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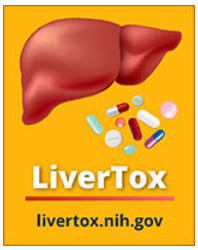


Fexinidazole

Updated: July 18, 2023.

OVERVIEW

Introduction

Fexinidazole is a nitroimidazole antimicrobial agent used to treat African trypanosomiasis, a severe and usually fatal parasitic infection caused by Trypanosoma brucei gambiense, also known as sleeping sickness. Fexinidazole is commonly associated with serum aminotransferase elevations when given in high doses for more than a few weeks, but elevations are uncommon and generally mild and transient when fexinidazole is given in the recommended doses for 10 days for African trypanosomiasis.

Background

Fexinidazole (fex" i nid' a zole) is a nitroimidazole antimicrobial agent developed as therapy for African trypanosomiasis, the severe parasitic infection also known as sleeping sickness. The disease is caused by infection with Trypanosoma brucei gambiense, a protozoa transmitted by the bite of the tsetse fly and found in Subsaharan Africa and occasionally among travelers returning from endemic areas, most commonly from the Central African Republic and the Democratic Republic of the Congo. African trypanosomiasis presents initially with intermittent fever, headaches, muscle and joint aches, weight loss and lymphadenopathy. During this early stage (Stage 1) of infection, trypanosomes are found in the bloodstream and lymph nodes only. With time, late stage symptoms of central nervous system involvement arise (Stage 2) with daytime sleepiness, personality changes, confusion and stupor followed by coma. In this stage, the trypanosomes are also detectable in cerebral spinal fluid and meninges. Fexinidazole was developed as therapy for African trypanosomiasis by the Drugs for Neglected Diseases Initiative in collaboration with Sanofi, a pharmaceutical company that had shelved the drug many years previously. In prospective controlled trials, a ten day course of oral fexinidazole was found to be non-inferior to the previous standard therapy of African trypanosomiasis, which requires 10 days of oral nifurtimox with 7 days of twice daily intravenous infusions of eflornithine (NECT), a difficult regimen in resource limited areas where trypanosomiasis is found. Fexinidazole was approved in the United States in 2021 and made available as tablets of 600 mg. The recommended dose in adults is 1800 mg once daily for 4 days followed by 1200 mg once daily for another 6 days. Lower doses are used in children [ages 6 years or older] below 35 but at least 20 kilograms in weight. Formal indications are for both first and second stage African trypanosomiasis due to infection with Trypanosoma brucei gambiense, but fexinidazole also appears to be effective for cases due to Trypanosoma brucei rhodesiense. Adverse events can include headache, nausea and vomiting, insomnia, fatigue, tremor, dizziness, poor appetite, back and abdominal pain, hyperkalemia and hypocalcemia – symptoms and abnormalities that are also frequent with the underlying disease. Rare but potentially severe adverse events include prolongation of the QTc interval, neuropsychiatric reactions, agitation, hallucinations, neutropenia, and alcohol reactions for which reason alcohol should be prohibited during therapy and concomitant medications scrutinized for possible drug-drug interactions or additive adverse effects.

Hepatotoxicity

Fexinidazole therapy was not associated with elevations in aminotransferase or bilirubin levels or with clinically apparent liver injury during the ten day regimens used to treat African trypanosomiasis. However, evaluation of longer courses of therapy and use of higher doses in Chagas disease caused by Trypanosoma cruzi demonstrated several instances of ALT or AST elevations above 3 times the upper limit of normal (ULN), which persisted for as long as 3 months after stopping fexinidazole. The enzyme elevations were usually hepatocellular and arose after 2 weeks of therapy. The liver injury was asymptomatic and not associated with jaundice or with rash, fever or other signs of hypersensitivity. Nevertheless, the hepatic injury as well as delayed neutropenia led to discontinuation of the clinical trials of fexinidazole in high doses in Chagas disease. Since approval of fexinidazole for African trypanosomiasis, there have been no individual reports of liver injury associated with its use.

Likelihood score: E* (unlikely but suspected cause of clinically apparent liver injury when given in the recommended regimens for African trypanosomiasis).

Mechanism of Injury

The mechanism by which fexinidazole causes liver injury is unknown. Fexinidazole is a prodrug that is activated to an reactive metabolite by parasites but not in human cells. It acts by binding tubulin in parasitic worms which it does with greater avidity than the tubulin in mammalian cells, but some of the toxicity of the may be related to this tubulin-binding activity.

Outcome and Management

Fexinidazole is usually well tolerated, and the liver injury reported with its use arose in regimens for Chagas disease which employed higher doses for a longer period. Similar episodes of hepatocellular injury have been reported with other nitroimidazoles and benzimidazoles. It is unknown whether there is cross sensitivity with these other antiparasitic agents.

Drug Class: Antiinfective Agents, Trypanosomiasis Agents

Other Drugs in the Subclass, Nitroimidazoles: Benznidazole, Metronidazole, Secnidazole, Tinidazole

Other Trypanosomiasis Agents: Benznidazole, Nifurtimox

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Fexinidazole – Fexinidazole®

