PRODUCT MONOGRAPH

^{Pr}Xtandi®

Enzalutamide capsules
40 mg

Anti-androgen (L02BB04)

Astellas Pharma Canada, Inc.
Markham, ON
L3R 0B8

Date of Initial Approval: May 28, 2013
Date of Revision: April 15, 2015

Control Number: 177983

14D024-XTA-CA

Table of Contents

Xtandi

Enzalutamide capsules

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
oral	Soft gelatin capsules/ 40 mg	sorbitol *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Xtandi (enzalutamide capsules) is indicated in the setting of medical or surgical castration for the treatment of metastatic castration-resistant prostate cancer (CRPC) in patients who:

- are chemotherapy-naïve with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy.
- have received docetaxel therapy.

Geriatrics (≥ 65 years of age): No overall differences in safety and effectiveness were observed between geriatric patients and younger patients in clinical studies (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Pediatrics (< 18 years of age): The safety and efficacy of enzalutamide has not been established for patients less than 18 years of age.

CONTRAINDICATIONS

- Patients who are hypersensitive to enzalutamide or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION and PACKAGING** section of the product monograph.
- Women who are or may become pregnant, or who are lactating.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Xtandi (enzalutamide capsules) should only be prescribed by a qualified healthcare professional who is experienced with the treatment of prostate cancer and the use of antineoplastic endocrine therapies.

The following are clinically significant adverse events:

- Seizures (see **Neurologic** section, below),
- Posterior Reversible Encephalopathy Syndrome (see **Neurologic** section, below).

General

Xtandi contains sorbitol (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**). Patients with rare hereditary problems of fructose intolerance should not take Xtandi.

Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2C9, and CYP2C19 should be avoided, as co-administration of Xtandi may decrease their exposure. If co-administration cannot be avoided, dose adjustment may be required to maintain therapeutic plasma concentrations (see **DRUG INTERACTIONS**).

Enzalutamide is metabolized by CYP2C8. Co-administration of Xtandi with strong CYP2C8 inhibitors should be avoided. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of Xtandi should be reduced to 80 mg once daily (see **DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis

Carcinogenicity studies were not conducted with enzalutamide. Enzalutamide was devoid of genotoxic potential in the standard panel of *in vitro* and *in vivo* genotoxicity tests. An inactive metabolite (M1) showed genotoxic potential in an *in vitro* mammalian genotoxicity assay, but only at concentrations that caused extensive cytotoxicity (see **TOXICOLOGY, Carcinogenesis and Genotoxicity**).

Cardiovascular

Patients with clinically significant cardiovascular disease including recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, bradycardia or uncontrolled hypertension (resting systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg) were excluded from the two phase 3 clinical trials (AFFIRM, PREVAIL; see **CLINICAL TRIALS**). Therefore the safety of Xtandi in these patients has not been established.

QTc Prolongation: In the AFFIRM trial, Xtandi was associated with QTc prolongation of 3.0 to 6.5 msec (placebo-adjusted mean change from baseline) during weeks 5-25 of treatment when administered to metastatic CRPC patients with pre-dose ECG recordings (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**). In the PREVAIL trial the largest placebo-adjusted mean increase from baseline was 3.4 msec observed at week 37. Consider these observations in clinical decisions to prescribe to patients with a known history of QT prolongation, risk factors for torsade de pointes (e.g., hypokalemia) or patients who are taking medications known to prolong the QT interval (see **DRUG-DRUG INTERACTIONS, Drugs that Cause QT/QTc Prolongation**).

Hypertension: Xtandi was associated with increases in systolic and diastolic blood pressure and an increased risk of hypertension or worsening of pre-existing hypertension when administered to patients in the two phase 3 clinical trials (see **ACTION AND CLINICAL PHARMACOLOGY, Blood Pressure**). The overall incidence of any hypertension- related events was higher in the Xtandi group compared to the placebo group (11.0% vs.4.3%). Hypertension rarely led to discontinuation or dose modification and in general was not associated with major cardiovascular adverse sequelae. However, approximately 75% of patients with this adverse event required initiation of new antihypertensive treatment or increase in dose of prior therapy.

Blood pressure should be measured at baseline and periodically during treatment. Treatment-emergent hypertension should be treated appropriately.

