Drug Monograph

A - Drug Name

enzalutamide

COMMON TRADE NAME(S): Xtandi®

back to top

B - Mechanism of Action and Pharmacokinetics

Enzalutamide is an androgen receptor inhibitor, which has no known agonistic properties. Enzalutamide competitively inhibits the binding of androgen to the receptor, inhibiting nuclear translocation of androgen receptors and their interaction with DNA.

Absorption	Bioavailability	At least 84.2%
	Effects with food	Food had no significant effect on enzalutamide exposure, although a C_{max} of 30% higher was observed when this drug was given in fasting state.
	Time to reach steady state	28 days; accumulates approximately 8.3x relative to a single dose.
	Peak plasma levels	~ 1 hr (range: 0.52 h to 3.02 h)
Distribution	Extensive extravascular distribution.	
	Cross blood brain barrier?	Yes, both enzalutamide and the active metabolite
	PPB	Enzalutamide: 97-98%; metabolites: 95%

		No protein binding displacement between enzalutamide and other highly bound drugs *in vitro*.
Metabolism	Extensively metabolized by CYP2C8 and a lesser extent by CYP3A4/5.	
	Active metabolites	Yes
	Inactive metabolites	Yes
Elimination	Cleared via renal excretion of hepatic metabolites.	
	Urine	71% (primarily as inactive metabolites)
	Feces	14% (0.4% unchanged)
	Half-life	5.8 days (enzalutamide); 8-9 days (active metabolite)

back to top

C - Indications and Status

Health Canada Approvals:

- Non-metastatic castration-sensitive prostate cancer (nmCSPC)
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)
- Metastatic castration-resistant prostate cancer (mCRPC)

Refer to the product monograph for a full list and details of approved indications

back to top

D - Adverse Effects

Emetogenic Potential: Not applicable

Extravasation Potential: Not applicable

The following adverse effects were reported in ≥ 2% of patients with nmCRPC in the phase III trial comparing enzalutamide to placebo, where incidence was at least 2% or more compared to placebo. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E D
	Hypertension (12%) (may be severe)	E
	Other - Ischemic heart disease (4% , may be severe)	E D
	QT interval prolonged (rare)	E
Dermatological	Rash (4%) (including dry skin)	E
Gastrointestinal	Anorexia, weight loss (10%)	E
	Constipation (9%)	E
	Diarrhea (22%)	E
	Nausea (11%)	E
	Other - Gastrointestinal bleed (<2%)	E
General	Edema (15%)	E
	Fatigue (40%) (4% severe)	E
Hematological	Myelosuppression ± infection (1%) (severe)	E
Hypersensitivity	Hypersensitivity (rare)	E
Musculoskeletal	Fracture (5%)	E D
	Musculoskeletal pain (26%)	E
	Other - fall (11%)	E D
Neoplastic	Secondary malignancy (rare)	L
Nervous System	Anxiety (6%)	E
	Cognitive disturbance (5%)	E
	Dizziness (12%)	E
	Hallucinations (<2%)	E
	Headache (9%)	E

	Insomnia (9%)	E
	Other - Hypoesthesia (4%)	E
	Paresthesia (7%)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Seizure (1%)	E
Reproductive and breast disorders	Androgen deprivation symptoms (13%)	E
Urinary	Urinary symptoms (7%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for enzalutamide include fatigue, musculoskeletal pain, diarrhea, edema, androgen deprivation symptoms, dizziness, hypertension, fall, nausea, anorexia and weight loss.

Enzalutamide is associated with an increased risk of **seizure**, especially at doses above 160mg. The lowering of the seizure threshold may be due to enzalutamide and its active metabolite crossing the blood brain barrier and inhibiting GABA-gated chloride channel activity.

Enzalutamide was associated with increases in systolic and diastolic blood pressure and an increased risk of **hypertension** or worsening of pre-existing hypertension in studies.

Posterior reversible encephalopathy syndrome (PRES) has been reported rarely, with and without associated hypertension.

Increases in non-pathological **fractures and falls** were observed as compared to placebo. Fall-related injuries included contusion, excoriation, head injury, joint injury, laceration, periorbital hematoma, and skeletal injury. Concomitant neurological symptoms or pre-syncope were rarely reported with the falls.

Hypersensitivity reactions, including facial, tongue, lip or pharyngeal edema have been observed with enzalutamide.

back to top

E - Dosing

Refer to protocol by which patient is being treated.

Patients with nmCRPC, mCRPC, or mCSPC, who have not had orchiectomy, should receive/remain on GnRH agonists during enzalutamide treatment.

Patients with nmCSPC with biochemical recurrence at high risk of metastasis (high-risk BCR) may be treated with or without a GnRH agonist.

