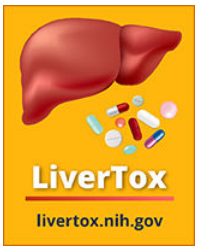
U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Darolutamide. [Updated 2023 Mar 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Darolutamide

Updated: March 15, 2023.

OVERVIEW

Introduction

Darolutamide is a third generation, oral nonsteroidal antiandrogen used to treat nonmetastatic castration-resistant prostate cancer. Darolutamide is associated with a low rate of serum enzyme elevation during therapy, but has not been linked to cases of clinically apparent liver injury with jaundice.

Background

Darolutamide (dar" oh loo' ta mide) is a small molecule androgen receptor antagonist which binds to the intracellular receptor and prevents its translocation to the nucleus and subsequent DNA binding, thereby blocking its activity. Therapy with darolutamide lowers residual testosterone levels after surgical castration in men with prostate cancer and has been shown to prolong metastatic free survival in castration-resistant prostate cancer patients with rising levels of prostate-associated antigen (PSA) without measurable metastatic disease. Darolutamide was approved for use in the United States in 2019 and is available as 300 mg tablets under brand name Nubeqa. The recommended initial dose is 600 mg (two tablets) twice daily. Darolutamide should be used in combination with testosterone suppression either with a gonadotrophin releasing hormone (GnRH) analogue or after bilateral orchiectomy to insure optimal androgen suppression. Common side effects include symptoms of androgen deficiency including fatigue, diarrhea, nausea, anorexia, weight loss, constipation, joint and muscle pain, hot flushes, headaches, dizziness, and edema. Rare, but potentially serious side effects associated with long term therapy include seizures, osteoporosis, bone fractures, and cardiovascular events.

Hepatotoxicity

In prelicensure controlled trials with 1508 patients, serum AST elevations were more common with darolutamide than placebo therapy [23% vs 14%], but were rarely above 5 times the ULN [<1%] and ALT elevations were uncommon, although the results were not provided. Similarly, serum bilirubin levels were more frequently elevated on darolutamide therapy than placebo [16% vs 7%] but were rarely markedly elevated [less than 0.5%], and there were no cases of clinically apparent liver injury. Since approval and general availability of darolutamide, there have been no published reports of liver injury attributed to darolutamide therapy.

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

Mechanism of Injury

The cause of the serum AST and bilirubin elevations that occur during darolutamide therapy is unknown. Darolutamide is extensively metabolized in the liver predominantly by CYP 3A4. Its use with strong inducers of

CYP 3A4 could result in decreased drug levels and reduced efficacy, while use with strong CYP 3A4 inhibitors could result in elevated drug levels and potentially increased adverse events.

Outcome and Management

The elevations in serum AST and bilirubin during darolutamide therapy have been asymptomatic, mild and transient, not requiring dose adjustments. Routine monitoring of liver tests is not recommended, but finding AST elevations above 5 times the upper limit of normal would warrant search for another cause of liver injury and stopping therapy or modifying the dose if no other cause is found. There is no information on cross sensitivity for hepatic injury between darolutamide and other antiandrogens, such as flutamide, bicalutamide, apalutamide, enzalutamide, or abiraterone.

Drug Class: Antineoplastic Agents, Antiandrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Darolutamide – Nubeqa®

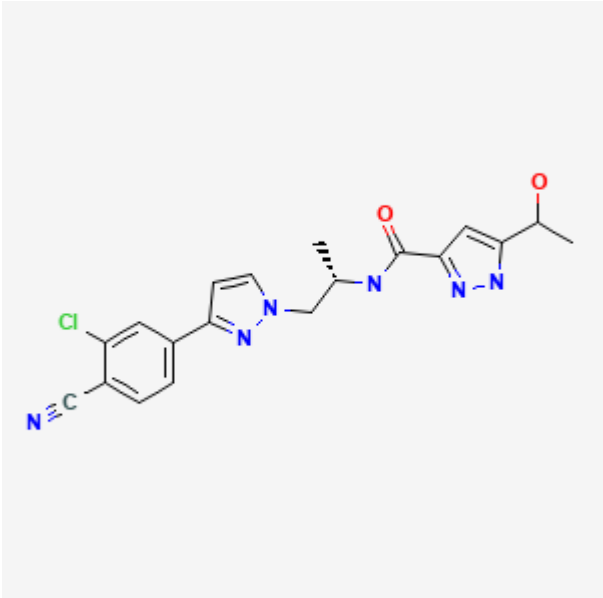
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Darolutamide	1297538-32-9	C19-H19-Cl-N6-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 March 2023

Abbreviations: PSA, prostate-specific antigen; LHRH, luteinizing hormone releasing hormone.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity of cancer chemotherapeutic agents published in 1999 before the availability of antineoplastic antiandrogens such as darolutamide).

DeLeve LD. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam, Elsevier, 2013, p. 541-68.

(Review of hepatotoxicity of cancer chemotherapeutic agents; darolutamide is not discussed).

Isaacs C, Wellstein A, Riegel AT. Hormones and related agents in the therapy of cancer. Natural products in cancer chemotherapy: hormones and related agents. 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. 1237-48.

