DRUG NAME: Enzalutamide

SYNONYM(S): MDV3100[1]

COMMON TRADE NAME(S): XTANDI®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Enzalutamide is an androgen receptor inhibitor which acts at several steps in the androgen receptor signaling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors with more affinity than other antiandrogen agents. It also inhibits nuclear translocation of the androgen receptors, DNA binding, and coactivator recruitment. It decreases cell proliferation and induces cell death in prostate cells *in vitro* and decreases tumour volume in xenograft models. Enzalutamide lacks androgen receptor agonist activity in cell growth assays.[2]

PHARMACOKINETICS:

Oral Absorption	rapid[3]; absorption estimated at 84%; food has no clinically significant effect on extent of absorption, however peak plasma concentration may be 30% higher when fasting	
Distribution	extensive extravascular distribution	
	cross blood brain barrier?	yes, including active metabolite
	volume of distribution	110 L
	plasma protein binding	parent (97-98%), primarily to albumin ; metabolites (95-98%)
Metabolism	extensively metabolized; substrate of CYP 2C8 and to a lesser extent CYP 3A4/5	
	active metabolite(s)	N-desmethyl enzalutamide (M2); primarily via CYP 2C8
	inactive metabolite(s)	carboxylic acid derivative (M1) primarily; up to 7 other unnamed phase I metabolites
Excretion	primarily via renal excretion of hepatic metabolites	
	urine	71% (primarily as M1; trace amounts of enzalutamide and M2)
	feces	14% (<1% as unchanged enzalutamide)
	terminal half life	5.8 days
	clearance	0.56 L/h (range 0.33 to 1.02 L/h)[4]
Elderly	no meaningful differences[4]	

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Prostate cancer

Other uses:

*Health Canada approved indication

Developed: 1 December 2013
Revised: 1 October 2023

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to enzalutamide, sorbitol, or fructose[2]
- women who are pregnant, may become pregnant, or are lactating[2]

Caution:
- not intended for use in ***women***[2]
- associated with ***neuropsychiatric events*** (i.e., seizure, memory impairment, and hallucination); caution is required for activities where mental impairment or sudden loss of consciousness may cause serious harm[2]
- enzalutamide dose reduction may be required for ***drug interactions*** involving the CYP 2C8 metabolic pathway[5]
- associated with ***QT prolongation***[2]; monitor ECG and electrolytes and use cautiously in patients with known history of QT prolongation, risk factors for torsades de pointes, or taking medications known to prolong the QT interval. associated with increases in systolic and diastolic ***blood pressure***, increased risk of hypertension, and worsening of pre-existing hypertension[2]

Carcinogenicity: Long-term animal studies have not been conducted.[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Enzalutamide is not clastogenic in mammalian *in vivo* chromosome tests.[2]

Fertility: Reproductive organ changes were seen in studies in mice, rats, and dogs. In rats, observed changes included atrophy of the prostate, seminal vesicles, and mammary glands in males, and pituitary and mammary gland hyperplasia in females. In dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed.[2] Based on the mechanism of enzalutamide and the pharmacological consequences of androgen receptor inhibition, effects on human male fertility cannot be excluded.[5]

Pregnancy: Studies in pregnant rodents have shown that enzalutamide and/or its metabolites are transferred to the fetus. In animal studies, enzalutamide caused embryo-fetal lethality (increased post-implantation loss, reduced numbers of live fetuses), and external abnormalities such as shortened anogenital distance, cleft palate, and absent palatine bone at exposures up to 1.1 times the AUC in humans. Based on the mechanism of action of enzalutamide and the pharmacological consequences of androgen receptor inhibition, maternal use of enzalutamide is expected to produce changes in hormone levels which may affect fetal development. It is not known if enzalutamide or its metabolites are present in semen. Barrier contraception is recommended during sexual activity with pregnant women and women of child-bearing potential. Contraception is recommended during treatment and for three months after treatment has ended.[5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Studies in lactating rodents show that enzalutamide and/or its metabolites are secreted in milk, and transferred to the infant.[5]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[6] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.[1,2]

