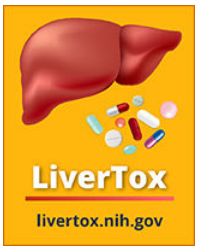
U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Momelotinib. [Updated 2023 Dec 28].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Momelotinib

Updated: December 28, 2023.

OVERVIEW

Introduction

Momelotinib is a small molecule Janus kinase inhibitor that is used in the treatment of intermediate or high risk, primary or secondary myelofibrosis. Momelotinib is associated with transient and usually mild elevations in serum aminotransferase levels during therapy and has also been linked to instances of clinically apparent acute liver injury including reactivation of hepatitis B.

Background

Momelotinib (moe" me, loe' ti nib) is an orally available, small molecular inhibitor of Janus kinase subtype 1 and 2 (JAK1/2) including mutant $JAK2^{V617F}$ and is used to treat resistant forms of myelofibrosis including secondary forms related to polycythemia vera and essential thrombocythemia. Myelofibrosis is a cancerous or pre-cancerous condition of the bone marrow that results in progressive bone marrow failure with enlargement of the spleen, anemia, neutropenia and thrombocytopenia. JAK1 and JAK2 are non-receptor tyrosine kinases that are critical components of pathways that lead to production and secretion of hematologic growth factors and inflammatory cytokines. These pathways are important in hematologic cell differentiation and proliferation, in cytokine-production, and inflammatory reactions. Mutations in JAK genes are frequent in patients with myelofibrosis including $JAK2^{V617F}$ which is found in more than 90% of patients with polycythemia vera and at least 50% of those with essential thrombocythemia. Inhibition of these kinases can result in antiproliferative and apoptotic effects in malignant cells. Momelotinib has been shown to improve symptoms, cause shrinkage of spleen size, and decrease circulating cytokine levels in patients with myelofibrosis independent of the known presence of Janus kinase mutations. Momelotinib was approved for use in the United States in 2023 for therapy of intermediate and high risk primary or secondary myelofibrosis with anemia. Momelotinib is available in capsules of 100, 150, and 200 mg under the brand name Ojjaara. The recommended initial dose is 200 mg once daily. Dose adjustments for hepatic dysfunction and for adverse reactions are recommended. Common side effects include myelosuppression, anemia, thrombocytopenia, fatigue, diarrhea, bruising, dizziness, peripheral neuropathy, dyspnea, headache and fatigue. Less common but potentially severe adverse events include risk of infections including reactivation of viruses, peripheral neuropathy, severe thrombocytopenia, and neutropenia. All small molecule JAK inhibitors have safety labeling for increased risk of major cardiovascular adverse events, increased mortality, venous and arterial thromboses, secondary malignancies, and increased risk of infection.

Hepatotoxicity

In the published preregistration clinical trials of momelotinib, rates of serum ALT or AST elevations ranged from 21% to 31% and were above 5 times the upper limit of normal (ULN) in 0.5% to 2.0%, and above 20 times

ULN in 0.5%. Two of 448 momelotinib treated patients evaluated in the safety cohort developed clinically apparent, but self-limiting liver injury with jaundice. A third patient developed liver injury with jaundice that appeared to be due to reactivation of hepatitis B. The liver injury was typically hepatocellular without immune allergic or autoimmune features, arising after 2 to 4 months of therapy, and resolving soon after drug discontinuation. Peak ALT elevations ranged from 308 to 1178 U/L and peak bilirubin from 2.3 to 7.0 mg/dL. There were no deaths from hepatic failure. Since its approval and more widespread clinical use, there have been no further reports of serum enzyme or bilirubin elevations or instances of clinically apparent liver injury, but it has been available for a limited time only.

Likelihood score: D (possible cause of clinically apparent liver injury including reactivation of hepatitis B).

