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Lesinurad

Updated: May 1, 2019.

OVERVIEW

Introduction

Lesinurad is a selective inhibitor of uric acid reabsorption which is used in combination with other agents in the therapy of gout. Lesinurad has had limited clinical use, but has not been associated with serum enzyme elevations during therapy or with instances of clinically apparent liver injury.

Background

Lesinurad (le sin' ure ad) is a selective inhibitor of the uric acid transporter (URAT1) in the kidneys that is responsible for reabsorption or urate in the distal tubules. Inhibition of uric acid reabsorption causes a decrease in serum levels of uric acid, but an increase in urinary urate. Lesinurad was found to lower uric acid levels in patients with gout and hyperuricemia who had not achieved adequate control of symptoms or uric acid levels with a xanthine oxidase inhibitor (allopurinol or febuxostat) alone. Lesinurad was approved in the United States in 2015 for use in combination with a xanthine oxidase inhibitor in patients with gout and hyperuricemia. Lesinurad is available in tablets of 200 mg under the brand name Zurampic. The typical dose is 200 mg once daily in combination with allopurinol or febuxostat. Side effects are not common with lesinurad, but can include headache, upper respiratory tract infections, reflux esophagitis and elevations in serum creatinine. Severe adverse reactions include acute renal failure, particularly in patients who are not receiving a xanthine oxidase inhibitor.

Hepatotoxicity

In large clinical trials, serum enzyme elevations were rare during lesinurad therapy and no more common than with placebo, and no instances of clinically apparent liver injury attributable to lesinurad were reported. Clinical experience with lesinurad therapy has been limited, but there have yet to be reports of clinically apparent liver injury attributable to its use.

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

Mechanism of Injury

The mechanism by which lesinurad might cause liver injury is unclear. Lesinurad is metabolized in the liver via the cytochrome P450 system, particularly CYP 2C9 and 3A and is susceptible to drug-drug interactions with substrates, inducers or inhibitors of those microsomal enzymes.

Outcome and Management

The serum enzyme elevations during lesinurad therapy are uncommon. In situations in which ALT or AST levels rise and remain above 5 times ULN, dose modification or temporary discontinuation of lesinurad is prudent.

Drug Class: Antigout Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lesinurad – Zurampic®

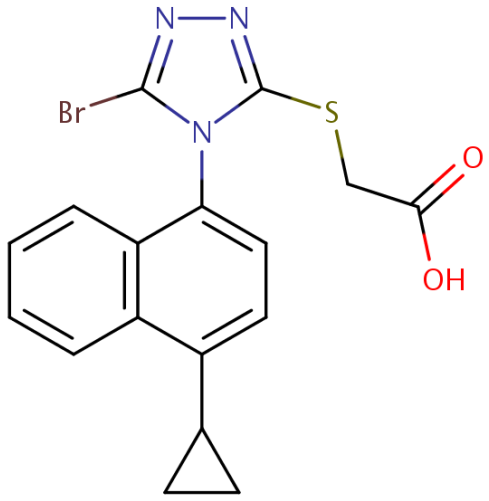
DRUG CLASS

Antigout Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Lesinurad	878672-00-5	C17-H14-Br-N3-O2-S	

ANNOTATED BIBLIOGRAPHY

References updated: 01 May 2019

Zimmerman HJ. Drugs used to treat gout. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 542-4.

(Textbook of hepatotoxicity published in 1999 and before the availability of lesinurad).

Grosser T, Smyth E, FitzGerald GA. Pharmacotherapy of inflammation, fever, pain, and gout. 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. 685-710.

(Textbook of pharmacology and therapeutics).

Fleischmann R, Kerr B, Yeh LT, Suster M, Shen Z, Polvent E, Hingorani V, et al.; RDEA594-111 Study Group. Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia. Rheumatology (Oxford) 2014; 53: 2167-74. PubMed PMID: 24509406.

(Among 20 patients treated with escalating doses of lesinurad in combination with allopurinol or febuxostat, side effects included headache and dyspepsia, but there were no serious adverse events and no "treatment-related changes in clinical laboratory evaluations").

Drugs for gout. Med Lett Drugs Ther 2014; 56 (1438): 22-4. PubMed PMID: 24791281.

(Update on medications for gout discusses the urate lowering agents allopurinol, febuxostat, probenecid and pegloticase, but not lesinurad).

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 in the US collected between 2004 and 2012, 8 cases were attributed to drugs used for gout [allopurinol in 7 and febuxostat in 1], but no cases were attributed to lesinurad).

Perez-Ruiz F, Sundy JS, Miner JN, Cravets M, Storgard C; RDEA594-203 Study Group. Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. Ann Rheum Dis 2016; 75: 1074-80. PubMed PMID: 26742777.

