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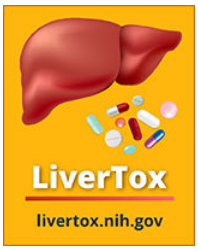
NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Selexipag. [Updated 2016 Nov 10].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Selexipag

Updated: November 10, 2016.

OVERVIEW

Introduction

Selexipag is prostacyclin receptor agonist that causes vasodilation in pulmonary vasculature and is used in the therapy of pulmonary arterial hypertension (PAH). Selexipag has been associated with a low rate of serum enzyme elevations during therapy, but has yet to be implicated in cases of clinically apparent acute liver injury.

Background

Selexipag (se lex' i pag) is a selective prostacyclin receptor agonist that is used to treat pulmonary arterial hypertension (PAH). Inhibition of the prostaglandin receptors disrupts the intracellular pathways that lead to vasoconstriction, thus causing vasodilation. Because these receptors are found in highest concentration in the lungs, selexipag primarily causes vasodilation in the pulmonary vasculature and decreases pulmonary vascular pressure. In prospective, randomized controlled trials, selexipag was effective in alleviating symptoms, improving exercise capacity and prolonging the time to clinical worsening in patients with idiopathic PAH. Selexipag was approved for use in the United States in 2015 and experience with its use is limited. The current indications are for symptomatic PAH, classified as WHO group 1 (idiopathic). Use of selexipag in other forms of PAH (due to heart failure, thromboembolic disease, or pulmonary disease) should be considered experimental as its efficacy in these forms of PAH has not been adequately shown. Selexipag is available in tablets of 200, 400, 800, 1000, 1200, 1400 and 1600 μg under the brand name Uptravi. The recommended starting dose is 200 μg twice daily, which can be increased weekly by 200 μg twice daily to the highest tolerated dose up to 1600 μg twice daily. Common side effects include headaches, diarrhea, jaw pain, nausea, vomiting, myalgia, pain in the extremities and flushing. Uncommon, but potentially severe adverse reactions include pulmonary edema and hypersensitivity reactions.

Hepatotoxicity

Selexipag is associated with a low rate of serum aminotransferase elevations (0% to 3%) that in clinical trials was similar to the rate among placebo recipients. These elevations were usually mild (rarely above 3 times ULN), transient and not associated with symptoms. There were no cases of serum enzyme elevations with jaundice in these preregistration clinical trials. Since licensure and more wide scale use, there have been no published reports of clinically apparent liver injury with jaundice associated with selexipag, but it has had limited general use.

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

Mechanism of Injury

The mechanism by which selexipag might cause liver injury is not known. Selexipag is metabolized by the cytochrome P450 system (CYP 2C9 and 3A4), which may lead to production of a toxic intermediate and can also cause drug-drug interactions, particularly with cyclosporine A. One reason for its lack of hepatotoxicity may be that selexipag is administered in relatively low doses of 0.4 to 3.2 mg daily.

Outcome and Management

The serum enzyme elevations associated with selexipag use have been mild-to-moderate and self-limited in course, often resolving despite drug continuation. There is no reason to believe that there is cross sensitivity to liver injury among the various therapies for PAH.

Drug Class: Pulmonary Arterial Hypertension Agents

Other Drugs in the Class: Ambrisentan, Bosentan, Riociguat, Macitentan; Prostacyclin Analogs, Epoprostenol, Iloprost, Treprostinil

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Selexipag – Uptravi®

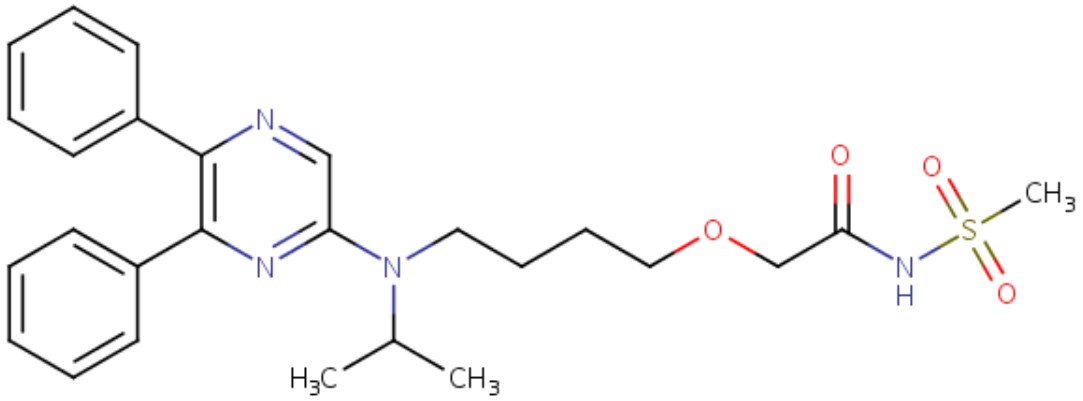
DRUG CLASS

Pulmonary Arterial Hypertension Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Selexipag	475086-01-2	C26-H32-N4-O4-S	