Mechanism of Injury

Momelotinib therapy has been clearly linked to serum enzyme elevations and to rare instances of clinically apparent liver injury. It is metabolized in the liver, and liver injury may be due to its metabolism to an immunogenic or toxic intermediate. Momelotinib is a weak inducer of CYP 2B6 and competes for hepatic uptake for the organic anion transporting polypeptide and hepatocyte secretion for the breast cancer resistance protein and thus may have significant drug-drug interactions. Because of its effects on intracellular signaling involved in immune responses, momelotinib (and other JAK inhibitors) may be capable of increasing hepatitis B viral replication, which can result in clinically apparent reactivation of hepatitis B.

Outcome and Management

Momelotinib has been clearly linked to serum aminotransferase elevations and significant liver injury. For this reason, routine monitoring of liver tests is recommended in the product label every month for six months, and "as needed" thereafter. Serum aminotransferase elevations above 5 times ULN should lead to dose reduction or temporary cessation until they fall into the normal or near normal range, or another cause for the elevations is found. ALT or AST elevations above 20 times ULN or any elevations accompanied by jaundice or symptoms should lead to discontinuation. Because of the possibility of reactivation of hepatitis B, it is appropriate to screen patients for hepatitis B markers before starting momelotinib and, if HBsAg or anti-HBc are present, providing antiviral prophylaxis or monitoring for reactivation during therapy. There does not appear to be cross reactivity in risk for hepatic injury among the various JAK kinase inhibitors, but few instances have been studied.

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

Janus Kinase Inhibitors: Abrocitinib, Baricitinib, Deucravacitinib, Fedratinib, Pacritinib, Ritlecitinib, Ruxolitinib, Tofacitinib, Upadacitinib

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Momelotinib – Ojjaara®

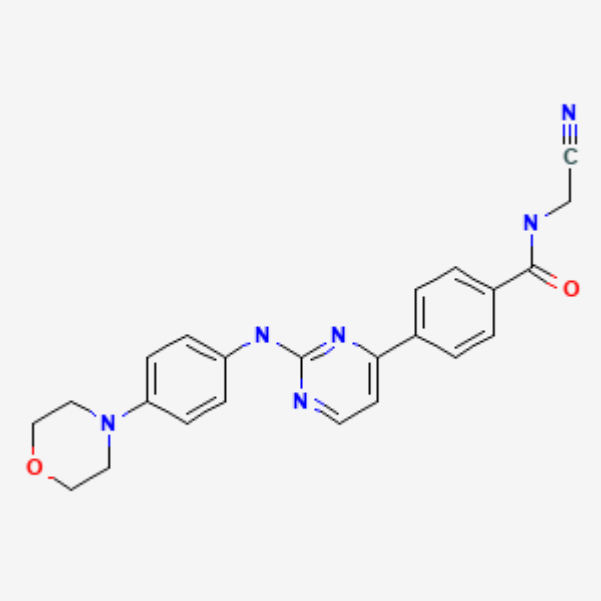
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Momelotinib	1056634-68-4	C23-H22-N6-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 28 December 2023

Abbreviations: JAK, Janus kinase; STAT, signal transducer activator of transcription.

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 inhibitors such as momelotinib).

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

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not momelotinib).

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/2023/216873Orig1s000IntegratedR.pdf

(Integrated FDA review of the data on safety and efficacy of momelotinib that formed the basis of its approval, mentions that ALT elevations arose in 22- 31% of patients, were above 5 times ULN in 0.5-2.0%, and that among 448 patients treated, there were 8 cases of suspected drug induced liver injury, 3 of which were considered probable or highly likely: 2 women and 1 man, ages 59, 77 and 54 years, with onset after 59, 112 and 54 days, and peak ALT 1178, 483 and 308 U/L, Alk P 617 566, and 83 U/L, bilirubin 7.0, 2.3 and 4.0 mg/dL, and all

improving once momelotinib was stopped, one with apparent reactivation of hepatitis B with evidence of cirrhosis).

Verstovsek S, Courby S, Griesshammer M, Mesa RA, Brachmann CB, Kawashima J, Maltzman JD, et al. A phase 2 study of momelotinib, a potent JAK1 and JAK2 inhibitor, in patients with polycythemia vera or essential thrombocythemia. Leuk Res. 2017;60:11–17. PubMed PMID: 28622623.