(Textbook of pharmacology and therapeutics discusses the androgen receptor antagonists flutamide, bicalutamide, nilutamide and enzalutamide, but not apalutamide or darolutamide).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212099Orig1s000MultidisciplineR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions that AST elevations were more frequent on darolutamide than placebo [23% vs 14%] as were bilirubin elevations [16% vs 7%], but that other liver test abnormalities were uncommon, and there were no cases of clinically apparent liver injury with jaundice).

Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, Wongvipat J, et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science. 2009;324:787–90. PubMed PMID: 19359544.

(Description of development of unique antiandrogen molecules that block the translocation of the androgen receptor to the nucleus and the transcriptional activity of the receptor).

Fizazi K, Massard C, Bono P, Jones R, Kataja V, James N, Garcia JA, et al; ARADES study group. Activity and safety of ODM-201 in patients with progressive metastatic castration-resistant prostate cancer (ARADES): an open-label phase 1 dose-escalation and randomised phase 2 dose expansion trial. Lancet Oncol. 2014;15:975–85. PubMed PMID: 24974051.

(Among 110 patients with castration-resistant, metastatic prostate cancer treated with 200, 400 or 1400 mg of darolutamide daily, PSA response rates were similar in all three doses and adverse events included fatigue [31%], back pain [21%], arthralgia [15%] and pain [15%]; no mention of ALT elevations or hepatotoxicity).

Fizazi K, Massard C, Bono P, Kataja V, James N, Tammela TL, Joensuu H, et al. Safety and antitumour activity of ODM-201 (BAY-1841788) in castration-resistant, CYP17 inhibitor-naïve prostate cancer: results from extended follow-up of the ARADES trial. Eur Urol Focus. 2017;3:606–614. PubMed PMID: 28753849.

(Among 41 patients with castration-resistant prostate cancer participating in preliminary trials of darolutamide who were enrolled in open label extension studies, results after 15 months of follow up showed continued antitumor activity and continued rates of mild-to-moderate adverse events; no mention of ALT elevations or hepatotoxicity).

Crawford ED, Schellhammer PF, McLeod DG, Moul JW, Higano CS, Shore N, Denis L, et al. Androgen receptor targeted treatments of prostate cancer: 35 years of progress with antiandrogens. J Urol. 2018;200:956–966. PubMed PMID: 29730201.

(Review of the development of antiandrogen therapies of prostate cancer starting with discovery of the androgen sensitive nature of prostate cancer, the effects of orchiectomy, followed by the development of androgen receptor antagonists, first generation agents flutamide and nilutamide, second generation agent bicalutamide and third generation agents enzalutamide, apalutamide and darolutamide that have more potent androgen receptor inhibition).

Darolutamide (Nubeqa) for prostate cancer. Med Lett Drugs Ther. 2019;61(1587):201–202. PubMed PMID: 31999669.

(Concise review of the mechanism of action, clinical efficacy, safety, and costs of darolutamide shortly after its approval for use in the US, mentions side effects of fatigue, pain, rash, neutropenia and elevations in AST and bilirubin without mention of hepatotoxicity).

Fizazi K, Shore N, Tammela TL, Ulys A, Vjaters E, Polyakov S, Jievaltas M, et al. ARAMIS Investigators. Nonmetastatic, castration-resistant prostate cancer and survival with darolutamide. N Engl J Med. 2020;383:1040–1049. PubMed PMID: 32905676.

(Among 1509 men with non-metastatic, castration-resistant prostate cancer treated in a controlled trial for a median of 29 months, metastasis free survival was longer and risk of death lower with darolutamide than placebo treatment; adverse events that were more frequent with active drug included fatigue, pain and rash; no mention of ALT elevations or hepatotoxicity).

Halabi S, Jiang S, Terasawa E, Garcia-Horton V, Ayyagari R, Waldeck AR, Shore N. Indirect comparison of darolutamide versus apalutamide and enzalutamide for nonmetastatic castration-resistant prostate cancer. J Urol. 2021;206:298–307. PubMed PMID: 33818140.

(Comparison of outcome and adverse events in published randomized, placebo-controlled trials of darolutamide, apalutamide and enzalutamide for castration-resistant prostate cancer suggested that efficacy as assessed by improvement in metastasis-free survival was similar for all three agents, but that darolutamide therapy was associated with lower rates of adverse events, particularly fatigue, rash, falls, seizures, fractures and cognitive disorders; no mention of ALT elevations or hepatotoxicity).

Gillessen S, Procopio G, Hayoz S, Kremer E, Schwitter M, Caffo O, Lorente D, et al. Darolutamide maintenance in patients with metastatic castration-resistant prostate cancer with nonprogressive disease after taxane treatment (SAKK 08/16). J Clin Oncol. 2023;8:JCO2201726.

(Among 92 patients with metastatic, castration-resistant prostate cancer treated with addition of darolutamide or placebo, radiologic progression free survival was 5.5 months with darolutamide vs 4.5 months with placebo and overall adverse event rates were similar, although fatigue was less with darolutamide [11% vs 20%]; no mention of ALT elevation or hepatotoxicity).