Developed: 1 December 2013
Revised: 1 October 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	neutropenia (15%, severe 1%)
gastrointestinal	*emetogenic potential:* rare[7]
	diarrhea[1] (21%, severe 1%)
general disorders and administration site conditions	***fatigue*** (34-51%, severe 6%)[2,3]
	peripheral edema[4] (15%, severe 1%)
infections and infestations	infection, miscellaneous[3] (≤6%)
	lower respiratory infection[3,4] (9%, severe 2%)
	upper respiratory infection[3] (11%)
injury, poisoning, and procedural complications	bone fractures, non-pathological (4%)
	falls (4-5%, severe <1%)[2,3]; not associated with loss of consciousness or seizure
investigations	ALT abnormalities (10%, severe <1%)
	AST abnormalities (23%, severe <1%)
	hyperbilirubinemia[3] (3%)
	QT prolongation[1,2]
musculoskeletal and connective tissue	arthralgia[3] (21%)
	back pain[3] (26%)
	muscle weakness[3] (10%)
	musculoskeletal pain[1] (14%, severe 1%)
nervous system	dizziness[3] (10%)
	headache (12%, severe 1%)
	hypoesthesia[3] (4%)
	mental impairment, including amnesia, cognitive disorder, memory impairment (4%)
	paresthesia[3] (7%)
	seizures (1%); see paragraph following **Side Effects** table
psychiatric	anxiety (6-7%, severe <1%)
	hallucinations[3] (2%)
	insomnia[3] (9%)
renal and urinary	hematuria[3] (7%)
respiratory, thoracic and mediastinal	epistaxis[3] (3%)
skin and subcutaneous tissue	dry skin (4%)
	pruritus (4%)

Developed: 1 December 2013
Revised: 1 October 2023

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	hot flush (20%)
	hypertension (6%, severe 2%); see paragraph following **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

Hypertension, increased systolic and diastolic blood pressure, or hypertensive crisis occurs in approximately 7% of patients. Hypertension rarely leads to discontinuation or dose modification of enzalutamide, however approximately 75% of patients reporting hypertension will require either initiation of antihypertensive treatment or an increase in the dose of their current therapy.[2]

An increased risk of ***seizure*** has been associated with enzalutamide; reported onset is1-20 months after treatment initiation. Doses higher than 160 mg may be associated with a greater risk of seizure. Seizures resolve after treatment cessation. Both enzalutamide and its active metabolite cross the blood brain barrier, where they bind to and inhibit the activity of the GABA-gated chloride channel, an off-target mechanism associated with the onset of seizure in animals. It is not clear if history of seizure or other predisposing factors increases the risk of seizure with enzalutamide, and therefore, caution is advised when using enzalutamide in this group.[2,3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
gemfibrozil[2]	2 fold increase in AUC of enzalutamide	inhibition of CYP 2C8 by gemfibrozil	avoid concurrent use if possible; otherwise, a 50% dose reduction for enzalutamide is recommended
itraconazole[2]	1 fold increase in AUC of enzalutamide	inhibition of CYP 3A4 by itraconazole	monitor for side effects of enzalutamide; dose adjustment is not required
midazolam[2]	86% decrease in AUC of midazolam	induction of CYP 3A4 by enzalutamide	avoid concurrent use
omeprazole[2]	70% decrease in AUC of omeprazole	induction of CYP 2C19 by enzalutamide	avoid concurrent use
warfarin[2]	56% decrease in AUC of S-warfarin	induction of CYP 2C9 by enzalutamide	monitor INR; adjust dose of warfarin as needed

NOTE: effects on enzymes ***may persist for one month*** or longer after discontinuation of enzalutamide due to the long half-life of enzalutamide.[2]

Enzalutamide has been associated with statistically significant **QTc prolongation** (mean increase of 3-5.6 msec from baseline during weeks 5-25). Use caution during concurrent therapy with drugs that prolong QT/QT_c interval. Consider monitoring ECG and serum electrolytes for patients at risk for QTc prolongation.[2]

Enzalutamide is a **substrate** of **CYP 2C8**. If co-administered with strong CYP 2C8 inhibitors, reduce enzalutamide starting dose to 80 mg once daily. Strong inducers of CYP 2C8 may reduce the effectiveness of enzalutamide and should be avoided if possible.[2].

