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Deucravacitinib

Updated: December 28, 2023.

OVERVIEW

Introduction

Deucravacitinib is a small molecule inhibitor of tyrosine kinase 2 that is used in the treatment of moderate-to-severe plaque psoriasis. Deucravacitinib is associated with transient and usually mild elevations in serum aminotransferase levels during therapy but has not been linked instances of clinically apparent acute liver injury.

Background

Deucravacitinib (deu krav" a sye' ti nib) is an orally available, small molecular inhibitor of tyrosine kinase 2 (TYK2) that is used to treat moderate-to-severe plaque psoriasis. TYK2 is a non-receptor tyrosine kinase and a member of the JAK kinase family, which 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, intracellular signaling by interferon alpha and gamma, and in cytokine-production and inflammatory reactions. Inhibition of TYK2 leads to decreases in expression of IL23, type 1 interferon, and beta defensin. Patients with psoriasis frequently have raised levels of cytokines that are modulated by TYK2, such as IL23, IL17, and type 1 interferon, and which are decreased by deucravacitinib therapy. Deucravacitinib has been shown to improve symptoms and rash in patients with plaque psoriasis and was approved in the United States in 2023 for adults with moderate-to-severe plaque psoriasis who are candidates for systemic or phototherapy. Deucravacitinib is available in tablets of 6 mg under the brand name Sotyktu. The recommended dose is 6 mg once daily. Common side effects include symptoms of upper respiratory infection, mouth ulcers, folliculitis, acne, herpes simplex, and creatine phosphokinase (CPK) elevations. Less common but potentially severe adverse events include hypersensitivity reactions, risk of infections including reactivation of tuberculosis, rhabdomyolysis, and malignancies. It is suspected that TYK2 inhibitors share the long term adverse events found with JAK inhibitors, which include increased risk of major cardiovascular adverse events, serious infections, venous and arterial thromboses, secondary malignancies, and overall mortality.

Hepatotoxicity

In the preregistration clinical trials of deucravacitinib that included data on 1519 subjects, only 1.8% of patients had serum ALT or AST elevations above 5 times ULN, none of which were considered likely due to drug induced liver injury, with myositis accounting for many of the elevations, and underlying alcoholic or nonalcoholic fatty liver disease accounting for a few. Elevations of ALT levels above 3 times the ULN arose in 1.1% to 1.3% of recipients of deucravacitinib in a 24 week trial compared to 1.2% of placebo recipients. While there were no instances of reactivation of hepatitis B in patients receiving deucravacitinib, patients with

preexisting HBsAg in serum were excluded from enrollment and most treatment courses were limited in duration. Since its approval and more widespread clinical use, there have been no further reports of clinically apparent liver injury attributed to deucravacitinib, but it has been available for a limited time only.

Likelihood score: E (suspected but unproven cause of clinically apparent liver injury including reactivation of hepatitis B).

Mechanism of Injury

Deucravacitinib therapy is associated with only a low rate of serum enzyme elevations and the mechanisms by which it might cause liver injury are unknown. It is metabolized in the liver largely by CYP 1A2 and to a lesser extent by CYP 2B6, 2D6, carboxylesterase 2, and uridine glucuronyl transferase. However, deucravacitinib neither induces nor inhibits these metabolizing enzymes, and it has not been found to have clinically significant drug-drug interactions. Because of its effects on intracellular signaling involved in immune responses, deucravacitinib (and other JAK inhibitors) may be capable of increasing hepatitis B viral replication which might result in clinically apparent reactivation of hepatitis B.

Outcome and Management

Deucravacitinib has been associated with a low rate of serum aminotransferase elevations. The product label recommends evaluation of routine liver tests at baseline and thereafter as needed for patient management or if liver disease is suspected. Serum aminotransferase elevations above 3 times ULN should lead to interruption until the diagnosis of drug induced liver injury can be excluded. ALT or AST elevations above 20 times ULN or any elevations accompanied by jaundice or symptoms should lead to prompt discontinuation. Because of the possibility of reactivation of hepatitis B, it is appropriate to screen patients for hepatitis B markers before starting deucravacitinib 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 and TYK2 kinase inhibitors, but few instances have been studied.

Drug Class: Dermatologic Agents, Psoriasis Agents, Protein Kinase Inhibitors

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Deucravacitinib – Sotyktu®

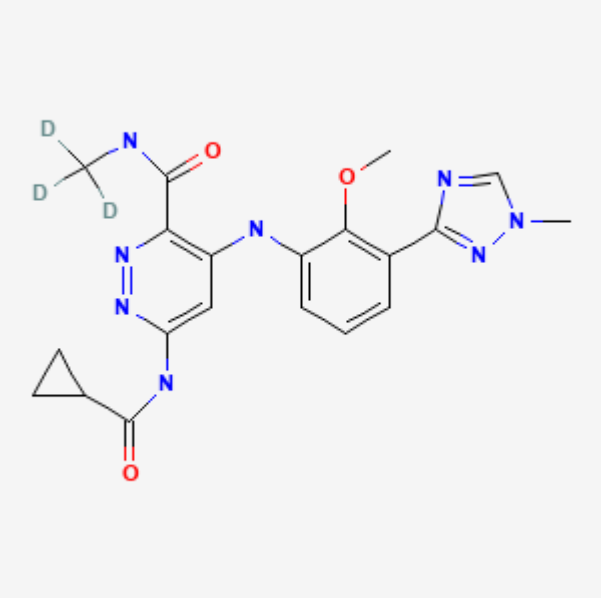
DRUG CLASS

Dermatologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Deucravacitinib	1609392-27-9	C20-H19-D3-N8-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 28 December 2023

