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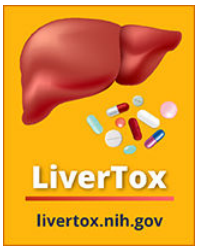


Asciminib

Updated: October 8, 2023.

OVERVIEW

Introduction

Asciminib is a tyrosine kinase inhibitor that specifically targets myristoyl pocket of ABL1 and is used to treat refractory forms of Philadelphia chromosome positive chronic myelocytic leukemia. Serum aminotransferase elevations occur in a proportion of patients treated with asciminib, but episodes of clinically apparent liver injury with jaundice have not been reported with its use.

Background

Asciminib (as kim' in ib) is an orally available, tyrosine kinase inhibitor that targets the myristoyl pocket of ABL1 resulting in inhibition of the abnormal fusion kinase BCR-ABL1 that drives cellular proliferation in chronic myelocytic leukemia (CML) associated with the Philadelphia chromosome (Ph+). The Philadelphia chromosome is an acquired genetic abnormality of chromosome 22 found in leukemic cells, which is created by a reciprocal translocation between chromosomes resulting in a fusion gene of ABL1 (for Abelson leukemia virus) from chromosome 9 and the breakpoint cluster region (BCR) of chromosome 22. The translocated gene creates a hybrid tyrosine kinase receptor that is continuously synthesized in an active form causing uncontrolled growth and proliferation of the affected cell. Referred to as a STAMP positive tyrosine kinase receptor inhibitor, asciminib specifically targets the ABL1 myristoyl pocket and has separate activity and resistance patterns compared to conventional anti-BCR-ABL1 kinases that target the catalytic site of the abnormal BCR-ABL1 kinase. Asciminib has potent specificity against the T315I mutant of ABL1 that is resistant to standard tyrosine kinase inhibitors used to treat CML, such as imatinib, sunitinib, nilotinib, bosutinib, ponatinib, and regorafenib, the first-, second-, and third-line therapies of Ph+ CML. Asciminib was granted accelerated approval in the United States in 2021 for adults with refractory or relapsed CML after therapy with at least two conventional BCR-ABL1 kinase inhibitors and in high doses for refractory cases harboring the T315I mutant. Asciminib is available in tablets of 20 and 40 mg under the brand name Scemblix. The recommended oral dose varies by indication, being 40 mg twice or 80 mg once daily for refractory cases of Ph+ CML, but 200 mg twice daily for cases harboring the highly resistant T315I mutation. Therapy should continue until disease progression or unacceptable toxicity. Side effects are dose related, but at the highest dose are common, arising in almost all patients. Common side effects include anemia, neutropenia, myelosuppression, musculoskeletal pain, fatigue, headache, rash, and diarrhea. Less common but potentially severe adverse events include severe myelosuppression, pancreatitis, hypertension, hypersensitivity reactions, cardiovascular toxicity, and embryo-fetal toxicity.

Hepatotoxicity

In the prelicensure clinical trials of asciminib in patients with refractory and extensively treated CML, ALT elevations arose in 13% of patients but were usually self-limited and mild. ALT elevations above 5 times the upper limit of normal (ULN) were uncommon, being found in 3% of treated patients. The ALT elevations were typically transient and rarely required dose interruption or modification. In the open label and controlled trials supporting the approval of asciminib, there were no instances of clinically apparent liver injury, hepatic failure or deaths from liver injury. Furthermore, patients with aminotransferase elevations during therapy with first and second line BCR-ABL1 inhibitors did not have an increased rate of such elevations during asciminib therapy. Since its approval in the United States and Europe, there have been no reported cases of clinically apparent liver injury associated with asciminib therapy.

Likelihood score: E* (unproven but suspected rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of serum aminotransferase elevations from asciminib is unknown, but the pattern of abnormalities suggests a mild degree of direct hepatotoxicity. Asciminib is metabolized in the liver via the cytochrome P450 system, largely CYP 3A4 and 2C9 and is susceptible to drug-drug interactions with agents that inhibit or induce the CYP enzyme reactivity. Asciminib itself inhibits CYP 3A4 and P-glycoprotein and can result in increased levels of drugs that are substrates of these hepatic metabolizing and transport proteins.

Outcome and Management

The product label for asciminib does not recommend routine monitoring of liver laboratory tests during therapy. Serum aminotransferase elevations above 5 times ULN (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 accompanied by jaundice or symptoms of liver injury should trigger permanent discontinuation of therapy. Cross sensitivity to liver injury is uncommon among the antineoplastic, small molecule enzyme and receptor inhibitors and in preregistration trials, shared liver injury sensitivity between asciminib and other antineoplastic BCR-ABL1 inhibitors was not found.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Asciminib – Scemblix®

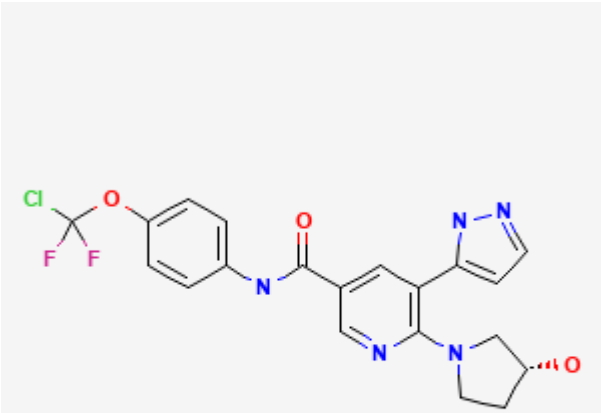
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Asciminib	1492952-76-7	C20-H19-Cl2-F2-N5-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 08 October 2023

Abbreviations: ABL1, Abelson leukemia virus 1 protein; BCR, breakpoint cluster region; 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 tyrosine kinase receptor 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 asciminib).

