

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XTANDI® safely and effectively. See full prescribing information for XTANDI.

XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel. (1)

DOSAGE AND ADMINISTRATION

XTANDI 160 mg (four 40 mg capsules) administered orally once daily. Swallow capsules whole. XTANDI can be taken with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Capsule 40 mg (3)

CONTRAINDICATIONS

Pregnancy (4, 8.1)

WARNINGS AND PRECAUTIONS

Seizure occurred in 0.9% of patients receiving XTANDI. There is no clinical trial experience with XTANDI in patients who have had a seizure, in patients with predisposing factors for seizure, or in patients using concomitant medications that may lower the seizure threshold. (5.1)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 5\%$) are asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. (2.2, 7.1)
- Avoid strong or moderate CYP3A4 or CYP2C8 inducers as they can alter the plasma exposure to XTANDI. (7.1, 7.2)
- Avoid CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring. (7.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of XTANDI is 160 mg (four 40 mg capsules) administered orally once daily. XTANDI can be taken with or without food [see *Clinical Pharmacology (12.3)*]. Swallow capsules whole. Do not chew, dissolve, or open the capsules.

2.2 Dose Modifications

If a patient experiences a \geq Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to \leq Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted.

Concomitant Strong CYP2C8 Inhibitors

The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the XTANDI dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with MDV.

4 CONTRAINDICATIONS

Pregnancy

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. XTANDI is not indicated for use in women. XTANDI is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss [see *Use in Specific Populations (8.1)*].

5 WARNINGS AND PRECAUTIONS

5.1 Seizure

In the randomized clinical trial, 7 of 800 (0.9%) patients treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizures.

The safety of XTANDI in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold.

Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

6 ADVERSE REACTIONS

The following is discussed in more detail in other sections of the labeling:

- Seizure [see Warnings and Precautions (5.1)]

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel, patients received XTANDI 160 mg orally once daily (N = 800) or placebo (N = 399). The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. All adverse events and laboratory abnormalities were graded using NCI CTCAE version 4.

The most common adverse drug reactions ($\geq 5\%$) reported in patients receiving XTANDI in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in the randomized clinical trial that occurred at a $\geq 2\%$ absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions ^a	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness ^b	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders ^c	4.3	0.3	1.8	0.0

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection ^d	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection ^e	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3
a Includes asthenia and fatigue. b Includes dizziness and vertigo. c Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention. d Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis. e Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.				

Laboratory Abnormalities

In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on XTANDI (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on XTANDI and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on XTANDI (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on XTANDI and 2% of patients on placebo.

Infections

In the randomized clinical trial, 1.0% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related serious adverse events were reported in approximately 6% of the patients on both treatment arms.

Falls and Fall-related Injuries

In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with XTANDI compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.

Hallucinations

In the randomized clinical trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

7 DRUG INTERACTIONS

7.1 Drugs that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended [see *Clinical Pharmacology (12.3)*].

7.2 Drugs that Inhibit or Induce CYP3A4

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3 fold in healthy volunteers [see *Clinical Pharmacology (12.3)*].

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also reduce the plasma exposure of XTANDI and should be avoided if possible [see *Clinical Pharmacology (12.3)*].

7.3 Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Contraindications (4)*].

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. XTANDI is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with XTANDI.

8.3 Nursing Mothers

XTANDI is not indicated for use in women. It is not known if enzalutamide is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from XTANDI, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

8.5 Geriatric Use

Of 800 patients who received XTANDI in the randomized clinical trial, 71 percent were 65 and over, while 25 percent were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic castration-resistant prostate cancer and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment ($30 \text{ mL/min} \leq \text{creatinine clearance [CrCL]} \leq 89 \text{ mL/min}$) compared to patients and volunteers with baseline normal renal function ($\text{CrCL} \geq 90 \text{ mL/min}$). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment ($\text{CrCL} < 30 \text{ mL/min}$) and end-stage renal disease have not been assessed [see *Clinical Pharmacology (12.3)*].

8.7 Patients with Hepatic Impairment

A dedicated hepatic impairment trial compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Baseline severe hepatic impairment (Child-Pugh Class C) has not been assessed [see *Clinical Pharmacology (12.3)*].

