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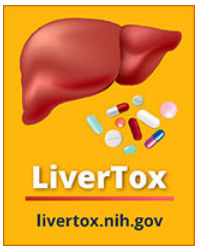


Enzalutamide

Updated: March 15, 2023.

OVERVIEW

Introduction

Enzalutamide is a third generation, oral nonsteroidal antiandrogen used in the treatment of metastatic castration-resistant prostate cancer. Enzalutamide 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

Enzalutamide (en" za loo' ta mide) is an 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 enzalutamide has been shown to prolong relapse free as well as overall survival in men with metastatic, castration-resistant prostate cancer who had previously failed other forms of treatment. Enzalutamide was approved for use in the United States in 2012. Current indications are for castration-resistant prostate cancer and for metastatic, high risk castration-sensitive prostate cancer. In patients without previous bilateral orchiectomy, enzalutamide should be used in combination with a gonadotropin releasing hormone (GnRH) analog to insure optimal androgen suppression. Enzalutamide is available as capsules of 40 mg and tablets of 40 mg and 80 mg under the brand name Xtandi. The recommended dose is 160 mg by mouth once daily. Common side effects include fatigue, diarrhea, anorexia, weight loss, constipation, joint and muscle pain, hot flushes, headaches, dizziness, hypertension, hypokalemia, fluid retention, and edema. Rare, but potentially serious side effects include seizures and posterior reversible encephalopathy.

Hepatotoxicity

In preregistration controlled trials, serum aminotransferase elevations occurred in up to 10% patients treated with enzalutamide, but similar somewhat high rates occurred in patients receiving placebo (~9%). The liver test abnormalities were generally mild, transient and not associated with symptoms or jaundice. ALT elevations above 5 times the ULN were rare (0.2%) and also no more frequent than with placebo therapy. In addition, clinically apparent liver injury with jaundice was not reported in the preregistration trials of enzalutamide, and clinically apparent liver injury and hepatitis are not mentioned in the product label. Since the approval and more wide scale use of enzalutamide, there have been no publications or descriptions of the clinical features of hepatotoxicity with jaundice associated with its use. Thus, clinically apparent liver injury due to enzalutamide must be rare, if it occurs at all.

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

Mechanism of Injury

The cause of the liver enzyme elevations that occur during enzalutamide therapy is unknown. Enzalutamide is extensively metabolized in the liver predominantly by CYP 3A4 and 2D6 and is a strong inducer of CYP 3A4 and a moderate inducer of 2D6. Enzalutamide is susceptible to drug-drug interactions with inhibitors, inducers or substrates of these microsomal enzymes.

Outcome and Management

The liver injury linked to enzalutamide therapy has been generally mild, consisting of transient and asymptomatic elevations in serum aminotransferase levels. Enzalutamide has not been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. There is no information on cross sensitivity to hepatic injury between enzalutamide and other antiandrogens, such as flutamide, bicalutamide, or abiraterone.

Drug Class: Antineoplastic Agents, Antiandrogens

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Enzalutamide – Xtandi®

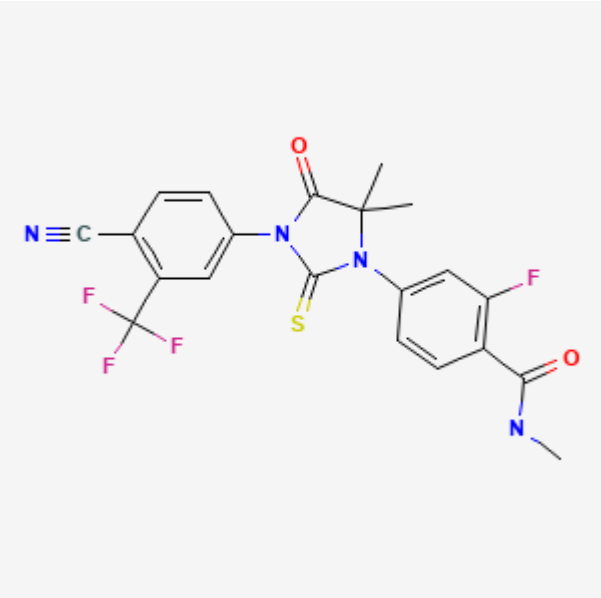
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Enzalutamide	915087-33-1	C21-H16-F4-N4-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 15 March 2023

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

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 enzalutamide).

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; enzalutamide is not discussed).

Moy B, Lee RJ, Smith M. Hormone therapy in prostate cancer. Natural products in cancer chemotherapy: hormones and related agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1763-9.

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

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).

Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, et al. AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187–97. PubMed PMID: 22894553.

(Among 1199 adult men with castration-resistant prostate cancer treated with enzalutamide [160 mg daily] or placebo, mean survival was improved from 13.6 to 17.3 months and side effects included abnormal ALT, AST or bilirubin in 1% on enzalutamide vs 2% on placebo).

