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Crofelemer

Updated: November 2, 2017.

OVERVIEW

Introduction

Crofelemer is an antidiarrheal agent derived from the red sap of the South American plant Croton lechleri, which is used to treat noninfectious diarrhea in HIV positive patients on antiretroviral therapy. Crofelemer is associated with occasional instances of serum enzyme elevations during therapy, but has not been linked to cases of clinically apparent acute liver injury.

Background

Crofelemer (kroe fel' e mer) is a botanical antidiarrheal agent that is used to treat noninfectious diarrhea in HIV seropositive patients taking antiretroviral medications. Crofelemer is derived from the red sap of the South American plant Croton lechleri, which has been used for centuries to treat diarrheal illness. The active antidiarrheal product in crofelemer appears to be a large macromolecular, oligomeric proanthocyanidin which has been shown to decrease chloride secretion in the intestine by inhibition of the cystic fibrosis transmembrane conductance regulator (CFTR), as well as calcium-activated chloride channels. In large clinical trials, daily therapy with crofelemer was found to decrease watery bowel movements and improve stool consistency in patients with HIV infection receiving antiretroviral therapy, and who had persistent diarrhea that could not be attributed to an infectious cause. Crofelemer was approved for use in the United States in 2013, the first herbal medication to be approved for a specific medical use and first agent approved for therapy of noninfectious diarrhea in HIV positive patients. Crofelemer is available in tablets of 125 mg under the commercial name Mytesi. The typical dose is one tablet twice daily. Side effects are uncommon and generally mild, but can include flatulence, bloating, nausea, constipation, increased bilirubin, cough and symptoms of upper respiratory illness.

Hepatotoxicity

During long term use of crofelemer in preregistration studies, serum ALT elevations occurred in 2.7% of treated subjects, but the background rate of serum enzyme elevations in this population was not defined in these open label studies. The elevations were generally mild and self-limited, rarely leading to dose reduction or discontinuation of therapy. There have been no reports of clinically apparent liver injury attributable to crofelemer, although it has had only limited wide scale use.

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

Mechanism of Injury

The mechanism by which crofelemer might lead to serum enzyme elevations or liver injury is not known. Very little of the agent is absorbed systematically and, although it can be metabolized by the hepatic cytochrome P450 system, there is little evidence that adequate levels are achieved during oral therapy to cause clinically significant drug-drug interactions with other agents. In clinical trials of crofelemer, no evidence of drug-drug interactions was identified.

Outcome and Management

Serum enzyme elevations during crofelemer therapy are generally mild and self-limited, resolving even without drug interruption or dose reduction. Other causes of liver injury should be sought before assuming that the abnormalities are due to crofelemer.