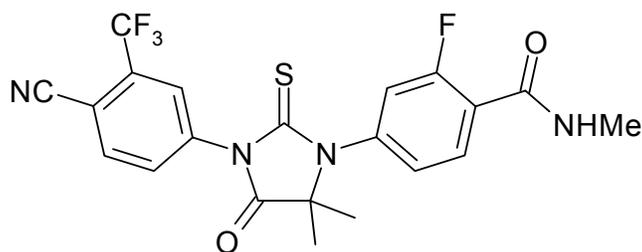
10 OVERDOSAGE

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at $\leq 240 \text{ mg}$ daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizures following an overdose.

11 DESCRIPTION

Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.

The molecular weight is 464.44 and molecular formula is $\text{C}_{21}\text{H}_{16}\text{F}_4\text{N}_4\text{O}_2\text{S}$. The structural formula is:



Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxyglycerides. The inactive ingredients are caprylocaproyl polyoxyglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

12.3 Pharmacokinetics

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic castration-resistant prostate cancer and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

Absorption

Following oral administration (XTANDI 160 mg daily) in patients with metastatic castration-resistant prostate cancer, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady state, the plasma mean C_{max} values for enzalutamide and N-desmethyl enzalutamide are 16.6 $\mu\text{g/mL}$ (23% CV) and 12.7 $\mu\text{g/mL}$ (30% CV), respectively, and the plasma mean predose trough values are 11.4 $\mu\text{g/mL}$ (26% CV) and 13.0 $\mu\text{g/mL}$ (30% CV), respectively.

With the daily dosing regimen, enzalutamide steady state is achieved by Day 28, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady state, enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg.

A single 160 mg oral dose of XTANDI was administered to healthy volunteers with a high-fat meal or in the fasted condition. A high-fat meal did not alter the AUC to enzalutamide or N-desmethyl enzalutamide. The results are summarized in Figure 1.

Distribution and Protein Binding

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Metabolism

Following single oral administration of ^{14}C -enzalutamide 160 mg, plasma samples were analyzed for enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N-desmethyl enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C -radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C -AUC_{0-inf}.

In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of enzalutamide. Based on *in vivo* and *in vitro* data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide).

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of ¹⁴C-enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of enzalutamide and N-desmethyl enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged enzalutamide and 1% as N-desmethyl enzalutamide).

The mean apparent clearance (CL/F) of enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h).

The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Pharmacokinetics in Special Populations

Renal Impairment:

A population pharmacokinetic analysis (based on pre-existing renal function) was carried out with data from 59 healthy male volunteers and 926 patients with metastatic castration-resistant prostate cancer enrolled in clinical trials, including 512 with normal renal function (CrCL \geq 90 mL/min), 332 with mild renal impairment (CrCL 60 to $<$ 90 mL/min), 88 with moderate renal impairment (CrCL 30 to $<$ 60 mL/min), and 1 with severe renal impairment (CrCL $<$ 30 mL/min). The apparent clearance of enzalutamide was similar in patients with pre-existing mild and moderate renal impairment (CrCL 30 to $<$ 90 mL/min) compared to patients and volunteers with normal renal function. The potential effect of severe renal impairment or end stage renal disease on enzalutamide pharmacokinetics cannot be determined as clinical and pharmacokinetic data are available from only one patient [see *Use in Specific Populations (8.6)*].

Hepatic Impairment:

The plasma pharmacokinetics of enzalutamide and N-desmethyl enzalutamide were examined in volunteers with normal hepatic function (N = 16) and with pre-existing mild (N = 8, Child-Pugh Class A) or moderate (N = 8, Child-Pugh B) hepatic impairment. XTANDI was administered as a single 160 mg dose. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. The results are summarized in Figure 1. Clinical and pharmacokinetic data are not available for patients with severe hepatic impairment (Child-Pugh Class C) [see *Use in Specific Populations (8.7)*].

Body Weight and Age:

Population pharmacokinetic analyses showed that weight (range: 46 to 163 kg) and age (range: 41 to 92 yr) do not have a clinically meaningful influence on the exposure to enzalutamide.

Gender:

The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated.