Enzalutamide (Xtandi) for prostate cancer. Med Lett Drugs Ther. 2013;55(1411):e20. PubMed PMID: 23467121.

(Concise summary of the mechanism of action, clinical efficacy, safety and costs of enzalutamide shortly after its approval in the US; does not mention ALT elevations or hepatotoxicity).

Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, Iversen P, et al. Enzalutamide monotherapy in hormone-naive prostate cancer: primary analysis of an open-label, single-arm, phase 2 study. Lancet Oncol. 2014;15:592–600. PubMed PMID: 24739897.

(Among 67 men with hormone treatment naive prostate cancer treated with enzalutamide [160 mg daily] for 25 weeks, prostate specific antigen levels decreased by more than 80% in 62 patients [93%], and side effects included gynecomastia, fatigue, hot flush, diarrhea, and nausea, while "no hepatic adverse events were reported for any patient").

Bennett LL, Ingason A. Enzalutamide (Xtandi) for patients with metastatic, resistant prostate cancer. Ann Pharmacother. 2014;48:530–7. PubMed PMID: 24458946.

(Review of the pharmacology, clinical efficacy and safety of enzalutamide, mentions that it is "generally well tolerated" and does not mention ALT elevations or hepatotoxicity).

Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, et al. PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;371:424–33. PubMed PMID: 24881730.

(Among 1717 men with metastatic prostate cancer treated with enzalutamide or placebo, overall and progression-free survival were improved with enzalutamide and its side effects included fatigue, back pain, constipation, arthralgia, hot flushes, diarrhea and poor appetite; ALT elevations occurred in 1% of patients in both groups and were rarely above 5 times ULN).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 [5.5%] were attributed to antineoplastic agents of which only 1 was due to an antiandrogen [bicalutamide]).

Joshua AM, Shore ND, Saad F, Chi KN, Olsson CA, Emmenegger U, Scholz M, et al; Enzalutamide Expanded Access Study Investigators. Safety of enzalutamide in patients with metastatic castration-resistant prostate cancer previously treated with docetaxel: expanded access in North America. Prostate. 2015;75:836–44. PubMed PMID: 25683285.

(Among 507 patients with metastatic, castration-resistant prostate cancer receiving enzalutamide in an open access program until commercial availability [mean duration 2.6 months], there was "no clinical laboratory evidence of drug-related hepatotoxicity").

Tombal B, Borre M, Rathenborg P, Werbrouck P, Van Poppel H, Heidenreich A, Iversen P, et al. Long-term efficacy and safety of enzalutamide monotherapy in hormone-naïve prostate cancer: 1- and 2-year open-label follow-up results. Eur Urol. 2015;68:787–94. PubMed PMID: 25687533.

(Among 67 patients with hormone naïve prostate cancer treated with enzalutamide for 25 weeks [Tombal 2014], 45 remained on therapy for 2 years with sustained decreases in prostate specific antigen [PSA] levels; no hepatic adverse events were mentioned).

Ning YM, Brave M, Maher VE, Zhang L, Tang S, Sridhara R, Kim G, et al. U.S. Food and Drug Administration Approval Summary: enzalutamide for the treatment of patients with chemotherapy-naïve metastatic castration-resistant prostate cancer. Oncologist. 2015;20:960–6. PubMed PMID: 26070917.

(Summary of the clinical efficacy and safety analysis of trials of enzalutamide therapy of advanced prostate cancer that led to its approval by the FDA; mentions side effects of fatigue, back pain, diarrhea, hot flush, edema, muscle pain and weakness, headache, diarrhea and insomnia, but does not mention ALT elevations or hepatotoxicity).

Higano CS, Beer TM, Taplin ME, Efstathiou E, Hirmand M, Forer D, Scher HI. Long-term safety and antitumor activity in the phase 1-2 study of enzalutamide in pre- and post-docetaxel castration-resistant prostate cancer. Eur Urol. 2015;68:795–801. PubMed PMID: 25698064.

(Among 140 patients with castration-resistant prostate cancer continued on enzalutamide therapy for up to 4 years, no new safety concerns arose and there was no mention of ALT elevations or hepatotoxicity).

Shore ND, Chowdhury S, Villers A, Klotz L, Siemens DR, Phung D, van Os S, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomised, double-blind, phase 2 study. Lancet Oncol. 2016;17:153–63. PubMed PMID: 26774508.

(Among 375 patients with metastatic prostate cancer treated with enzalutamide [160 mg] vs bicalutamide [50 mg] once daily, median progression free survival was greater with enzalutamide [15.7 vs 5.8 months] and side effect rates were similar, ALT elevations occurring in 2.2% vs 1.1% with only 1 patient in each group having elevations above 5 times ULN; no mention of clinically apparent liver injury).

Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, Iversen P, et al. Enzalutamide in men with chemotherapy-naïve metastatic castration-resistant prostate cancer: extended analysis of the phase 3 PREVAIL Study. Eur Urol. 2017;71:151–154. PubMed PMID: 27477525.

