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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Safinamide. [Updated 2019 Apr 8].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Safinamide

Updated: April 8, 2019.

OVERVIEW

Introduction

Safinamide is an inhibitor of monoamine oxidase used as adjunctive therapy in combination with levodopa and carbidopa in the management of Parkinson's disease. Safinamide has been associated with a low rate of serum enzyme elevations during treatment, but has not been linked to instances of clinically apparent acute liver injury.

Background

Safinamide (sa fin' a mide) is a potent and highly specific inhibitor of monoamine oxidase (MAO) type B which is a major enzyme in the degradation pathway of dopamine and levodopa metabolism. As a result, safinamide results in an increase in the bioavailability of levodopa enhancing and increasing the duration of its effects in Parkinson disease. Safinamide was approved for use in the United States in 2017, the third MAO-B inhibitor approved for use in Parkinson disease, and is currently approved for use only as an adjunct to levodopa therapy. Safinamide is available in tablets of 50 and 100 mg under the brand name Xadago. Safinamide is typically given in oral doses of 50 or 100 mg once daily in combination with levodopa/carbidopa. Common side effects include dyskinesia, falls, nausea, abdominal pain, cough, hypertension, headache, blurred vision, dizziness, insomnia and tremor–most of which are attributable to enhanced dopaminergic effects. Rare, but potentially severe side effects include severe hypertension, serotonin syndrome, daytime sleepiness, hallucinations, difficulties with impulse control, hypersexuality and compulsive behavior. Unlike some other MAO inhibitors, safinamide has not been shown to cause increased susceptibility to dietary tyramine inducing hypertensive crises ("cheese effect").

Hepatotoxicity

Safinamide has been reported to cause serum enzyme elevations in a small proportion of patients treated long term, although the abnormalities were usually mild and self-limiting and were usually no more frequent than with placebo or comparator agents. Safinamide has not been implicated in cases of acute liver injury, but such instances have been reported with nonspecific MAO inhibitors.

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

Mechanism of Injury

The mechanism by which safinamide might cause liver injury is not known. Safinamide is extensively metabolized but has no effect on cytochrome P450 enzymes or hepatic transporters and significant drug-drug

interactions have not been demonstrated. Patients taking MAO inhibitors should avoid use of serotonin reuptake inhibitors and sympathomimetic medications.

Outcome and Management

Instances of hepatotoxicity attributed to safinamide have been mild and self-limiting elevations in serum enzymes. No instances of severe liver injury, acute liver failure, chronic hepatitis or vanishing bile duct syndrome have been linked to safinamide use.

Drug Class: Antiparkinson Agents

Other Drugs in the Subclass, Selective MAO-B Inhibitors: Rasagiline, Selegiline

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Safinamide – Generic, Xadago®

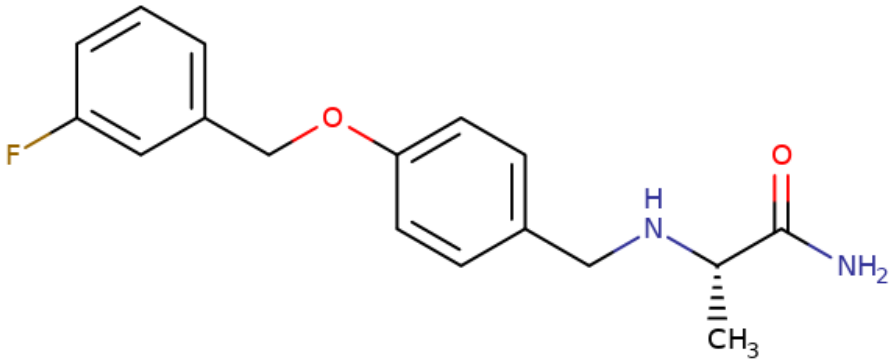
DRUG CLASS

Antiparkinson Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Safinamide	133865-89-1	C17-H19-F-N2-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 08 April 2019

Zimmermam HJ. Antiparkinsonism drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 715-7.

(Expert review of hepatotoxicity published in 1999; among anticholinergic agents, "only trihexyphenidyl has been incriminated in hepatic injury"; other antiparkinsonism drugs discussed include levodopa, lergotrile [no longer available], pergolide and bromocriptine, but not selegiline, rasagiline or safinamide).

Larrey D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier Inc, 2013, pp. 443-62.

(Review of hepatotoxicity of agents acting on the central nervous system).

Roberson ED. Treatment of central nervous system degenerative disorders. 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. 327-38.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(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; mentions that "shifts from baseline to high levels" of ALT and AST were more frequent with safinamide than placebo treatments in several clinical trials but no actual values, timing or duration of elevations were provided).

(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; mentions that "shifts from baseline to high levels" of ALT and AST were more frequent with safinamide than placebo treatments in several clinical trials but no actual values, timing or duration of elevations were provided).

Lambert D, Waters CH. Comparative tolerability of the newer generation antiparkinsonian agents. Drugs Aging 2000; 16: 55-65. PubMed PMID: 10733264.

(Review of mechanism of action, tolerability and safety of selegiline, pramipexole, ropinirole, tolcapone and entacapone in Parkinson disease).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to agents used for Parkinson disease).