(Among 39 patients with polycythemia or essential thrombocythemia treated with momelotinib [100 or 200 mg] once daily for 24 weeks, only 2 patients had a cytological response while 80% of patients had adverse events including headache, dizziness, somnolence, nausea and fatigue; no mention of ALT elevations or hepatotoxicity).

Mesa RA, Kiladjian JJ, Catalano JV, Devos T, Egyed M, Hellmann A, McLornan D, et al. SIMPLIFY-1: a phase III randomized trial of momelotinib versus ruxolitinib in Janus kinase inhibitor-naïve patients with myelofibrosis. J Clin Oncol. 2017;35:3844–3850. PubMed PMID: 28930494.

(Among 432 patients with high or intermediate risk myelofibrosis treated with momelotinib [200 mg, once daily] or ruxolitinib [20 mg, twice daily] for 24 weeks, spleen size decreased in 26.5% vs 29% and adverse events arose in 92% vs 95%, serious adverse events in 23% vs 18%, resulting in discontinuations in 13% vs 6%, and peripheral neuropathy in 10% vs 5%, while there were no hepatic serious adverse events or deaths; no mention of ALT elevations).

Harrison CN, Vannucchi AM, Platzbecker U, Cervantes F, Gupta V, Lavie D, Passamonti F, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol. 2018;5:e73–e81. PubMed PMID: 29275119.

(Among 156 patients with myelofibrosis and an inadequate response to or intolerance of ruxolitinib treated with momelotinib [200 mg once daily] or "best available therapy" for 24 weeks, reduction in spleen size [by 35% or greater] was achieved in 7% vs 6% and adverse events arose in 97% vs 89%, serious adverse events in 35% vs 23%, peripheral neuropathy in 11% vs none, deaths in 6% vs 8%, and there were no hepatic deaths or serious adverse events noted; no mention of ALT elevations).

Coltro G, Vannucchi AM. The safety of JAK kinase inhibitors for the treatment of myelofibrosis. Expert Opin Drug Saf. 2021;20:139–154. PubMed PMID: 33327810.

(Extensive review of the mechanism of action, rationale for use, current status, and safety of JAK kinase inhibitors for myelofibrosis including 2 FDA approved agents [ruxolitinib and fedratinib] and 2 in clinical development [pacritinib and momelotinib], focusing on common hematologic and gastrointestinal adverse events and special concerns on increased rates of infections, peripheral neuropathy and secondary cancer including lymphomas; no discussion of hepatotoxicity and ALT elevations mentioned only for fedratinib).

Verstovsek S, Gerds AT, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, Grosicki S, et al; MOMENTUM Study Investigators. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): results from an international, double-blind, randomised, controlled, phase 3 study. Lancet. 2023;401(10373):269–280. PubMed PMID: 36709073.

(Among 195 patients with intermediate or high risk symptomatic myelofibrosis treated with momelotinib [200 mg once daily] or danazol [300 mg twice daily] for 24 weeks, symptom improvement occurred in 25% vs 9% and transfusion independence in 30% vs 20%, while adverse event rates were similar 94% vs 95%, serious adverse events 35% vs 40%, discontinuations in 18% vs 23%, fatal outcome in 12% vs 17%, and ALT elevations in 7% vs 8%).

Gerds AT, Verstovsek S, Vannucchi AM, Al-Ali HK, Lavie D, Kuykendall AT, Grosicki S, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis previously treated with a JAK inhibitor (MOMENTUM): an updated analysis of an international, double-blind, randomised phase 3 study. Lancet Haematol. 2023;10:e735–e746. PubMed PMID: 37517413.

(Among 82 patients who continued on or were crossed over to open-label momelotinib after participation in a controlled trial [Verstovek 2023], rates of symptom improvement [45-50%] and transfusion independence [55-60%] increased while "there were no new safety signals", no liver related serious adverse events or fatalities, although therapy was discontinued in one subject because of ALT and AST elevations [no details given]; no mention of rates of ALT elevations).