Musculoskeletal

Xtandi is indicated for use in patients who are maintaining castration status through GnRH analogue therapy or surgical castration. In the two phase 3 clinical trials (see **CLINICAL TRIALS**), no assessments of bone mineral density were conducted. A higher incidence of non-pathological bone fractures was reported in the Xtandi group compared to the placebo group (see **ADVERSE REACTIONS**).

Falls and Fall-related Injuries: In the two phase 3 clinical trials, adverse events of falls were reported in 8.8% Xtandi-treated patients and 4.0% placebo-treated patients. A fall of Grade 3 or greater was reported in 1% of patients in the Xtandi-treated group and in 0.5% of patients in the placebo group. Non-pathological fractures associated with falls were reported in 2.9% of patients treated with Xtandi and in 0.9% of patients in the placebo arms. Additionally, fall-related injuries were reported at a greater frequency in the Xtandi arm than the placebo arm (2.4% vs. 1.0%) and included contusion, excoriation, head injury, joint injury, laceration, periorbital haematoma, and skeletal injury. Concomitant neurological symptoms such as dizziness or syncope were rarely reported as an adverse event with the falls.

Neurologic

Xtandi is associated with neuropsychiatric adverse events including seizure, memory impairment, and hallucination.

Seizures: Patients with a history of seizure or conditions that may pre-dispose them to seizure including brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, and brain arteriovenous malformation, were generally excluded from clinical trials. Limited safety data are available in these patients. The AFFIRM trial excluded the use of concomitant medications that may lower the seizure threshold, whereas the PREVAIL trial permitted the use of these medications.

Data from *in vitro* studies show that enzalutamide and its active metabolite (M2) cross the blood brain barrier, bind to, and inhibit the activity of the GABA-gated chloride channel (see **DETAILED PHARMACOLOGY, Animal Pharmacology**).

The dose of Xtandi may be a predictor of seizure in humans, with a greater risk of seizure at daily doses higher than 160 mg. In a dose escalation study involving 140 patients, no seizures were reported at or below daily doses of 240 mg, whereas three seizures were reported, one each at 360, 480, and 600 mg per day.

In the AFFIRM trial (see **CLINICAL TRIALS**), which enrolled patients who previously received docetaxel, seven patients (0.9%) out of 800 patients treated with a daily dose of Xtandi 160 mg experienced a seizure, whereas no seizures occurred in patients treated with placebo. In the PREVAIL trial, 1 of 871 (0.1%) chemotherapy-naïve patients treated with Xtandi 160 mg once daily, and 1 of 844 (0.1%) patients treated with placebo experienced a seizure. In the integrated safety population of patients treated with 160 mg daily, the incidence of seizure is 0.6% (14/2415). Patients experiencing a seizure were discontinued from therapy, and all seizures resolved. There is no clinical trial experience re-administering Xtandi to patients who experienced a seizure.

Mental Impairment Disorders: In the two phase 3 clinical trials, the combined adverse events of amnesia, cognitive disorder, disturbance in attention, memory impairment, and the related term dementia were reported more frequently in Xtandi-treated patients than placebo-treated patients (5.1% vs. 1.6%).

Patients should be advised of the risk of engaging in any activity where mental impairment or sudden loss of consciousness could cause serious harm to themselves or others.

Posterior Reversible Encephalopathy Syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi. PRES is a rare, reversible neurological disorder which can present with rapidly evolving symptoms including seizure, headache, consciousness impairment (including confusion, somnolence, lethargy, encephalopathy or coma), blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of Xtandi in patients who develop PRES is recommended.

<u>Sexual Function/Reproduction</u>

It is not known whether enzalutamide or its metabolites are present in semen. A condom should be used if the patient engages in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of child-bearing potential, a condom is recommended along with another effective contraceptive method. These measures are recommended during and for three months after treatment with Xtandi.

Animal studies showed that enzalutamide affected the reproductive organs in rats and dogs (see **TOXICOLOGY**). Considering the pharmacological consequences of androgen receptor inhibition, an effect on male fertility cannot be excluded in humans.

<u>Special Populations</u>

Pregnant Women: Animal studies demonstrated that enzalutamide can cause fetal harm when administered during pregnancy (see **TOXICOLOGY**). Pregnant women who have taken Xtandi should be informed about the potential hazards to embryo-fetal developmental and the risk of pregnancy loss. There are no human data on the use of enzalutamide in pregnancy. Considering the pharmacological consequences of androgen receptor inhibition, maternal use of enzalutamide is expected to produce changes in hormone levels that could affect development of the fetus.