Stocchi F, Borgohain R, Onofrj M, Schapira AH, Bhatt M, Lucini V, Giuliani R, Anand R; Study 015 Investigators. A randomized, double-blind, placebo-controlled trial of safinamide as add-on therapy in early Parkinson's disease patients. Mov Disord 2012; 27: 106-12. PubMed PMID: 21913224.

(Among 269 patients with early Parkinson disease on a dopamine agonist to which was added safinamide [100 or 200 mg daily] or placebo for 24 weeks, responses were more frequent with the 100 mg dose than with placebo or the 200 mg dose, while adverse event rates were similar in all three groups and "the incidence of clinically notable values for laboratory parameters and vital signs were comparable between groups").

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the 96 were attributed to an agent used to treat Parkinson disease).

Drugs for Parkinson's disease. Treat Guidel Med Lett 2017; 59 (1534): 198-94. PubMed PMID: 29136401.

(Concise review of recommendations for therapy of Parkinson disease with description of mechanisms of action, efficacy, adverse events and costs; does not mention ALT elevations or hepatotoxicity, "whether safinamide is more effective or has a more favorable safety profile than the other irreversible MAO-B inhibitors is unknown").

Schapira AH, Stocchi F, Borgohain R, Onofrj M, Bhatt M, Lorenzana P, Lucini V, et al.; Study 017 Investigators. Long-term efficacy and safety of safinamide as add-on therapy in early Parkinson's disease. Eur J Neurol 2013; 20: 271-80. PubMed PMID: 22967035.

(Among 227 patients who enrolled in an extension study after participation in a randomized controlled trial [Stocchi 2012] and were treated with either safinamide [100 or 200 mg] or placebo, changes in symptoms and response rates were similar in the 3 groups as well total and serious adverse event rates; no mention of ALT elevations or hepatotoxicity).

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 America published between 1996 and 2012, none were attributed to an agent to treat Parkinson disease).

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, Stocchi F, et al.; Study 018 Investigators. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov Disord 2014; 29: 1273-80. PubMed PMID: 25044402.

(Among 669 patients with Parkinson disease on long term levodopa therapy who were treated with safinamide [50 or 100 mg] or placebo, troublesome dyskinesia was less with safinamide and adverse event rates were similar in all 3 groups and "there were no significant findings for clinical laboratory tests").

Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, et al.; Study 016 Investigators. Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord 2014; 29: 229-37. PubMed PMID: 24323641.

(Among 669 patients with mid- to late-stage Parkinson disease treated with safinamide [50 or 100 mg daily] or placebo as add-on therapy to levodopa and other therapies for 24 weeks and then continued on same regimen for another 12 months, improvement in total dyskinesia score was similar in all 3 groups as were most adverse event rates; no mention of ALT elevations or hepatotoxicity).

Deeks ED. Safinamide: first global approval. Drugs 2015; 75: 705-11. PubMed PMID: 25851099.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of safinamide; mentions common adverse events of dyskinesia, insomnia, somnolence, dizziness, headache, cataract, orthostatic hypotension, nausea and falls but not ALT elevations or hepatotoxicity).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, none were attributed to an agent used to treat Parkinson disease).

Safinamide(Xadago) for Parkinson's disease. Med Lett Drugs Ther 2017; 59 (1529): 151-3. PubMed PMID: 28880847.

(Concise review of the standard therapy of Parkinson disease, the mechanism of action of safinamide, its clinical efficacy, safety and costs shortly after its approval for use in the US; mentions that it can cause mild ALT and AST elevations but does not mention clinically apparent liver injury).

Jiménez-Jiménez FJ, Alonso-Navarro H, Valle-Arcos D. Hypersexuality possibly associated with safinamide. J Clin Psychopharmacol 2017; 37: 635-6. PubMed PMID: 28796020.

(75 year old woman with Parkinson disease on multiple agents for several years developed increased libido and obsessive sexual urges 5 months after switching from rasagiline to safinamide [100 mg daily] combined with levodopa/carbidopa, symptoms becoming increasingly distressful and then resolving completely and permanently one week after stopping safinamide).

Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, et al. Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial. JAMA Neurol 2017; 74: 216-24. PubMed PMID: 27942720.

(Among 549 patients with Parkinson disease who were treated with safinamide [50 mg raised to 100 mg after 2 weeks] or placebo added to levodopa [with or without other agents] for 24 weeks, there was an increase in time with control of motor fluctuations without troublesome dyskinesia with safinamide therapy while overall and severe adverse event rates were similar and there were "no clinically meaningful mean changes in…laboratory values").

Mancini F, Di Fonzo A, Lazzeri G, Borellini L, Silani V, Lacerenza M, Comi C. Real life evaluation of safinamide effectiveness in Parkinson's disease. Neurol Sci 2018; 39: 733-9. PubMed PMID: 29441484.

(Among 91 patients with Parkinson disease treated with safinamide for motor fluctuations and dyskinesias, most patients experienced improvement while 8 discontinuation therapy because of side effects, but none because of ALT elevations or hepatotoxicity).