Race:

The majority of patients in the randomized clinical trial were Caucasian ($>$ 92%). There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Drug Interactions

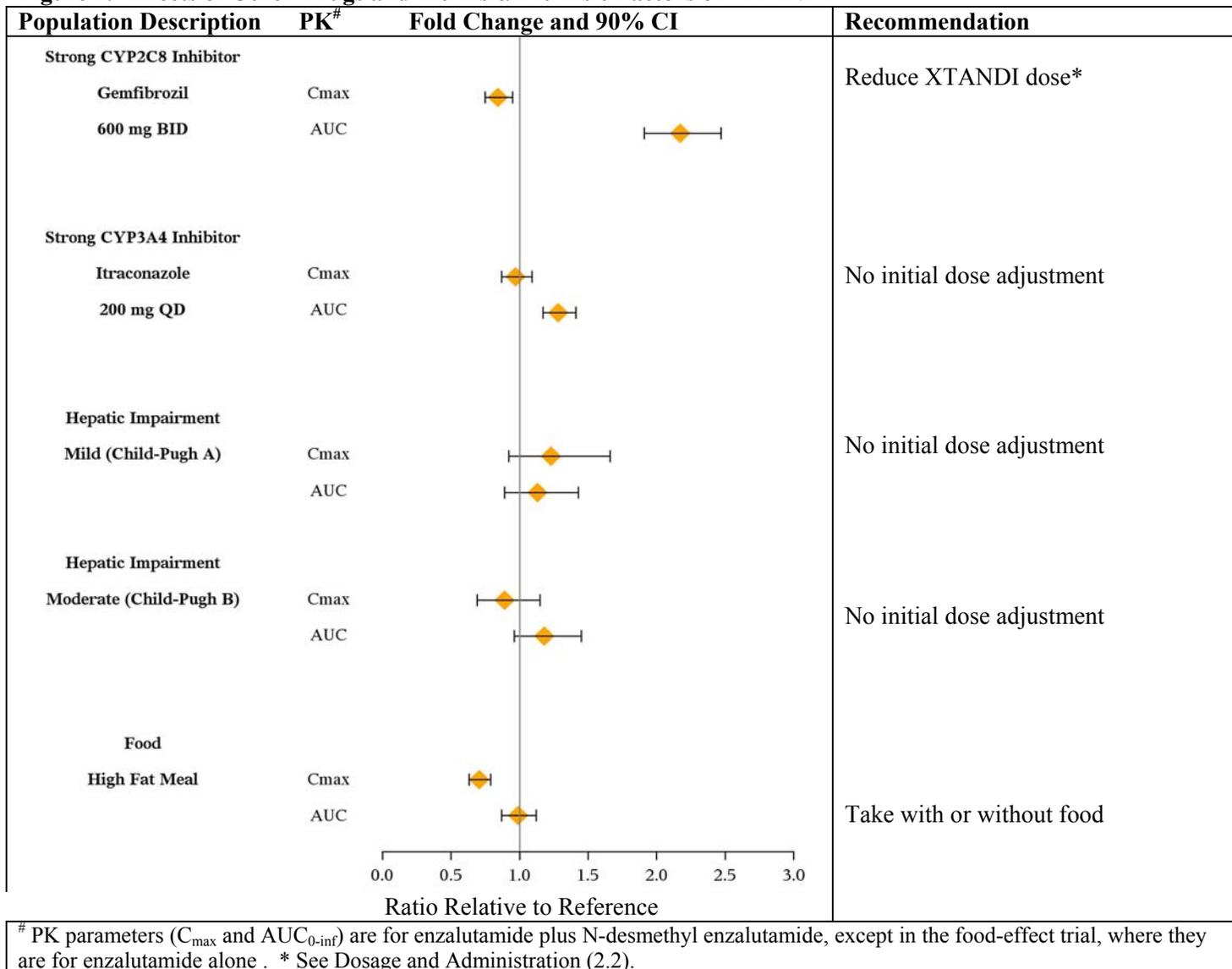
Effect of Other Drugs on XTANDI:

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of gemfibrozil (strong CYP2C8 inhibitor). Gemfibrozil increased the AUC_{0-inf} of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}. The results are summarized in Figure 1 [see *Dosage and Administration (2.2)* and *Drug Interactions (7.1)*].

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of XTANDI was administered alone or after multiple oral doses of itraconazole (strong CYP3A4 inhibitor). Itraconazole increased the AUC_{0-inf} of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max} . The results are summarized in Figure 1 [see Dosage and Administration (2.2) and Drug Interactions (7.2)].