Xtandi is not indicated for use in women. Xtandi is contraindicated in women who are or may become pregnant (see **CONTRAINDICATIONS; TOXICOLOGY**). If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Women: It is unknown whether enzalutamide or its metabolites are excreted in human milk. Xtandi is not indicated for use in women, and is contraindicated in women who are lactating.

Geriatrics (≥ 65 years of age): Of the 1671 patients in the two phase 3 trials (AFFIRM and PREVAIL) who received Xtandi, 75% of patients were 65 years and over and 31% were 75 years and over. No overall differences in safety and effectiveness were observed between geriatric patients and younger patients in clinical studies. However, an increased frequency of dose interruption, dose reduction and treatment discontinuation was observed with higher age (≥ 65 years) and greater sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age): The safety and efficacy of Xtandi has not been established for patients less than 18 years of age.

Hepatic impairment: Mild or moderate hepatic impairment (Child-Pugh Class A or B) had no significant effects on the pharmacokinetics of enzalutamide. The effect of severe hepatic impairment (Child-Pugh Class C) on enzalutamide pharmacokinetics has not been studied. Xtandi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C; see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Renal impairment: Mild or moderate renal impairment (calculated creatinine clearance (CrCL) values ≥ 30 ml/min) had no significant effects on the pharmacokinetics of enzalutamide (based on population pharmacokinetic analysis). The effect of severe renal impairment on enzalutamide pharmacokinetics has not been studied. Caution is advised in patients with severe renal impairment or end-stage renal disease (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Monitoring and Laboratory Tests
Monitoring for laboratory or clinical parameters should be conducted as per routine practice. Blood pressure should be measured at baseline and periodically during treatment.

Monitoring of ECG and serum electrolyte levels at baseline and during treatment should be considered for patients at risk for electrolyte abnormality and QTc prolongation.

Enzalutamide is a moderate inducer of CYP2C9. If Xtandi is co-administered with an anticoagulant metabolised by CYP2C9 (e.g., warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse reactions were defined as treatment emergent adverse events if the incidences in the Xtandi group were greater than those in the placebo group and if the treatment differences were maintained when the event rates were adjusted per 100 patient-years of exposure.

In the two phase 3 clinical trials, the most common adverse reactions (≥ 10%) seen with Xtandi were fatigue/asthenia (48.7%), hot flush (19.1%), headache (11.5%), and hypertension (10.5%). The rate of serious adverse events was 36.0% for Xtandi and 30.9% for placebo. Patients treated with Xtandi also had a higher incidence of Grade 3 or higher adverse events (of any causality) than patients treated with placebo (46.7% vs 42.6%). Adverse events as the primary reason that led to treatment discontinuation were reported for 7.1% of Xtandi-treated patients and 7.4% of placebo-treated patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

PREVAIL Study: Chemotherapy-naive Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy

In the PREVAIL trial of patients with metastatic prostate cancer that progressed on a GnRH analogue or after bilateral orchiectomy and had not received prior cytotoxic chemotherapy, Xtandi was administered at a dose of 160 mg daily (N = 871) versus placebo (N = 844). The median duration of treatment was 17.5 months with Xtandi and 4.6 months with placebo. All patients continued on a GnRH analogue or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate corticosteroids (maximum daily dose allowed was 10 mg prednisone or equivalent).

Table 1 shows adverse reactions occurring at an incidence of ≥ 2% in patients randomized to Xtandi in the PREVAIL study.