Enzalutamide is a strong **inducer** of **CYP 3A4** and a moderate inducer of **CYP 2C9** and **CYP 2C19**. Co-administration may result in decreased exposure to substrates of these enzymes. Avoid co-administration with substrates with a narrow therapeutic index if possible. Dose adjustment of the substrate may be required to maintain therapeutic concentrations and additional monitoring may be required.[2]

Developed: 1 December 2013
Revised: 1 October 2023

Enzalutamide is a **substrate** of **CYP 3A4**. Dose adjustment of enzalutamide is not necessary when co-administered with CYP 3A4 **inhibitors.** Grapefruit or grapefruit juice may inhibit CYP 3A4 metabolism in the intestinal wall, and theoretically may increase the plasma level of enzalutamide, however, avoiding grapefruit or grapefruit juice does not appear to be necessary during treatment. The effect of CYP 3A4 **inducers** has not been studied *in vivo*.[2]

In vitro studies suggest that enzalutamide may **induce** uridine 5'-diphospho-glucuronosyltransferase (**UGT1A1)** and decrease exposure to substrates of this enzyme. Avoid co-administration with UGT1A1 substrates with a narrow therapeutic index.[2]

Enzalutamide has been reported to have both an inhibiting and an inducing effect on **P-glycoprotein** *in vitro* and has been reported to inhibit breast cancer resistant protein (**BCRP**) and multidrug resistance-associated protein 2 (**MRCP2**) *in vitro.* These effects have not been evaluated *in vivo*; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Astellas Pharma Canada, Inc. supplies enzalutamide as 40 mg liquid filled soft gelatin capsules. Capsules contain sorbitol. Store at room temperature.[5]

Additional information: Capsules are supplied in bottles of 120 capsules and cartons of 112 capsules (4 blister cards per box; each blister card containing a total of 28 capsules per card and organized into 7 blisters with 4 capsules per blister).[5]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[5]:	***160 mg*** (range 80-160 mg) ***PO once daily**** *(dose adjustment may be required for some drug interactions) Administer with food or on an empty stomach. Do not chew, open, or dissolve capsules.[5]
Concurrent radiation:	no information found
Dosage in myelosuppression:	modify according to protocol by which patient is being treated
Dosage in renal failure:	mild to moderate impairment (calculated CrCl ≥30 mL/min): no adjustment required[2] severe impairment (CrCl <30 mL/min): no information found calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild to moderate impairment: no adjustment required[2] severe impairment: no information found

Developed: 1 December 2013
Revised: 1 October 2023

BC Cancer usual dose noted in ***bold, italics***

Dosage in dialysis:	unlikely to be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis due to its large volume of distribution and low unbound free fraction[2]
Children:	no information found

REFERENCES:

1. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367(13):1187-1197
2. Astellas Pharma Canada Inc. XTANDI® product monograph. Markham, Ontario; May 28 2013
3. Lexi-Drugs. Lexi-Comp Online® (database on the Internet). Enzalutamide. Lexi-Comp Inc., 2013. Available at: http://online.lexi.com. Accessed 26 June, 2013
4. Astellas Pharma US Inc. XTANDI® product monograph. Northbrook, Illinois; August 2012
5. Astellas Pharma Canada Inc. XTANDI® product monograph. Markham, Ontario; March 14 2023
6. Kim Chi MD. BC Cancer Agency Genitourinary Tumour Group. Personal communication. 7 August2013
7. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012

Developed: 1 December 2013
Revised: 1 October 2023