The effects of CYP2C8 and CYP3A4 inducers on the exposure of XTANDI have not been evaluated *in vivo*.

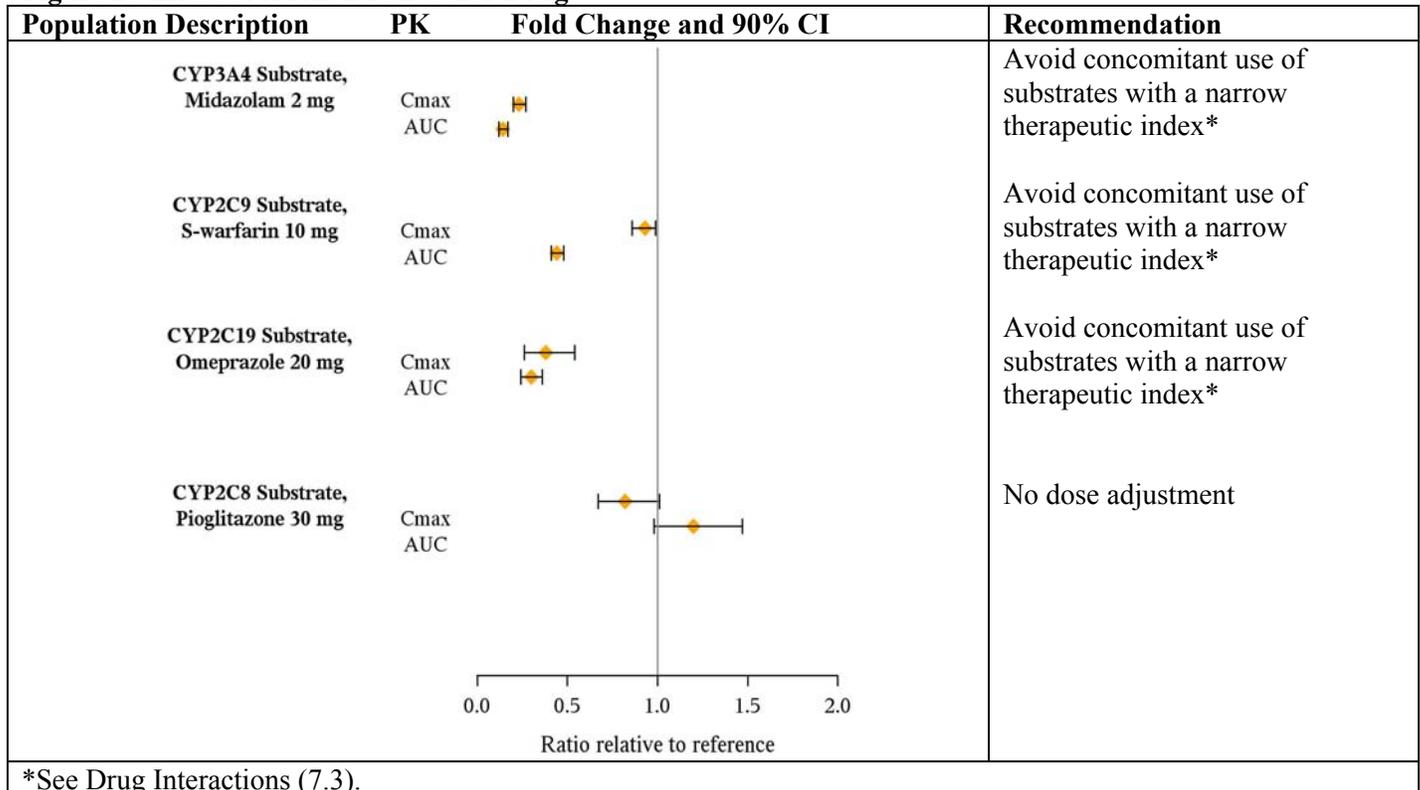
Figure 1. Effects of Other Drugs and Intrinsic/Extrinsic Factors on XTANDI



Effect of XTANDI on Other Drugs:

In an *in vivo* phenotypic cocktail drug-drug interaction trial in patients with castration-resistant prostate cancer, a single oral dose of the CYP probe substrate cocktail (for CYP2C8, CYP2C9, CYP2C19, and CYP3A4) was administered before and concomitantly with XTANDI (following at least 55 days of dosing at 160 mg daily). The results are summarized in Figure 2. Results showed that *in vivo*, at steady state, XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer [see Drug Interactions (7.3)]. XTANDI did not cause clinically meaningful changes in exposure to the CYP2C8 substrate.