Table 1: Adverse Reactions* Occurring at an Incidence of ≥ 2% in Patients Randomized to Xtandi in the PREVAIL Study

System Organ Class/ MedDRA Preferred Term, MedDRA v16.0	Xtandi N = 871		Placebo N = 844	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
General disorders and administration site conditions				
Asthenic Conditions[a]	409 (47.0%)	30 (3.4%)	280 (33.2%)	24 (2.8%)
Influenza like illness	21 (2.4%)	0 (0.0%)	12 (1.4%)	0 (0.0%)
Vascular disorders				
Hot Flush	157 (18.0%)	1 (0.1%)	66 (7.8%)	0
Hypertension	124 (14.2%)	63 (7.2%)	35 (4.1%)	19 (2.3%)
Nervous system disorders				
Mental Impairment Disorders[b]	52 (6.0%)	0	13 (1.5%)	2 (0.2%)
Restless Legs Syndrome	18 (2.1%)	1 (0.1%)	3 (0.4%)	0
Somnolence	19 (2.2%)	0 (0.0%)	6 (0.7%)	0 (0.0%)
Injury, poisoning and procedural complications				
Contusion	26 (3.0%)	0 (0.0%)	10 (1.2%)	0 (0.0%)
Fall	111 (12.7%)	14 (1.6%)	45 (5.3%)	6 (0.7%)
Non-Pathological Fracture	68 (7.8%)	18 (2.1%)	25 (3.0%)	9 (1.1%)
Reproductive system and breast disorder				
Gynecomastia	30 (3.4%)	0	12 (1.4%)	0
Ear and labyrinth disorders				
Vertigo	24 (2.8%)	1 (0.1%)	7 (0.8%)	0 (0.0%)
Infections and infestations				
Herpes Zoster	19 (2.2%)	0 (0.0%)	3 (0.4%)	1 (0.1%)
Respiratory, thoracic and mediastinal disorders				
Epistaxis	24 (2.8%)	0 (0.0%)	11 (1.3%)	1 (0.1%)

* Adverse Events (AEs) were considered Adverse Reactions if the incidences of AEs in the Xtandi group were greater than those in the placebo group, and if the treatment differences were maintained when the event rates were adjusted per 100 patient-years of exposure.

a Includes asthenia and fatigue.

b Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.

AFFIRM Study: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy

In the AFFIRM trial of patients with metastatic castration-resistant prostate cancer who maintained treatment with a GnRH analogue or who had had previously undergone surgical castration and had received docetaxel therapy, Xtandi was administered at a dose of 160 mg daily (N = 800) versus placebo (N = 399). The median duration of treatment with Xtandi was 8.3 months while with placebo it was 3.0 months. Patients were allowed, but not required, to continue or initiate corticosteroids (e.g. prednisone).

Table 2 shows adverse reactions occurring at an incidence of ≥ 2% in patients randomized to Xtandi in the AFFIRM study.

Table 2: Adverse Reactions* Occurring at an Incidence of ≥ 2% in Patients Randomized to Xtandi in the AFFIRM Study

	Xtandi N = 800		Placebo N = 399	
System Organ Class/ MedDRA Preferred Term, MedDRA v11.0	**All Grades (%)**	**Grade 3 § (%)**	**All Grades (%)**	**Grade 3 § (%)**
General disorders and administration site conditions				
Fatigue	269 (33.6%)	50 (6.3%)	116 (29.1%)	29 (7.3%)
Injury, poisoning and procedural complications				
Fall	32 (4.0%)	2 (0.3%)	5 (1.3%)	0
Nervous system disorders				
Headache	93 (11.6%)	6 (0.8%)	22 (5.5%)	0
Psychiatric disorders				
Anxiety	51 (6.4%)	2 (0.3%)	16 (4.0%)	0
Skin and subcutaneous tissue disorders				
Dry skin	28 (3.5%)	0	5 (1.3%)	0
Pruritus	29 (3.6%)	0	5 (1.3%)	0
Vascular disorders				
Hot flush	162 (20.3%)	0	41 (10.3%)	0
Hypertension	49 (6.1%)	16 (2.0%)	11 (2.8%)	5 (1.3%)

§ Grade 4 and 5 events were not observed

* Adverse Events (AEs) were considered Adverse Reactions if the incidences of AEs in the Xtandi group were greater than those in the placebo group, and if the treatment differences were maintained when the event rates were adjusted for patient-years of exposure.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)

In the two phase 3 clinical trials, the following less common (< 2%) and clinically significant adverse reactions were reported with higher frequencies in patients treated with Xtandi.

Psychiatric Disorders: Hallucinations (0.8%, including hallucination, hallucination tactile and hallucination visual).
Infections and Infestations: Infections and sepsis with fatal outcome (0.5%)
Nervous System Disorders: Seizure (0.5%)
Gastrointestinal Disorders: Gastrointestinal bleeding (0.8%)

Abnormal Hematologic and Clinical Chemistry Findings

Tables 3 and 4 show laboratory values of interest from the two phase 3 placebo controlled trials.