(Extended analysis of the randomized controlled trial of enzalutamide for chemotherapy-naïve metastatic castration-resistant prostate cancer [Beer et al; 2014] found that response rates remained higher in the enzalutamide treated group and the adverse event profile remained the same).

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).

Attard G, Borre M, Gurney H, Loriot Y, Andresen-Daniil C, Kalleda R, Pham T, et al; PLATO collaborators. Abiraterone alone or in combination with enzalutamide in metastatic castration-resistant prostate cancer with rising prostate-specific antigen during enzalutamide treatment. J Clin Oncol. 2018;36:2639–2646. PubMed PMID: 30028657.

(Among 251 patients with metastatic prostate cancer who had rising PSA levels despite enzalutamide therapy who were treated with abiraterone with or without enzalutamide, progression free survival was similar with both groups [5.7% vs 5.6%], while ALT elevations were more frequent with combination therapy [10% vs 2%] as was hypertension [6% vs 2%]).

Liu J, Agyapong G, Misra D, Taylor CD, Hirsh DA. A rare case of idiopathic cholestasis: Clinical conundrums complicating enzalutamide therapy in metastatic prostate cancer. Clin Case Rep. 2019;7:2068–2073. PubMed PMID: 31788253.

(88 year old man with metastatic prostate cancer developed jaundice one week after stopping a 5 month course of bicalutamide and starting enzalutamide while continuing on leuprolide [bilirubin 3.8 mg/dL, ALT 45 U/L, Alk P 654 U/L, GGT 988 U/L, INR 1.2], with little improvement after stopping all therapy and death from suspected progressive disease 2 weeks later).

Ryoo BY, Palmer DH, Park SR, Rimassa L. Efficacy and safety results from a phase 2, randomized, double-blind study of enzalutamide versus placebo in advanced hepatocellular carcinoma. Clin Drug Investig. 2021;41:795–808. Debashis Sarker, Daniele B, Steinberg J, et al.

(Among 165 patients with advanced hepatocellular carcinoma treated with enzalutamide [160 mg] or placebo once daily, the median overall survival rates were similar in both groups [7.8 vs 7.1 months] and adverse event rates were higher with enzalutamide [98% vs 89%] including fatigue [35% vs 18%], decreased appetite [32% vs 22%] and nausea [32% vs 22%], while rates of AST elevation above 5 times ULN were similar [11% vs 11%]; no mention of serious hepatic adverse events).

Vaishampayan UN, Heilbrun LK, Monk P 3rd, Tejwani S, Sonpavde G, Hwang C, Smith D, et al. Clinical efficacy of enzalutamide vs bicalutamide combined with androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a randomized clinical trial. JAMA Netw Open. 2021;4:e2034633. PubMed PMID: 33496795.

(Among 71 men with advanced prostate cancer treated with either enzalutamide [160 mg] or bicalutamide [50 mg] daily with androgen-depletion therapy using a LHRH analog, the biochemical and overall survival outcomes were greater with enzalutamide than bicalutamide, particularly in Black subjects; no mention of hepatic adverse events).

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).

Fleshner L, Berlin A, Hersey K, Kenk M, Lajkosz K, Nguyen S, Wise J, et al. Time trends of drug-specific actionable adverse events among patients on androgen receptor antagonists: implications for remote monitoring. Can Urol Assoc J. 2022;16:E146–E149. PubMed PMID: 34672938.

(Among 828 patients with prostate cancer who received abiraterone or enzalutamide or both, adverse events arose in 29% on abiraterone, 26% on enzalutamide, usually within the first 3 months; abnormal liver tests arose in 48% vs 23% and hypertension in 47% vs 77%, but there were no adverse event related deaths).

Payne H, Robinson A, Rappe B, Hilman S, De Giorgi U, Joniau S, Bordonaro R, et al. A European, prospective, observational study of enzalutamide in patients with metastatic castration-resistant prostate cancer: PREMISE. Int J Cancer. 2022;150:837–846. PubMed PMID: 34648657.

(Among 1732 men with metastatic castration-resistant prostate cancer in a prospective, open-label study, the mean time to treatment failure was 12.9 months and adverse event rates ranged from 51-62% per year; no mention of liver related adverse events).

Scailteux LM, Despas F, Balusson F, Campillo-Gimenez B, Mathieu R, Vincendeau S, Happe A, et al. Hospitalization for adverse events under abiraterone or enzalutamide exposure in real-world setting: A French population-based study on prostate cancer patients. Br J Clin Pharmacol. 2022;88:336–346. PubMed PMID: 34224605.

(Among 11,534 patients newly started on abiraterone or enzalutamide therapy for prostate cancer who were enrolled in the French National Health Insurance System Database between 2013 and 2017, liver test abnormalities were more frequent with abiraterone [17% vs 6%] as were acute kidney injury and atrial fibrillation, while "hepatitis" was rare [<0.1%]).