Figure 2. Effect of XTANDI on Other Drugs



In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite caused direct inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; however, subsequent clinical data showed that XTANDI is an inducer of CYP2C9, CYP2C19, and CYP3A4 and had no clinically meaningful effect on CYP2C8 (see Figure 2). *In vitro*, enzalutamide caused time-dependent inhibition of CYP1A2.

In vitro studies showed that enzalutamide caused induction of CYP3A4 and that enzalutamide is not expected to induce CYP1A2 at therapeutically relevant concentrations.

In vitro, enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for human P-glycoprotein. *In vitro*, enzalutamide and N-desmethyl enzalutamide are inhibitors of human P-glycoprotein, while the major inactive carboxylic acid metabolite is not.

12.6 Cardiac Electrophysiology

The effect of enzalutamide 160 mg/day at steady state on the QTc interval was evaluated in 796 patients with castration-resistant prostate cancer. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with XTANDI and that in patients treated with placebo, based on the Fridericia correction method. However, small increases in the mean QTc interval (i.e., less than 10 ms) due to enzalutamide cannot be excluded due to limitations of the study design.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4- and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES

The efficacy and safety of XTANDI in patients with metastatic castration-resistant prostate cancer who had received prior docetaxel-based therapy were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. The primary endpoint was overall survival. A total of 1199 patients were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). All patients continued androgen deprivation therapy. Patients were allowed, but not required to continue or initiate glucocorticoids. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible [see *Warnings and Precautions* (5.1)].

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score of ≥ 4 . Ninety-one percent of patients had metastases in bone and 23% had visceral involvement in the lung and/or liver. Fifty-nine percent of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

The pre-specified interim analysis at the time of 520 events showed a statistically significant improvement in overall survival in patients on the XTANDI arm compared to patients on the placebo arm (Table 2 and Figure 3).

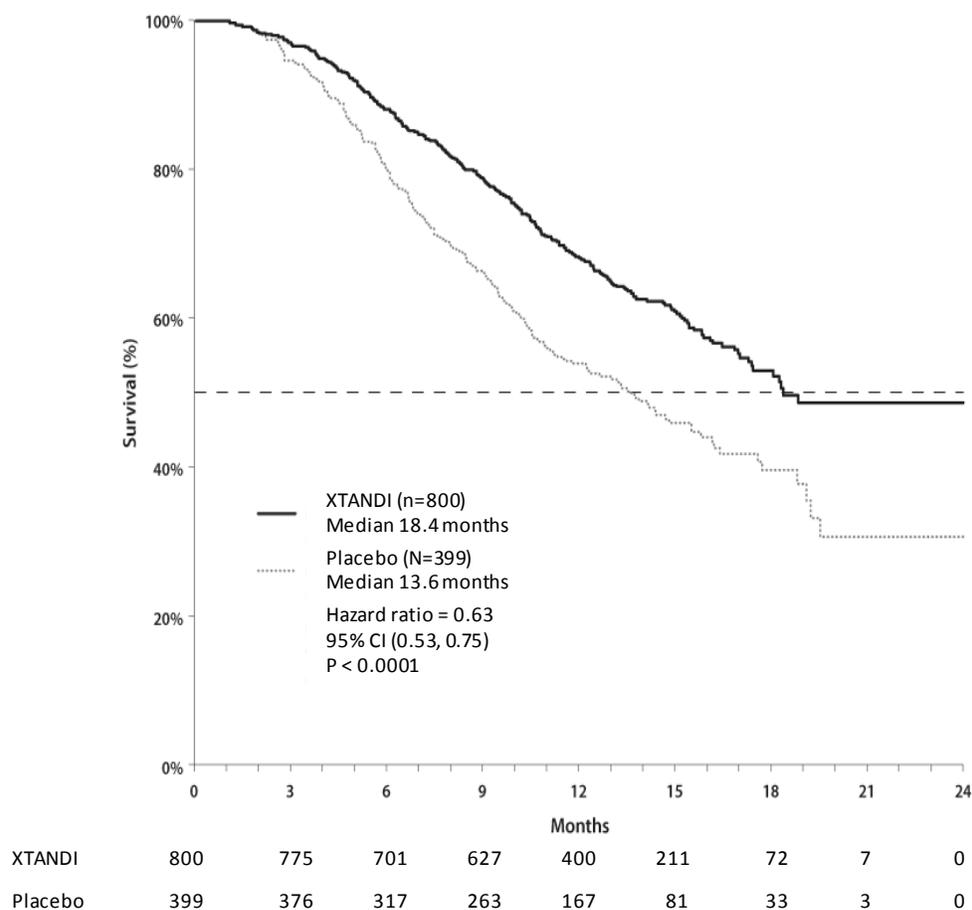
Table 2. Overall Survival of Patients Treated with Either XTANDI or Placebo (Intent-to-Treat Analysis)