Table 3: Selected Laboratory Abnormalities in Patients Receiving Xtandi in the PREVAIL Phase 3 Study				
Parameter	**Xtandi N = 871**		**Placebo N = 844**	
	All Grades N (%)	**Grade 3-4 N (%)**	**All Grades N (%)**	**Grade 3-4 N (%)**
Hematologic Parameters				
Neutrophils (low)	122 (14.0%)	9 (1.0%)	47 (5.6%)	6 (0.7%)
Chemistry Parameters				
AST	129 (14.8%)	3 (0.3%)	177 (21.0%)	0 (0.0%)
ALT	93 (10.7%)	2 (0.2%)	132 (15.6%)	0 (0.0%)
Bilirubin	28 (3.2%)	0 (0.0%)	13 (1.5%)	0 (0.0%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Table 4: Selected Laboratory Abnormalities in Patients Receiving Xtandi in the AFFIRM Phase 3 Study				
Parameter	**Xtandi N = 800**		**Placebo N = 399**	
	All Grades N (%)	**Grade 3-4 N (%)**	**All Grades N (%)**	**Grade 3-4 N (%)**
Hematologic Parameters				
Neutrophils (low)	121 (15.1%)	9 (1.1%)	25 (6.3%)	0 (0.0%)
Chemistry Parameters				
AST	181 (22.6%)	3 (0.4%)	149 (37.3%)	4 (1.0%)
ALT	81 (10.2%)	2 (0.3%)	71 (17.8%)	2 (0.5%)
Bilirubin	23 (2.9%)	2 (0.3%)	7 (1.8%)	0 (0.0%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Post-Market Adverse Drug Reactions

The following adverse reaction has been identified during the post-approval use of Xtandi. Because post market events are reported voluntarily from a population of uncertain size, is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorders: posterior reversible encephalopathy syndrome (PRES)

DRUG INTERACTIONS

Overview

Enzalutamide is a substrate of CYP2C8 and to a lesser extent CYP3A4, both of which play a role in the formation of the active metabolite, N-desmethyl enzalutamide (M2). Therefore, the metabolism of enzalutamide may be influenced by medicinal products that affect CYP2C8 and CYP3A4 (see **ACTION AND CLINICAL PHARMACOLOGY**).

Drug-Drug Interactions

Potential for other medicinal products to affect enzalutamide exposures

CYP2C8 inhibitors: Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male volunteers, the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus M2 increased 2.17-fold. Therefore, co-administration of Xtandi with CYP2C8 inhibitors (e.g. gemfibrozil) may increase the plasma exposure of enzalutamide and should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, a dose adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

CYP2C8 inducers: The effects of CYP2C8 inducers (e.g. rifampin) on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Avoid the use of concomitant strong CYP2C8 inducers due to the risk of reduced effectiveness of the drug.

CYP3A4 inhibitors: Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male volunteers, the AUC of enzalutamide plus M2 increased by 1.28-fold. No dose adjustment is necessary when Xtandi is co-administered with inhibitors of CYP3A4.

CYP3A4 inducers: The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*.

Potential for Xtandi to affect exposures to other medicinal products

Enzyme induction: Enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of Xtandi (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). An *in vitro* study suggests that CYP2B6, and uridine 5'-diphospho-glucuronosyltransferases (UGT1A1 and UGT1A4) are also induced by enzalutamide. Medicinal products with a narrow therapeutic range that are substrates of CYP3A4, CYP2B6, CYP2C9, CYP2C19, UGT1A1 and UGT1A4 should be avoided, as enzalutamide may decrease their exposure. Such substrates include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Anticoagulants (e.g. acenocoumarol, dabigatran etexilate, warfarin)
- Anti-epileptics (e.g. phenobarbitone, phenytoin)

- Antigout agents (e.g. colchicine)
- Antipsychotics (e.g. haloperidol)
- Benzodiazepines (e.g. diazepam, midazolam)
- Beta blockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Corticosteroids (e.g. dexamethasone, prednisone)
- Certain anti-cancer agents (e.g. cabazitaxel, irinotecan, sunitinib)
- HIV antivirals (e.g. indinavir, ritonavir)
- Immune modulators (e.g. cyclosporine, tacrolimus)
- Macrolide antibiotics (e.g. clarithromycin)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

If co-administration cannot be avoided, dose adjustment may be required to maintain therapeutic plasma concentrations. If Xtandi is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

In vitro studies showed that enzalutamide causes time-dependent inhibition of CYP1A2. While the effect of enzalutamide on CYP1A2 pharmacokinetics has not been evaluated *in vivo*, enzalutamide is unlikely to induce CYP1A2 at clinically relevant concentrations.

