rolapitant is available as tablets of 90 mg under the brand name Varubi. The typical adult oral dose is 180 mg within 2 hours of starting each emetogenic chemotherapy cycle, generally in combination with a 5-HT3 receptor blocker, and dexamethasone. It has been used off label to treat postoperative nausea and vomiting. Side effects are uncommon, but can include anorexia, headache, neutropenia, and dizziness. Rolapitant has the potential significant drug-drug interactions with substrates and inducers of cytochrome P450 enzymes.

Hepatotoxicity

Serum aminotransferase elevations following initial cycles of chemotherapy occurred in less than 2% of rolapitant treated patients and a similar proportion of controls (1.3% vs 1.4% for AST). The aminotransferase elevations were transient, mild-to-moderate in severity, and not associated with symptoms or jaundice. There was no increase in frequency of serum enzyme elevations with subsequent chemotherapy cycles. No cases of clinically apparent liver injury attributable to rolapitant were described in the preregistration clinical trials of this agent, and there have been no cases published in the literature since its approval and more widescale use. Thus, significant liver injury from rolapitant must be rare if it occurs at all.

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

Mechanism of Injury

Rolapitant is metabolized by and inhibits hepatic CYP 2D6 and is a substrate of CYP 3A4 and thus has the potential to cause significant drug-drug interactions with substrates of CYP 2D6 and inducers or inhibitors of CYP 3A4. The mechanism by which rolapitant might cause liver injury is unknown. Rolapitant is generally given as a single, somewhat low oral dose which may account for why it is not associated with significant liver injury.

Drug Class: Gastrointestinal Agents, Antiemetic Agents

Other Drugs in the Subclass, Substance P/Neurokinin-1 Receptor Antagonists: Aprepitant, Fosaprepitant, Fosnetupitant,

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rolapitant – Varubi®

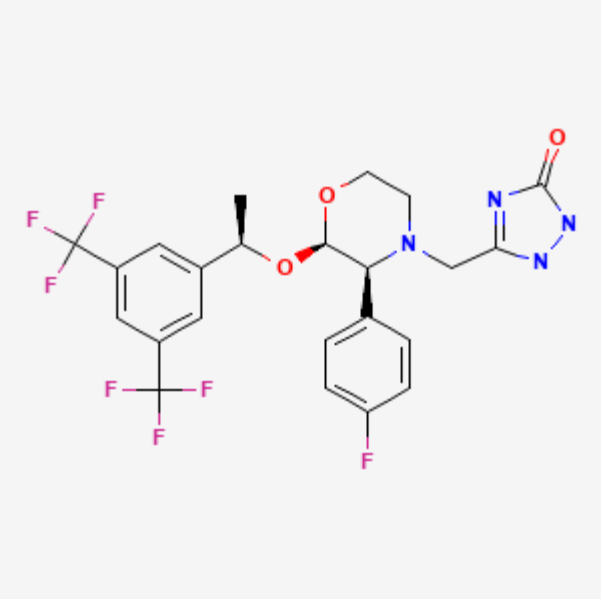
DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Aprepitant	170729-80-3	C23-H21-F7-N4-O3	

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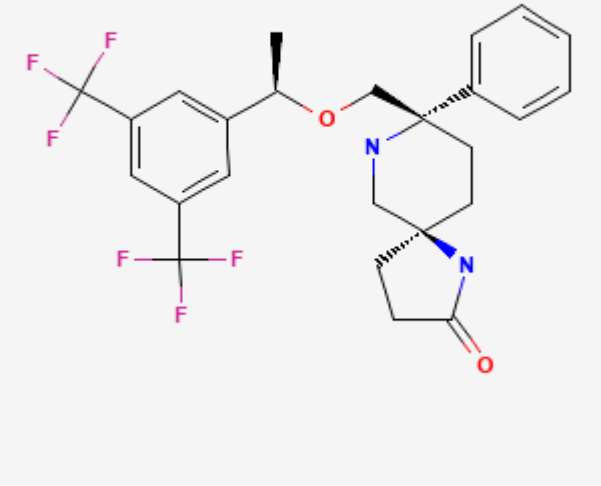
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Rolapitant	552292-08-7	C25-H26-F6-N2-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 29 February 2024

Zimmerman HJ. Antiemetic and prokinetic compounds. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 721.

(Expert review of hepatotoxicity published in 1999 before the availability of aprepitant or rolapitant).

Sharkey KA, McNaughton 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).

Gan TJ, Gu J, Singla N, Chung F, Pearman MH, Bergese SD, Habib AS, et al; Rolapitant Investigation Group. Rolapitant for the prevention of postoperative nausea and vomiting: a prospective, double-blinded, placebo-controlled randomized trial. Anesth Analg. 2011;112:804–812. PubMed PMID: 21385988.

(Among 619 women undergoing open abdominal surgery who received rolapitant [5, 20, 70 or 200 mg] or ondansetron or placebo, nausea and vomiting were less on the higher doses of rolapitant and ondansetron compared to placebo, yet adverse event rates were similar across all groups and "laboratory findings...were not significantly different when compared to placebo").

Schwartzberg LS, Modiano MR, Rapoport BL, Chasen MR, Gridelli C, Urban L, Poma A, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol. 2015;16:1071–1078. PubMed PMID: 26272768.