Patients were allowed, but not required, to take glucocorticoids in several phase III CRPC clinical trials (Beer 2014, Hussain 2018, Scher 2012).

Prior to starting enzalutamide treatment:

- Patients with cardiac history should be assessed for active cardiac disease.
- Management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia should be optimized.
- Patients should be assessed for the risk of fracture and fall and managed according to guidelines with consideration given to the use of bone-targeted agents.

Adults:

Oral: 160 mg Daily

For nmCSPC with high-risk BCR, refer to the product monograph for details on intermittent treatment.

Dosage with Toxicity:

Dose Level	Enzalutamide Dose (mg/day)
0	160
-1	120
-2	80
-3	Discontinue

Toxicity	Grade	Action
Hypersensitivity reactions	Any	Hold and promptly seek medical care.
	≥ grade 3	Discontinue.
PRES	Any	Discontinue.
Seizure		
Ischemic heart disease	≥ grade 3	Discontinue.
Treatment emergent hypertension	Any	Monitor blood pressure and treat appropriately.
All other toxicities	Intolerable or ≥ grade 3	Hold until ≤ grade 2. Resume at the same dose OR ↓ dose level, if warranted. Consider discontinuing if grade 4.

Dosage with Hepatic Impairment:

Hepatic Impairment	Enzalutamide Dose (mg/day)
Mild or moderate (Child-Pugh Class A or B)	No adjustment required
Severe (Child-Pugh C)	Increased drug half-life was observed; clinical significance unknown. No dosage adjustment required.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Enzalutamide Dose (mg/day)
≥ 30	No adjustment required
< 30	Has not been studied. Exercise caution.

Dosage in the elderly:

No dose adjustment required. No overall differences in safety or efficacy were found in patients ≥ 65 years compared to younger patients; however, an increased frequency of dose interruption/reduction and discontinuation was observed.

Dosage based on ethnicity:

Based on a pharmacokinetic study in Japanese patients, no clinically relevant differences in exposure were found between Japanese and Caucasians.

Children:

Safety and efficacy have not been established.

back to top

F - Administration Guidelines

- Swallow capsules whole with a glass of water, with or without food.
- Do not chew, dissolve, or open the capsules.
- Take the dose at around the same time each day.
- If a dose is missed for the day, give it as soon as it is remembered on the same day. If it is forgotten for the whole day, skip this dose and give the next usual dose. Do not double the dose to make up for the missed one.
- Store at room temperature (15 to 30°C).

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components
- Patients who are or may become pregnant, or who are lactating

Other Warnings/Precautions:

- Exercise caution in these patient populations:
    - nmCRPC at low risk of developing metastatic disease: Enzalutamide has not been studied in this population and the benefit and risk profile in these patients is unknown.
    - nmCSPC with high-risk BCR: Enzalutamide was studied in combination with leuprolide during clinical trials. Other GnRH agonists may have potential differences in patterns of testosterone recovery, PSA expression, duration of treatment suspension and compliance to treatment.
    - Significant cardiovascular disease. Patients with significant cardiovascular disease (i.e. recent MI, unstable angina, LVEF < 45%, bradycardia or uncontrolled hypertension) were excluded from clinical trials.
    - History of QT prolongation, risk factors for Torsades de Pointes, or on medications known for QT prolongation.
    - History of seizures or have risk factors for seizures (e.g. brain injury with loss of consciousness, recent TIA, CVA, brain metastases). These patients were excluded from clinical trials. Avoid dosing above 160mg as this was observed to have a greater risk of seizures.
    - Enzalutamide may cause neuropsychiatric events such as cognitive or memory impairment, seizures, hallucinations, etc. Patients should take caution and avoid tasks in which mental impairment or loss of consciousness may harm themselves or others.
    - Severe hepatic impairment (Child-Pugh C) at baseline. These patients were excluded from clinical trials.
- Patients with hereditary fructose intolerance should not take enzalutamide as it contains sorbitol.

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Genotoxicity: Yes
  (metabolite, only at cytotoxic concentrations)
- Embryotoxicity: Yes
- Fetotoxicity: Yes
  Enzalutamide is **contraindicated** in pregnancy. Adequate contraception (one of which must include condoms) should be used by patients and their patients and their partners during treatment and for **3 months** after the last dose.
- Excretion into breast milk: Yes
  Breastfeeding is **contraindicated**.
- Fertility effects: Yes

back to top

H - Interactions

Enzalutamide is a substrate of CYP2C8 and to a lesser extent, CYP3A4. It is an inducer and inhibitor of several CYP isoenzymes and susceptible to many drug interactions. Since the half-life of enzalutamide is 5.8 days, the effects on enzymes may persist for ≥1 month after stopping the drug.

