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Rolapitant

Updated: January 1, 2017.

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 90 mg on day one of 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.

Hepatotoxicity

Serum aminotransferase elevations following initial cycles of chemotherapy occurred in <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. 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, Substance P/Neurokinin-1 Receptor Antagonists

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

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

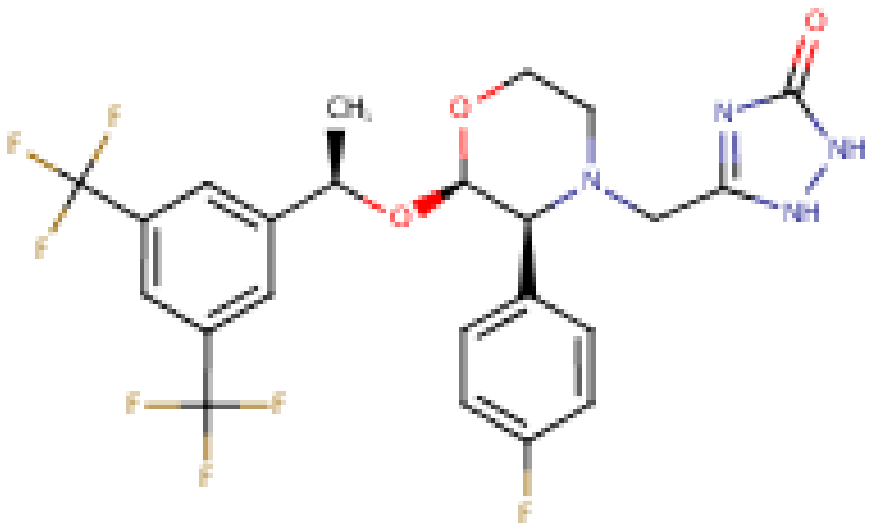
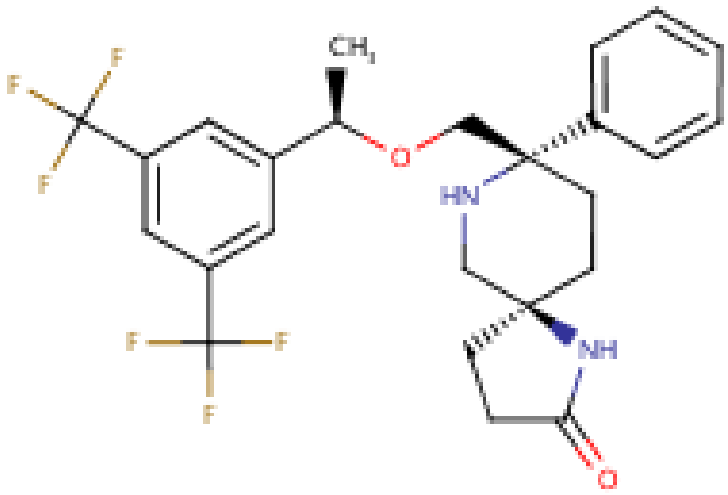
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Aprepitant	170729-80-3	C23-H21-F7-N4-O3	

Table continued from previous page.

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

ANNOTATED BIBLIOGRAPHY

References updated: 01 Junel 2017

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; does not discuss aprepitant or rolapitant).

Sharkey KA, Wallace JL. Treatment of disorders of bowel motility and water flux: anti-emetics; agents used in biliary and pancreatic disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1323-50.

(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: 804-12. 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: 1071-8. 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: 1079-89. 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: 1006-7. 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: 1941-5. 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 (1487): 17-8. 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).