(Among 1369 patients receiving cyclic emetogenic cancer chemotherapy who received pretreatment with granisetron and dexamethasone with or without rolapitant, delayed phase nausea and vomiting were less with rolapitant while adverse event rates were similar in both groups, the most frequent being constipation, fatigue, dizziness and headache; no mention of ALT elevations or hepatotoxicity).

Rapoport BL, Chasen MR, Gridelli C, Urban L, Modiano MR, Schnadig ID, Poma A, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015;16:1079–1089. PubMed PMID: 26272769.

(Among 1087 patients receiving cisplatin based cancer chemotherapy who received granisetron and dexamethasone with or without rolapitant [180 mg on day 1], delayed nausea and vomiting were less with rolapitant, and adverse events were uncommon and similar between the two groups; no mention of ALT elevations or hepatotoxicity).

Olver I. Role of rolapitant in chemotherapy-induced emesis. Lancet Oncol. 2015;16:1006–1007. PubMed PMID: 26272772.

(Commentary on results of the three large randomized controlled trials of rolapitant described by Schwartzberg [2015] and Rapoport [2015]).

Syed YY. Rolapitant: first global approval. Drugs. 2015;75:1941–1945. PubMed PMID: 26467681.

(Review of the problem of chemotherapy induced nausea and vomiting, the acute [<24 hours] and delayed [1-5 days] phases, the standard approach to therapy, as well as the pharmacology, clinical efficacy and toxicity of rolapitant).

Rapoport B, Schwartzberg L, Chasen M, Powers D, Arora S, Navari R, Schnadig I. Efficacy and safety of rolapitant for prevention of chemotherapy-induced nausea and vomiting over multiple cycles of moderately or highly emetogenic chemotherapy. Eur J Cancer. 2016;57:23–30. PubMed PMID: 26851398.

(Pooled analysis of efficacy and safety of rolapitant based on four large placebo controlled trials; mentions that adverse events rates were similar in rolapitant [5.5%] vs placebo [6.8%] arms and there were no treatment related deaths and no mention of ALT elevations or hepatotoxicity).

Rolapitant (Varubi) for prevention and delayed chemotherapy-induced nausea and vomiting. Med Lett Drugs Ther. 2016;58:17–18. PubMed PMID: 26812124.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of rolapitant shortly after its approval in the US, mentions the more common adverse events including neutropenia, hiccups, decreased appetite and dizziness, but makes no mention of ALT elevations or hepatotoxicity).

Abdel-Rahman O, Fouad M. Rolapitant: a pooled analysis of its efficacy and safety in the prophylaxis of chemotherapy-induced nausea and vomiting. Future Oncol. 2016;12:871–879. PubMed PMID: 26806790.

(Among 2856 patients enrolled in 4 trials of rolapitant vs placebo for prevention of nausea and vomiting after cancer chemotherapy, rolapitant was associated with a higher rate of both early and late complete responses [no vomiting], no mention of ALT elevations or hepatotoxicity).

Barbour S, Smit T, Wang X, Powers D, Arora S, Kansra V, Aapro M, Herrstedt J. Integrated safety analysis of rolapitant with coadministered drugs from phase II/III trials: an assessment of CYP2D6 or BCRP inhibition by rolapitant. Ann Oncol. 2017;28:1268–1273. PubMed PMID: 28327932.

(Among 2595 patients treated with rolapitant vs placebo to prevent nausea and vomiting after emetogenic chemotherapy, there was no increase in adverse events in those concurrently receiving CYP2D6 substrates or CYP 3A4 inducers; provides data on fatigue, constipation, anorexia, alopecia, and febrile neutropenia, but not ALT elevations or hepatotoxicity).

IV aprepitant (Cinvanti) for chemotherapy-induced nausea and vomiting. Med Lett Drugs Ther. 2018;60:e200–e201. PubMed PMID: 30653479.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of aprepitant, the first substance P inhibitor approved for prevention of nausea and vomiting after highly emetogenic chemotherapy; in discussing adverse events, does not mention ALT elevations or hepatotoxicity).

Wang X, Zhang ZY, Wang J, Powers D, Arora S, Lu S, Kansra V. Pharmacokinetics, safety, and tolerability of rolapitant administered intravenously following single ascending and multiple ascending doses in healthy subjects. Clin Pharmacol Drug Dev. 2019;8:160–171. PubMed PMID: 29905976.

(In two pharmacokinetic studies in healthy adults, ascending dose infusions of rolapitant were "safe and well tolerated" with only mild and transient adverse events of headache, drug mouth, and fatigue, while the calculated half-life of rolapitant ranged from 5 to 10 days; routine clinical laboratory results were obtained, but results were not reported).

Navari RM. The safety of rolapitant for the treatment of nausea and vomiting associated with chemotherapy. Expert Opin Drug Saf. 2019;18:1127–1132. PubMed PMID: 31622113.

(Review of the safety and efficacy of oral and intravenously administered NK1 antagonists used for the prevention of chemotherapy induced nausea and vomiting, mentions that the most common adverse events are headache, constipation, and fatigue, but are no more frequent with rolapitant than with placebo and that it has no evidence of clinically significant drug-drug interactions, but that intravenous formulations were withdrawn cause of hypersensitivity reactions that occur with all parenteral NK1 formulations though appear least frequent with fosnetupitant).