Abbreviations: JAK, Janus kinase; STAT, signal transducer activator of transcription; TYK2, Tyrosine Kinase 2.

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 deucravacitinib).

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 deucravacitinib).

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/2022/214958Orig1s000MultidisciplineR.pdf

(Integrated FDA review of the data on safety and efficacy of deucravacitinib that formed the basis of its approval mentions that, in a 24-week controlled trial of deucravacitinib, ALT elevations above 3 times ULN arose at a rate of 3.6 per patient year of exposure, and that analysis of the total safety cohort of 1519 patients identified 24 instances of ALT or AST elevations above 5 times ULN, most of which were transient and unrelated and none of which on thorough evaluation were considered due to drug induced liver injury).

Chimalakonda A, Burke J, Cheng L, Catlett I, Tagen M, Zhao Q, Patel A, et al. Selectivity profile of the tyrosine kinase 2 inhibitor deucravacitinib compared with Janus kinase 1/2/3 inhibitors. Dermatol Ther (Heidelb). 2021;11:1763–1776. PubMed PMID: 34471993.

(Among JAK kinase inhibitors, deucravacitinib binds to a regulatory rather than catalytic site on TYK2, which gives it a high selectivity so that it has little or no activity against JAK1, JAK2 or JAK3, and pilot studies suggest that it has fewer adverse side effects and is less likely to affect serum aminotransferase levels compared to other JAK kinase inhibitors).

Armstrong AW, Gooderham M, Warren RB, Papp KA, Strober B, Thaçi D, Morita A, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J Am Acad Dermatol. 2023;88:29–39. PubMed PMID: 35820547.

(Among 666 adults with plaque psoriasis treated with deucravacitinib [6 mg daily], apremilast [30 mg twice daily] or placebo for 16 weeks, symptomatic scores improved in 58% vs 54% vs 7-12% on placebo, while overall adverse events were similar in the 3 groups but serious adverse events were less with deucravacitinib [2.1% vs 5.5% with placebo] and mean serum ALT levels did not change in any group).

Strober B, Thaçi D, Sofen H, Kircik L, Gordon KB, Foley P, Rich P, et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 program for evaluation of TYK2 inhibitor psoriasis second trial. J Am Acad Dermatol. 2023;88:40–51. PubMed PMID: 36115523.

(Abstract only: Among 1020 adults with moderate to severe plaque psoriasis treated with deucravacitinib [6 mg daily], apremilast [30 mg twice daily], or placebo for up to 52 weeks, 16 week-clinical response rates were highest with deucravacitinib [49.5% vs 33.9% vs 8.6%], and efficacy was maintained to 52 weeks, while adverse events were mostly mild and transient, and serious adverse events and discontinuations were "infrequent").

Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, Delev N, et al. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2023;75:242–252. PubMed PMID: 36369798.

(Among 363 adults with systemic lupus erythematosus treated with deucravacitinib [3 or 6 mg twice daily or 12 mg once daily] vs placebo for 48 weeks, symptomatic response rates were higher with deucravacitinib [58% vs 30%], while overall adverse event rates were similar [84% to 93% vs 88%] as were severe adverse events [7.7% to 8.6% vs 12.2%] and discontinuations [6.5% to 12.4% vs 3.3%]; mean ALT levels did not change, and there were no discontinuations for enzyme elevations in treated patients).

Deucravacitinib (Sotyktu) for plaque psoriasis. Med Lett Drugs Ther. 2023;65:29–31. PubMed PMID: 36757835.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of deucravacitinib shortly after its approval as therapy of psoriasis in 2023, mentions that serum enzyme elevations have occurred in patients taking deucravacitinib).

Truong TM, Pathak GN, Singal A, Taranto V, Rao BK. Deucravacitinib: The first FDA-approved oral TYK2 inhibitor for moderate to severe plaque psoriasis. Ann Pharmacother. 2023;•••:10600280231153863.

(Summary of the efficacy and safety of deucravacitinib mentions that adverse events appear to be less common than with JAK kinase inhibitors, with an adverse event rate of 75%, only 4% serious, and 3-4% requiring discontinuation, known adverse events being hypersensitivity reactions, infections [29%], viral reactivation [herpes simplex 2% and zoster <1%], tuberculosis [<1%], lymphoma [<1%], liver function test abnormalities [2%], but no mention of hepatotoxicity or clinically apparent liver injury).