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/2021/215358Orig1s000,Orig2s000MultidisciplineR.pdf

(FDA website with initial multidiscipline clinical review of the safety and efficacy of asciminib; describes the adverse events observed in a pooled safety population of 356 patients of whom 96% had at least one adverse event which were scored as serious in 21% and included ALT elevations 13% which were above 5 times ULN in 3%, but the elevations were often single values and none were associated with jaundice and there were no instances of hepatic failure, or fatalities due to liver injury).

Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ, Breccia M, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med. 2019;381:2315-2326. PubMed PMID: 31826340.

(Among 150 adults with CML refractory to at least two conventional BCR-ABL1 targeted tyrosine kinase inhibitors [TKIs] who were treated with asciminib in varying doses for 12 months, 48% had a major molecular response and adverse events were frequent, most commonly fatigue, headache, arthralgias, hypertension and decreases in platelet counts, with ALT elevations in 11% that were above 5 times the ULN in 3%; no mention of clinically apparent liver injury or hepatotoxicity).

Réa D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, Turkina A, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021;138:2031-2041. PubMed PMID: 34407542.

(Among 233 adults with Ph+ CML refractory to at least two conventional BCR-ABL1 TKIs treated with asciminib [40 mg twice daily] vs bosutinib [500 mg once daily] for a median of 15 months, the week 24 major molecular response rates were 26% vs 13%, while adverse events occurred in 90% vs 96% which required discontinuation in 6% vs 21%, and ALT elevations arose in 4% vs 28% and were above 5 times ULN in 0.6% vs 15%, but there were cases of clinically apparent liver injury in those receiving asciminib).

Hochhaus A, Réa D, Boquimpani C, Minami Y, Cortes JE, Hughes TP, Apperley JF, et al. Asciminib vs bosutinib in chronic-phase chronic myeloid leukemia previously treated with at least two tyrosine kinase inhibitors: longer-term follow-up of ASCEMBL. Leukemia. 2023;37:617-626. PubMed PMID: 36717654.

(Among the 233 adults with TKI refractory Ph+ CML treated with asciminib or bosutinib [Rea et al 2021], longer follow up to a median of 2.3 years continued to show the greater major molecular response rate with asciminib [38% vs 16% at week 96] while adverse event rates were less, ALT elevations in 4.5% vs 30% which were above 5 times ULN in 0.6% vs 14.5%).

Luna A, Pérez-Lamas L, Boque C, Giraldo P, Xicoy B, Ruiz Nuño C, Vega MM, et al. Real-life analysis on safety and efficacy of asciminib for ponatinib pretreated patients with chronic myeloid leukemia. Ann Hematol. 2022;101:2263-2270. PubMed PMID: 35997804.

(Among 52 Spanish adults with refractory Ph+ CML previously treated BCR-ABL1 targeted TKIs [including ponatinib] who were switched to asciminib, 52% had a major molecular response while half developed an adverse event on therapy; no mention of ALT elevations or hepatotoxicity).

Tesileanu CMS, Michaleas S, Gonzalo Ruiz R, Mariz S, Fabriek BO, van Hennik PB, Dedorath J, et al. The EMA assessment of asciminib for the treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase who were previously treated with at least two tyrosine kinase inhibitors. Oncologist. 2023;28:628-632. PubMed PMID: 37141403.

(Summary of the basis for the approval of asciminib for use in CML by the European Medicines Agency mentions that hepatotoxicity and reactivation of hepatitis B "were considered important potential risks").

Pérez-Lamas L, Luna A, Boque C, Xicoy B, Giraldo P, Pérez López R, Ruiz Nuño C, et al. Toxicity of asciminib in real clinical practice: analysis of side effects and cross-toxicity with tyrosine kinase inhibitors. Cancers (Basel). 2023;15:1045. PubMed PMID: 36831388.

(Further analysis of Spanish adults with previously TKI-refractory Ph+ CML who were switched to asciminib therapy included data on 77 patients with a median follow up of 14 months, 55% had at least one adverse event, most being less frequent that with previous TKIs, ALT elevations arose in 2 patients which were above 5 times ULN in one).

Asciminib (Scemblix) for chronic myeloid leukemia. Med Lett Drugs Ther. 2023;65:e107-e108. PubMed PMID: 37339100.

(Brief review of the mechanism of action, clinical efficacy, safety and cost of asciminib shortly after its approval in the US as therapy of CML refractory of conventional BCR-ABL1 targeted TKIs mentions that ALT, triglyceride, creatinine, amylase and lipase elevations can occur during therapy).