U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Ripretinib. [Updated 2023 Oct 12].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Ripretinib

Updated: October 12, 2023.

OVERVIEW

Introduction

Ripretinib is a multikinase inhibitor that is used to treat refractory forms of advanced gastrointestinal stromal tumors. Serum aminotransferase elevations occur in a small proportion of patients treated with ripretinib, but episodes of clinically apparent liver injury with jaundice have not been reported with its use.

Background

Ripretinib (rip re' tin ib) is an orally available multikinase inhibitor that targets the proto-oncogene KIT and platelet derived growth factor receptor alpha (PDGFRA) and is used to treat patients with advanced and refractory gastrointestinal stromal tumors (GIST) after failure of other therapies. GIST is a rare mesenchymal tumor found most commonly in the stomach and small intestine that varies greatly in aggressiveness from indolent to rapidly progressive. GIST often harbors mutant forms of oncogenes that drive cancer cell proliferation and spread, most commonly KIT (80%) and PDGFRA (5% to 10%). Inhibition of these oncogene receptors can result in marked regression in tumor size. Ripretinib has activity against several other kinases such as PDGFR beta, vascular endothelial growth factor receptor 1 (VEGFR1), TIE2 (angiopoietin receptor), and BRAF, some of which may play a role in the efficacy as well as adverse effects of ripretinib. The first line therapy of GIST is with imatinib which is highly effective, but limited by development of resistant mutations in KIT and other genes which then may require second and third line kinase inhibitors such as sunitinib, nilotinib, regorafenib, bosutinib, ponatinib, or avapritinib. Ripretinib was found to have activity in vitro and in vivo against GIST derived tumor cells with resistant mutations. Ripretinib therapy was subsequently shown to improve progression-free and overall survival in patients with advanced GIST who were refractory to or intolerant of standard kinase inhibitors. Ripretinib was approved in the United States in 2020 as therapy for adults with refractory advanced GIST who have failed therapy with at least 3 standard tyrosine kinase inhibitors. Ripretinib is available in tablets of 50 mg under the brand name Qinlock. The recommended regimen is 150 mg orally once daily until disease progression or unacceptable toxicity. Side effects are common and can include alopecia, fatigue, nausea and vomiting, diarrhea, constipation, decreased appetite, musculoskeletal pain, myelosuppression, and palmar-plantar erythrodysesthesia (hand-foot syndrome). Potent severe adverse events include new onset cutaneous malignancies (including melanoma), photosensitivity, hypertension, cardiac dysfunction, impaired wound healing, and embryo-fetal toxicity.

Hepatotoxicity

In the prelicensure placebo-controlled clinical trial in patients with refractory and extensively treated GIST, ALT elevations arose in 13% of ripretinib- vs 5% of placebo-treated subjects. ALT elevations were generally transient

and mild, and were above 5 times the ULN in only 1% of treated patients and did not require dose modification or discontinuation. Bilirubin elevations were reported in 22% of ripretinib treated patients but only 7.5% of placebo controls. The bilirubin elevations were transient and mild, but were not characterized as to their timing, severity and whether conjugated or unconjugated (direct or indirect). In the open label and controlled trials supporting the approval of ripretinib, there were no instances of clinically apparent liver injury, hepatic failure, or deaths from liver injury. Since its approval in the United States and Europe, there have been no reported cases of clinically apparent liver injury associated with ripretinib therapy.

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

Mechanism of Injury

The possible cause of liver injury from ripretinib therapy is unknown. While serum bilirubin elevations occurred in more than 20% of patients in preregistration trials, the timing, duration and degree of elevations and whether conjugated or unconjugated were not described. Ripretinib is metabolized in the liver via the cytochrome P450 system, largely CYP3A4 and 2D9. Ripretinib is susceptible to drug-drug interactions with agents that inhibit or induce the CYP 3A4 activity and concurrent use of strong inhibitors of CYP 3A4 should be avoided.

Outcome and Management

The product label for ripretinib does not recommend routine monitoring of liver laboratory tests during therapy. Serum aminotransferase elevations above 5 times the upper limit of normal (if detected) should lead to dose reduction or temporary cessation of treatment with careful monitoring if restarted after resolution of the abnormalities. Elevations of aminotransferase levels above 20 times ULN and any elevation accompanied by jaundice or symptoms of liver injury should trigger permanent discontinuation of therapy. Cross sensitivity to liver injury is uncommon among the antineoplastic kinase inhibitors, and in preregistration trials, shared liver injury sensitivity between ripretinib and previous administered antineoplastic kinase inhibitors was not found.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Other Kinase Inhibitor Therapies of GIST: Avapritinib, Bosutinib, Imatinib, Nilotinib, Ponatinib, Regorafenib, Sunitinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ripretinib – Qinlock®

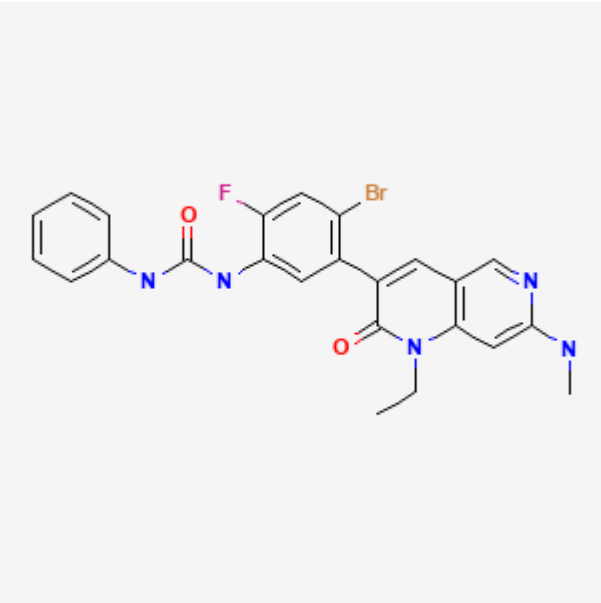
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ripretinib	1442472-39-0	C24-H21-Br-F-N5-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 12 October 2023

Abbreviations: SMI, small molecule inhibitor; TKI, tyrosine kinase inhibitor.