Drug Class: Gastrointestinal Agents; Herbal and Dietary Supplements

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Crofelemer – Mytesi®

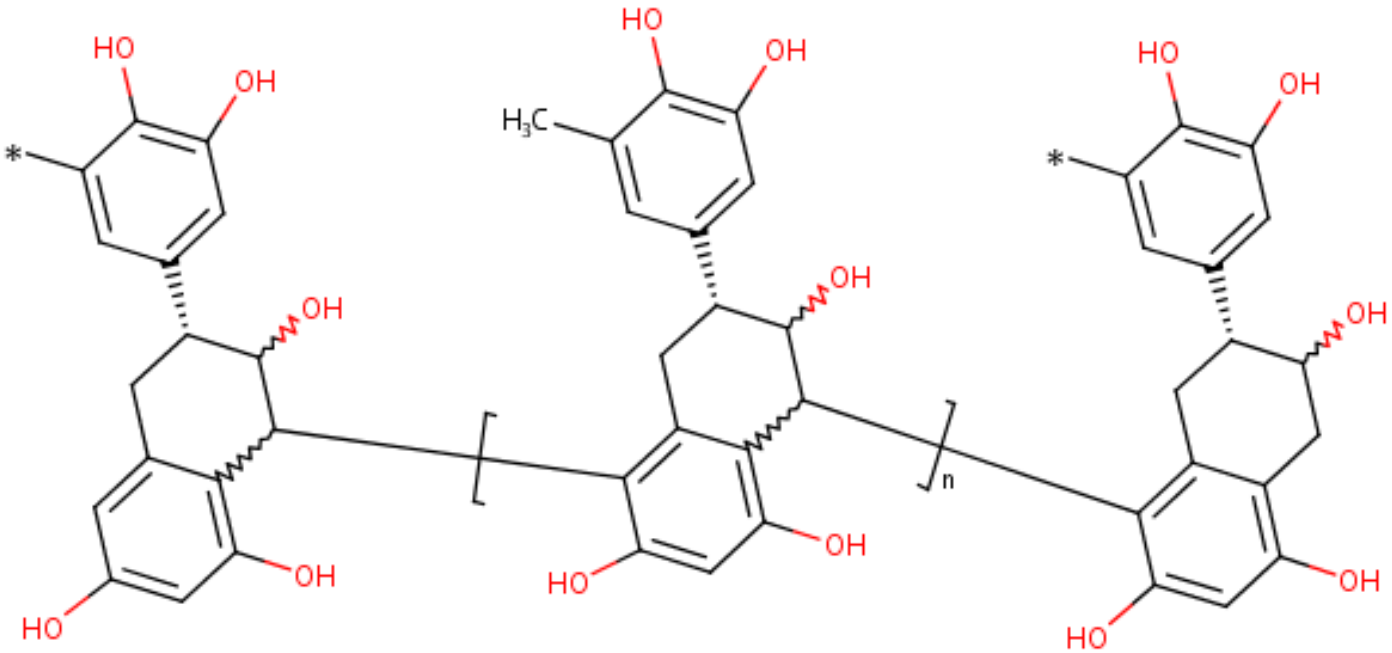
DRUG CLASS

Antidiarrheal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Crofelemer	148465-45-6	Unspecified	

ANNOTATED BIBLIOGRAPHY

References updated: 02 November 2017

Zimmerman HJ. Unconventional drugs. 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. 731-4.

(Expert review of hepatotoxicity published in 1999; crofelemer is not discussed).

Seeff L, Stickel F, Navarro VJ. Hepatotoxicity of herbals and dietary supplements. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 631-58.

(Review of hepatotoxicity of herbal and dietary supplements [HDS]; crofelemer is not discussed).

Tradtrantip L, Namkung W, Verkman AS. Crofelemer, an antisecretory antidiarrheal oligomer extracted from Croton lechleri, targets two distinct intestinal chloride channels. Mol Pharmacol 2010; 77: 69-78. PubMed PMID: 19808995.

(Investigation of the antidiarrheal mechanism of action of crofelemer found that it inhibited two different chloride channels [CFTR and calcium-activated chloride channels] in vitro in human intestinal cell lines).

MacArthur RD, Hawkins TN, Brown SJ, LaMarca A, Clay PG, Barrett AC, Bortey E, et al. Efficacy and safety of crofelemer for noninfectious diarrhea in HIV-seropositive individuals (ADVENT trial): a randomized, double-blind, placebo-controlled, two-stage study. HIV Clin Trials 2013; 14: 261-73. PubMed PMID: 19808995.

(Among 374 adults with HIV infection and noninfectious diarrhea attributed to antiretroviral therapy enrolled in a two stage, placebo controlled study of different doses of crofelemer, serum levels were undetectable in 96% of patients and adverse event rates were similar to those of placebo; during an open label extension study, serum ALT elevations occurred in 2.7% of crofelemer treated subjects, but all resolved and there were no serious adverse hepatic events or instances of clinically apparent liver injury).

Crofelemer (Fulyzaq) for antiretroviral-induced diarrhea. Med Let Drug Therap 2013; 55 (1421): 59-60. PubMed PMID: 23863919.

(Concise review of the mechanism of action, efficacy, safety and costs of crofelemer as therapy of noninfectious diarrhea in patients with HIV infection taking antiretroviral agents mentions that adverse events are uncommon and mild; no mention of ALT elevations or hepatotoxicity).

Frampton JE. Crofelemer: a review of its use in the management of non-infectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy. Drugs 2013; 73: 1121-9. PubMed PMID: 23807722.

(Systematic review of the literature on the mechanism of action, efficacy and safety of crofelemer in noninfectious diarrhea among antiretroviral treated adults with HIV infection, mentions that adverse events were uncommon and mild, but could include flatulence [3.1%], abdominal distention [1/7%], constipation [1.7%], dyspepsia [1.3%], nausea [1.3%] and ALT elevations [1.3%]).