	XTANDI N = 800	Placebo N = 399
Number of Deaths (%)	308 (38.5%)	212 (53.1%)
Median Survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value ^a	< 0.0001	
Hazard Ratio (95% CI) ^b	0.63 (0.53, 0.75)	

^a) P-value is derived from a log-rank test stratified by baseline ECOG performance status score (0-1 vs. 2) and mean baseline pain score (BPI-SF score < 4 vs. ≥ 4)

^b) Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors XTANDI
NR denotes “not reached”.

Figure 3. Kaplan-Meier Overall Survival Curves (Intent-to-Treat Analysis)



16 HOW SUPPLIED/STORAGE AND HANDLING

- XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with MDV. XTANDI capsules are available in the following package sizes:
 - Bottles of 120 capsules (NDC 0469-0125-99)

Recommended storage: Store XTANDI capsules at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (PATIENT INFORMATION).

- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- Inform patients receiving a GnRH analog that they need to maintain this treatment during the course of treatment with XTANDI.
- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.
- Inform patients that XTANDI may cause dizziness, mental impairment, paresthesia, hypoesthesia, and falls.

- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Apprise patients of the common side effects associated with XTANDI: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Inform patients that XTANDI may be harmful to a developing fetus. Patients should also be informed that they should use a condom if having sex with a pregnant woman. A condom and another effective method of birth control should be used if the patient is having sex with a woman of child-bearing potential. These measures are required during and for three months after treatment with XTANDI.

Manufactured by: Catalent Pharma Solutions, LLC, St. Petersburg, FL 33716

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Marketed by:

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Medivation, Inc., San Francisco, CA 94105

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Rx Only

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PATIENT INFORMATION
XTANDI® (ex TAN dee)
(enzalutamide)
capsules

Read this Patient Information before you start taking XTANDI and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is XTANDI?

XTANDI is a prescription medicine used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body and who have received treatment with docetaxel.

It is not known if XTANDI is safe and effective in children.

Who should not take XTANDI?

XTANDI is not for use in women.

Do not take XTANDI if you are pregnant or may become pregnant. XTANDI may harm your unborn baby.

What should I tell my healthcare provider before taking XTANDI?

Before you take XTANDI, tell your healthcare provider if you:

- have a history of seizures, brain injury, stroke, or brain tumors
- have any other medical conditions
- have a partner who is pregnant or plans to become pregnant. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after treatment with XTANDI. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for 3 months after treatment. Talk with your healthcare provider if you have questions about birth control. See “Who should not take XTANDI?”

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. XTANDI can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI capsules exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI one time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI capsules can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules.
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do

- not take more than your prescribed dose of XTANDI.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** Some people have had seizures during treatment with XTANDI. If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- diarrhea
- pain in your joints
- hot flashes
- swelling in your hands, arms, legs or feet
- muscle or bone pain
- headache
- cold like symptoms
- muscle weakness
- dizziness
- trouble falling or staying asleep (insomnia)
- trouble breathing (pneumonia)
- back pain with nerve problems in the lower body, including leg numbness or weakness
- pink or red urine (hematuria)
- sensation of tingling, burning, pricking, or numbness of skin (paresthesia)
- anxiety
- high blood pressure (hypertension)

Tell your healthcare provider if you have any falls or problems thinking clearly.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XTANDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- Store XTANDI between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about XTANDI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about XTANDI. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for healthcare professionals.

For more information go to www.AboutXtandi.com or call 1-800-727-7003.

What are the ingredients in XTANDI?

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides , butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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