(Among 208 patients with hyperuricemia and gout treated with lesinurad [200, 400 or 600 mg] or placebo daily in addition of allopurinol, uric acid levels decreased with active drug but not placebo, and there were no serious adverse events or deaths; no mention of ALT changes or clinically apparent liver injury).

Hoy SM. Lesinurad: first global approval. Drugs 2016; 76: 509-16. PubMed PMID: 26861027.

(Review of the development, mechanism of action, pharmacology, clinical efficacy and safety of lesinurad shortly after its approval in the US mentions that it was "generally well tolerated" with pooled adverse event rates similar to those with placebo, with headache in 5.3% vs 4.1%, gastroesophageal reflux in 2.7% vs 0.8%, creatinine elevations in 3.9% vs 1.8%; no mention of ALT elevations or hepatotoxicity).

Bardin T, Keenan RT, Khanna PP, Kopicko J, Fung M, Bhakta N, Adler S, et al. Lesinurad in combination with allopurinol: a randomised, double-blind, placebo-controlled study in patients with gout with inadequate response to standard of care (the multinational CLEAR 2 study). Ann Rheum Dis 2017; 76 (5): 811-20. PubMed PMID: 27821644.

(Among 610 patients with gout an an inadequate response to allopurinol treated with lesinurad [200 or 400 mg daily] or placebo, those on lesinurad had a greater rate of uric acid control and "clinical laboratory results" excluding creatinine levels "were comparable between treatment groups").

Saag KG, Fitz-Patrick D, Kopicko J, Fung M, Bhakta N, Adler S, Storgard C, et al. Lesinurad combined with allopurinol: randomized, double-blind, placebo-vontrolled dtudy in gout subjects with inadequate response to standard of care allopurinol (a US-based study). Arthritis Rheumatol 2017; 69: 203-12. PubMed PMID: 27564409.

(Among 603 patients with gout and an inadequate response to allopurinol who were started on lesinurad [200 or 400 mg daily] vs placebo, those on lesinurad had a greater rate of uric acid control and "clinical laboratory test results, including ...liver function tests... demonstrated no notable differences between the treatment groups over time").

Lesinurad (Zurampic) for gout-associated hyperuricemia. Med Lett Drugs Ther 2016; 58 (1508): 148-50. PubMed PMID: 27849193.

(Concise review of the mechanism of action, clinical efficacy, safety, drug-interactions and costs of lesinurad, shortly after its approval for treament of gout associated hyperuricemia in the US, mentions creatinine but not aminotransferase elevations occurring on therapy).

Lesinurad/allopurinol (Duzallo) for gout-associated hyperuricemia. Med Lett Drugs Ther 2017; 59 (1533): 182-3. PubMed PMID: 29125593.

(Concise review of the efficacy, safety and costs of the fixed combination of lesinurad and allopurinol for once-daily treatment of gout; mentions renal toxicity of lesinurad and hepatotoxicity of allopurinol).

Dalbeth N, Jones G, Terkeltaub R, Khanna D, Fung M, Baumgartner S, Perez-Ruiz F. Efficacy and safety during extended treatment of lesinurad in combination with febuxostat in patients with tophaceous gout: CRYSTAL extension study. Arthritis Res Ther 2019; 21: 8. PubMed PMID: 30616614.

(Among 193 patients completing a 12-month controlled trial of lesinurad and febuxosat who were enrolled in an extension study for a total of 2 years, there were "no notable changes from baseline" of clinical safety laboratory values).

Perez-Gomez MV, Bartsch LA, Castillo-Rodriguez E, Fernandez-Prado R, Kanbay M, Ortiz A. Potential dangers of serum urate-lowering therapy. Am J Med 2019; 132: 457-67. PubMed PMID: 30611833.

(Commentary on the trend for higher mortality rates in trials of uric acid lowering drugs among patients who achieve the lowest levels, suggesting that serum uric acid values below 5.0 mg/dL may be unsafe).

Terkeltaub R, Saag KG, Goldfarb DS, Baumgartner S, Schechter BM, Valiyil R, Jalal D, et al. Integrated safety studies of the urate reabsorption inhibitor lesinurad in treatment of gout. Rheumatology (Oxford) 2019; 58: 61-9. PubMed PMID: 30124941.

(Pooled analysis of 3 controlled trials found no increase in renal, cardiovascular or other adverse events associated with addition of lesinurad to allopurinol).

Drugs for gout. Med Lett Drugs Ther 2019; 61 (1567): 33-7. PubMed PMID: 30845096.

(Concise review of medications used to treat gout; mentions that meta-analysis of 5 randomized controlled trials found that addition of lesinurad to a xanthine oxidase inhibitor did not improve clinical gout related outcomes and the fixed combination of lesinurad and allopurinol has been withdrawn from the US market).