CYP3A4 inhibitors may increase enzalutamide exposure, but no dosage adjustment is recommended.

Enzalutamide is an inhibitor of CYP2C8 and an inducer/inhibitor of CYP2B6, but no dosage adjustment is required.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP2C8 inhibitors (i.e. gemfibrozil, montelukast)	↑ enzalutamide exposure (up to 2.2x) and/or toxicity	↓ metabolism of enzalutamide	Avoid; if concomitant use with strong CYP2C8 inhibitor cannot be avoided, reduce enzalutamide dose to 80mg daily.
CYP3A4 and CYP2C8 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ enzalutamide concentration and/or efficacy (rifampin ↓ enzalutamide AUC 37% with no effect on Cmax)	↑ metabolism of enzalutamide	No dosage adjustment required. Avoid concomitant use with strong CYP3A4 inducers.
CYP3A4 substrates (i.e. midazolam, cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↓ substrate exposure and/or efficacy (up to 86% ↓)	enzalutamide is a strong CYP3A4 inducer	Avoid substrates with narrow therapeutic range; consider dose adjustment of substrate if concomitant use cannot be avoided.
CYP 2C9 substrates (i.e. warfarin, meloxicam, fluvastatin)	↓ substrate exposure and/or efficacy (up to 56% ↓), or ↑ substrate exposure	enzalutamide is a moderate CYP2C9 inducer, also has potential to inhibit CYP2C9	Avoid substrates with narrow therapeutic range; monitor INR closely (e.g. with warfarin); consider dose adjustment of substrate if concomitant use cannot be avoided.
CYP2C19 substrates (i.e. omeprazole)	↓ substrate exposure and/or efficacy (up to 70% ↓), or ↑ substrate exposure	enzalutamide is a moderate CYP2C19 inducer, also has potential to inhibit CYP2C19	Avoid substrates with narrow therapeutic range; consider dose adjustment of substrate if concomitant use cannot be avoided.

UGT1A1 substrates (i.e. irinotecan), CYP2B6 or UGT1A4 substrates	↓ substrate exposure and/or efficacy	enzalutamide can induce these enzymes or transporters	Avoid substrates with narrow therapeutic range; consider dose adjustment of substrate if concomitant use cannot be avoided.
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ P-gp substrate exposure/toxicity (↑ single dose digoxin exposure by 33%, after at least 55 days of enzalutamide 160 mg); ↓ in substrate concentration at higher enzalutamide concentrations	Inhibition or possible induction of P-gp	Caution with substrates with a narrow therapeutic range; dose adjustment of substrate may be required.
MRP2 substrates (i.e. topotecan, cisplatin)	↑ substrate exposure and/or toxicity	enzalutamide can inhibit MRP2	Caution with substrates with a narrow therapeutic range; dose adjustment of substrate may be required.
Substrates of OATP1B1/3 (i.e. statins), OAT3 (i.e. furosemide, methotrexate), and OCT1 (i.e. metformin)	↑ substrate exposure and/or toxicity	enzalutamide may inhibit these enzymes	Caution
Drugs that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron, etc)	↑ risk of QT prolongation	Additive	Caution

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline and as clinically indicated
ECG and electrolytes	Baseline and as clinically indicated, in patients at risk of QT prolongation
Disease progression radiographically in addition to serum PSA	As clinically indicated, in patients with nmCRPC or nmCSPC with high-risk BCR
INR monitoring for patients on warfarin	Baseline and as clinically indicated
Clinical toxicity assessment for ischemic heart disease, androgen withdrawal, gastrointestinal effects, hypersensitivity, fatigue, seizures and other neuropsychiatric effects, musculoskeletal effects including falls/fractures and edema	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- enzalutamide - For the treatment of metastatic castrate-resistant prostate cancer (mCRPC), with specific clinical criteria
- enzalutamide - For the treatment of high risk non-metastatic castration-resistant prostate cancer (nmCRPC), with specific clinical criteria
- enzalutamide - For the treatment metastatic castration sensitive prostate cancer (mCSPC), with specific clinical criteria

back to top

K - References

Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019 Nov 10;37(32):2974-2986.

Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014 Jul 31;371(5):424-33.

Hussain M, et al. Enzalutamide in Men with Nonmetastatic, Castration-Resistant Prostate Cancer. N Engl J Med. 2018 Jun 28;378(26):2465-2474.

Prescribing Information: Xtandi® (enzalutamide). Astellas Pharma US Inc., December 2019.

Product Monograph: Xtandi® (enzalutamide). Astellas Pharma Canada Inc., January 5, 2024.

Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187-97.

June 2024 Updated Adverse Effects, Dosing, Special Precautions, and Monitoring sections

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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The format and content of the drug monographs, regimen monographs, appendices and symptom management

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back to top