ANNOTATED BIBLIOGRAPHY

References updated: 10 November 2016

Abbreviations used: PAH, pulmonary arterial hypertension

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Textbook of hepatotoxicity published in 1999, before the availability of selexipag).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Textbook on drug induced liver injury; clinical features of liver injury due to the selexipag are not specifically discussed).

Barnes PJ. Pharmacotherapy of pulmonary arterial hypertension. Pulmonary Pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1059-61.

(Textbook of pharmacology and therapeutics).

Hill NS, Badesch D, Benza RL, D'Eletto TA, Farber HW, Gomberg-Maitland M, Hassoun PM, Preston I. Perspectives on oral pulmonary hypertension therapies recently approved by the U.S. Food and Drug Administration. Ann Am Thorac Soc 2015; 12: 269-73. PubMed PMID: 25590376.

(Review of recently approved drugs for pulmonary arterial hypertension [PAH] including macitentan, riociguat and oral treprostinil, only briefly mentions selexipag and does not discuss its side effects in any detail).

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: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, one was attributed to bosentan, but none to selexipag or other agents used primarily to treat pulmonary artery hypertension).

Kaufmann P, Okubo K, Bruderer S, Mant T, Yamada T, Dingemanse J, Mukai H. Pharmacokinetics and tolerability of the novel oral prostacyclin IP receptor agonist selexipag. Am J Cardiovasc Drugs 2015; 15: 195-203. PubMed PMID: 25850750.

(Among 64 healthy men given single or multiple doses of selexipag as a part of a phase 1 pharmacokinetic study, side effects included headache, but there were no changes in clinical laboratory tests).

Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani HA, et al.; GRIPHON Investigators. Selexipag for the Treatment of Pulmonary Arterial Hypertension. N Engl J Med 2015; 373: 2522-33. PubMed PMID: 26699168.

(Among 1156 patients with PAH treated with selexipag [200-1600 μg twice daily] or placebo for an average of 1.2 years, therapy was associated with improved outcomes and adverse events included headache [65% vs 3%] diarrhea [42% vs 2%], nausea [34% vs 2%], jaw pain [26% vs 6%] and myalgia [16% vs 6%]; no mention of ALT elevations or hepatotoxicity).

O'Connell C, Amar D, Boucly A, Savale L, Jaïs X, Chaumais MC, Montani D, et al. Comparative safety and tolerability of prostacyclins in pulmonary hypertension. Drug Saf 2016; 39: 287-94. PubMed PMID: 26748508.

(Review of the mechanism of action and safety of prostacyclins focusing upon selexipag, which is a non-prostanoid prostacyclin receptor agonist that can be taken orally and has similar adverse event profile to the inhaled, subcutaneous and intravenous forms of prostacyclins used to treat PAH; no mention of ALT elevations or hepatotoxicity).

Kaufmann P, Cruz HG, Krause A, Ulč I, Halabi A, Dingemanse J. Pharmacokinetics of the novel oral prostacyclin receptor agonist selexipag in subjects with hepatic or renal impairment. Br J Clin Pharmacol 2016; 82: 369-79. PubMed PMID: 27062188.

(Pharmacokinetic studies of single doses of selexipag in 17 patients with hepatic impairment found higher levels in those with greater impairment, but any clinically significant difference from normal would be mitigated by the recommended slow escalation of the dose based upon tolerance).

Velayati A, Valerio MG, Shen M, Tariq S, Lanier GM, Aronow WS. Update on pulmonary arterial hypertension pharmacotherapy. Postgrad Med 2016; 128: 460-73. PubMed PMID: 27232660.

(Review of the clinical features and outcome of PAH and current therapies including endothelin 1 antagonists, guanylate cyclase stimulators, and prostacyclin synthetics and analogues such as selexipag mentions that its tolerability "was consistent with other therapies targeting the prostacyclin pathway").

Selexipag (Uptravi) for pulmonary arterial hypertension. Med Lett Drugs Ther 2016; 58 (1488): 21-3. PubMed PMID: 26859660.

(Concise review of the mechanism of action, clinical efficacy, safety and cost of selexipag shortly after its approval for use in the US, mentions the typical prostacyclin side effects but does not mention ALT elevations or hepatotoxicity).