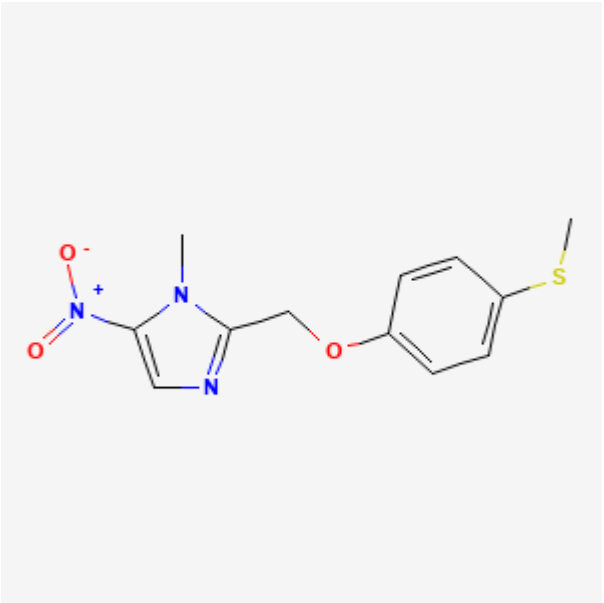
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Fexinidazole	59729-37-2	C12-H13-N3-O3-S	

ANNOTATED BIBLIOGRAPHY

References updated: 18 July 2023

Abbreviations used: NECT, nifurtimox and eflornithine combination therapy.

Zimmerman HJ. Antihelminthics. Hepatic injury from antimicrobial agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 626-8.

(Expert review of hepatotoxicity of drugs for parasite infections written in 1999, before the availability of drugs for trypanosomiasis).

Wetzel DM, Phillips MA. Chemotherapy of protozoal infections: amebiasis, giardiasis, trichomoniasis, trypanosomiasis, Leishmaniasis, and other protozoal infections. 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. 987-99.

(Textbook of pharmacology and therapeutics).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin American published between 1996 and 2012, none were attributed for agents used to treat trypanosomiasis including Chagas disease).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to medications for parasitic diseases).

Maxmen A. Sleeping sickness can now be cured with pills. Nature. 2017;550:441. PubMed PMID: 29072286.

(News report describing the successful results of all oral therapy with fexinidazole in African trypanosomiasis [91% response rates], the result of a collaboration between the non-profit research organization "Drugs for Neglected Diseases" initiative and the Sanofi pharmaceutical company).

Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, Delhomme S, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018;391:144-154. PubMed PMID: 29113731.

(Among 394 patients [ages 15 years or above] with late stage African trypanosomiasis treated with fexinidazole or NECT therapy for 20 days, success rates at 18 months after enrollment were 91% vs 98% [a non-inferior result], and adverse events rates were similar [94% vs 92%] including severe adverse events [12% vs 10%]; and while ALT elevations and hepatotoxicity were not specifically mentioned, "There were no clinically significant changes in any…laboratory values over the duration of treatment").

Pelfrene E, Harvey Allchurch M, Ntamabyaliro N, Nambasa V, Ventura FV, Nagercoil N, Cavaleri M. The European Medicines Agency's scientific opinion on oral fexinidazole for human African trypanosomiasis. PLoS Negl Trop Dis. 2019;13:e0007381. PubMed PMID: 31246956.

(The European Medicines Agency's scientific report on the efficacy and safety of oral fexinidazole as therapy for African trypanosomiasis endorsing its use in Europe as well as regions outside the European Union where the disease is endemic and a major cause of morbidity and mortality).

Deeks ED. Fexinidazole: first global approval. Drugs. 2019;79:215-220. PubMed PMID: 30635838.

(Review of the history of development, mechanism of action, pharmacokinetics, clinical efficacy, and safety of fexinidazole shortly after its approval by the European Medicines Agency makes no mention of ALT elevations or hepatotoxicity).

Kande Betu Ku Mesu V, Mutombo Kalonji W, Bardonneau C, Valverde Mordt O, Ngolo Tete D, Blesson S, Simon F, et al. Oral fexinidazole for stage 1 or early stage 2 African Trypanosoma brucei gambiense trypanosomiasis: a prospective, multicentre, open-label, cohort study. Lancet Glob Health. 2021;9:e999-e1008. PubMed PMID: 34143998.

(Among 232 patients with early stage African trypanosomiasis treated with open-label fexinidazole, the response rate at 12 months was 98% and adverse events were frequent [93%] but did not result in deaths or treatment discontinuation and there were no "acute or delayed liver abnormalities").

Kande Betu Kumesu V, Mutombo Kalonji W, Bardonneau C, Valverde Mordt O, Ngolo Tete D, Blesson S, Simon F, et al. Safety and efficacy of oral fexinidazole in children with gambiense human African trypanosomiasis: a multicentre, single-arm, open-label, phase 2-3 trial. Lancet Glob Health. 2022;10:e1665-e1674. PubMed PMID: 36179736.

(Among 125 children with stage 1 or early stage 2 African trypanosomiasis treated with open-label fexinidazole [either 1800 mg for 4 days followed by 1200 mg for 6 days, or 1200 mg followed by 600 mg if body weight <35 kilograms], the 12 month success rate was 98% and adverse events were frequent but mostly mild-to-moderate and "Assessment of laboratory values…did not raise any safety concerns").

Torrico F, Gascón J, Ortiz L, Pinto J, Rojas G, Palacios A, Barreira F, et al. A phase 2, randomized, multicenter, placebo-controlled, proof-of-concept trial of oral fexinidazole in adults with chronic indeterminate Chagas Disease. Clin Infect Dis. 2023;76:e1186-e1194. PubMed PMID: 35925555.

(Among 47 adults with chronic indeterminate Chagas disease treated with 1 of 6 regimens of fexinidazole given orally for 2, 4 or 8 weeks or placebo [n=7], rapid sustained clearance of parasitemia was achieved in all subjects but adverse events included delayed onset neutropenia [20%] and serum aminotransferase elevations [16: 40%

above 3 times ULN], which often arose after therapy was stopped and persisted beyond 3 months in 23% but were asymptomatic and ultimately resolved in all).