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

(Review of hepatotoxicity published in 1999 before the availability of kinase inhibitors).

DeLeve LD. Kinase inhibitors. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents, does not discuss ripretinib).

Wellstein A, Giaccone G, Atkins MB, Sausville EA. Pathway targeted therapies: monoclonal antibodies, protein kinase inhibitors, and various small molecules. 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. 1203-36.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213973Orig1s000MultidisciplineR.pdf

(FDA website with product labels and initial multidiscipline clinical review of the safety and efficacy of ripretinib; describes the adverse events observed in a placebo controlled trial with 85 patients receiving ripretinib and 43 placebo, mentioning that at least one adverse event occurred in 99% vs 98%, bilirubin elevations in 17% vs none, and ALT elevations 14% vs 15% which were above 5 times ULN in 1.2% [1 patient] vs none, but no patient developed concurrent ALT elevations and jaundice).

Blay JY, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, Schöffski P, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21:923-934. PubMed PMID: 32511981.

(Among 129 adults with advanced GIST with disease progression or intolerance on 3 previous kinase inhibitors treated with ripretinib [150 mg] vs placebo once daily, the median progression free survival was 6.3 vs 1.0 months while adverse event rates included alopecia [59% vs 2%], myalgia [28% vs 9%], fatigue [26% vs 16%], palmar-plantar erythrodysesthesia [21% vs none], and constipation [15% vs 7%]; there was no mention of ALT elevations, and no serious hepatic adverse events).

Dhillon S. Ripretinib: First approval. Drugs. 2020;80:1133-1138. PubMed PMID: 32578014.

(Summary of mechanism of action, history of development, pharmacokinetics, clinical efficacy, and safety of ripretinib shortly after its approval in the US as therapy of advanced, refractory GIST discusses adverse event rates which were 52% vs 5% for alopecia, 42% vs 23% for fatigue, and 21% vs 0% for palmar-plantar erythrodysesthesia; no mention ALT elevations or hepatotoxicity).

Roskoski R Jr. Properties of FDA-approved small molecule protein kinase inhibitors: A 2021 update. Pharmacol Res. 2021;165:105463. PubMed PMID: 33513356.

(Extensive review of the human kinases and their approved small molecule inhibitors, their chemical structure, interaction with kinase targets, mechanism of action, clinical efficacy, and clinical indications; mentions that ripretinib is a 4th line therapy for advanced refractory GIST; no mention of adverse events or hepatotoxicity).

Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. Nat Rev Dis Primers. 2021;7:22. PubMed PMID: 33737510.

(Review of the epidemiology, natural history, pathophysiology, activated molecular pathways, molecular subgroups, clinical diagnosis, management, and treatment of GIST).

Ripretinib (Qinlock) for GIST. Med Lett Drugs Ther. 2021;63(1621):e56-e57. PubMed PMID: 33830971.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of ripretinib shortly after its approval as therapy of advanced, refractory GIST, discusses its common and its serious adverse effects [skin cancers, hypertension, cardiac dysfunction, impaired wound healing], but does not mention ALT elevations or hepatotoxicity).

Bauer S, Jones RL, Blay JY, Gelderblom H, George S, Schöffski P, von Mehren M, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. J Clin Oncol. 2022;40:3918-3928. PubMed PMID: 35947817.

(Among 453 adults with imatinib-refractory, advanced GIST treated with ripretinib [150 mg daily] or sunitinib [50 mg daily for 4 weeks in 6 week cycles], progression free survival was similar in both groups [8.3 vs 7.0 months] while ripretinib was claimed to be better tolerated; adverse event rates being 99% vs 99%, serious adverse event rates 25.6% vs 25.7%, dose reductions 29% vs 42% and discontinuations 4% vs 8%; no mention of ALT elevations or hepatotoxicity).

Kumar V, Doros L, Thompson M, Mushti SL, Charlab R, Spehalski EI, Zhao H, et al. FDA approval summary: ripretinib for advanced gastrointestinal stromal tumor. Clin Cancer Res. 2023;29:2020-2024. PubMed PMID: 36485007.

(Summary of data on efficacy and safety of ripretinib that provided the basis for its FDA approval for use in advanced, refractory GIST mentions adverse events of special interest occurring in the safety population of 351 patients, which included cardiac dysfunction in 1.7%, hypertension in 17%, new primary cutaneous malignancies in 9%, palmar-plantar erythrodysesthesia in 29%, but does not mention ALT elevations or hepatotoxicity).

Serrano C, Martín-Broto J, Asencio-Pascual JM, López-Guerrero JA, Rubió-Casadevall J, Bagué S, García-Del-Muro X, et al. 2023 GEIS Guidelines for gastrointestinal stromal tumors. Ther Adv Med Oncol. 2023;15:17588359231192388. PubMed PMID: 37655207.

(General guidelines on diagnosis, staging, management, and medical therapy of GIST prepared by a multidisciplinary expert panel from the Spanish Group for Sarcoma Research mentions that ripretinib is a 4th line kinase inhibitor generally recommended after failure of imatinib and 2 other conventional kinase inhibitors, and that its toxicity is similar to that of imatinib except for a higher rate of alopecia and palmar-plantar erythrodysesthesia; no mention of ALT elevations or hepatotoxicity).