In consideration of the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping Xtandi.

CYP2C8 substrates: Xtandi (160 mg once daily) did not cause a clinically relevant change in the AUC of pioglitazone (CYP2C8 substrate) and no dose adjustment is indicated when a CYP2C8 substrate is co-administered with Xtandi.

P-gp substrates: In vitro, enzalutamide and N-desmethyl enzalutamide (M2) are inducers and inhibitors of the efflux transporter P-gp, while the inactive carboxylic acid metabolite (M1) does not affect this transporter. The effect of enzalutamide on P-gp substrates has not been evaluated *in vivo* and under conditions of clinical use its effect is unknown. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1 and OATP1B3: In vitro, enzalutamide and its major metabolites are inhibitors of breast cancer resistant protein (BCRP) and multidrug resistance-associated protein 2 (MRP2). The effects of enzalutamide on BCRP and MRP2 substrates have not been evaluated *in vivo*. Xtandi may increase the plasma concentrations of co-administered medicinal products that are BCRP or MRP2 substrates. Thus, oral medicinal products with a narrow therapeutic range that are BCRP or MRP2 substrates (e.g. methotrexate) should be used with caution when administered concomitantly with Xtandi and may require dose adjustments to maintain optimal plasma concentrations.

In vitro data indicate that enzalutamide and its major metabolites do not inhibit organic anion transporter 1 (OAT1) or OCT2 at clinically relevant concentrations. Based on *in vitro* data, the possibility of *in vivo* inhibition of OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3 and OCT1 cannot be excluded. Therefore, enzalutamide may alter the pharmacokinetics of drugs that are substrates of OATP1B1/3 (e.g. statins), OAT3 (e.g. furosemide, methotrexate), and OCT1 (e.g. metformin). The effects of enzalutamide on these transporters have not been evaluated *in vivo*.

Drugs That Cause QT/QTc Prolongation

Caution should be observed if Xtandi is administered with drugs that cause QTc prolongation, including, but not limited to, the following: Class IA, IC, and III antiarrhythmics; antipsychotics (e.g. chlorpromazine, pimozide, haloperidol, droperidol, ziprasidone); antidepressants (e.g. fluoxetine, citalopram, venlafaxine, tricyclic/tetracyclic antidepressants (e.g. amitriptyline, imipramine)); opioids (e.g. methadone); macrolide antibiotics and analogues (e.g. erythromycin, clarithromycin, telithromycin, tacrolimus); quinolone antibiotics (e.g. moxifloxacin, levofloxacin); antimalarials (e.g. quinine, chloroquine); azole antifungals; domperidone; 5-HT3 receptor antagonists (e.g. dolasetron, ondansetron); tyrosine kinase inhibitors (e.g. vandetanib, sunitinib, nilotinib, lapatinib); histone deacetylase inhibitors (e.g. vorinostat); beta-2 adrenoceptor agonists. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QTc prolongation and/or torsade de pointes (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

Drug-Food Interactions

Food has no clinically significant effect on the extent of exposure (AUC) to enzalutamide. However, the peak plasma enzalutamide concentration (C_{max}) was 30% higher when administered to subjects in the fasted state. In clinical trials, Xtandi was administered without regard to food.

Drug-Herb Interactions

Products that contain St. John's Wort might induce CYP3A, leading to decreased plasma concentrations of enzalutamide.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations:

Xtandi is for use in patients who are maintaining treatment with a GnRH analogue or who have had previously undergone surgical castration. Patients started on Xtandi who are receiving a GnRH analogue should continue to receive a GnRH analogue.

Recommended Dose and Dosage Adjustment

The recommended dose of Xtandi is 160 mg (four 40 mg capsules) as a single oral daily dose. Xtandi can be taken with or without food.

Co-administration of Xtandi with CYP2C8 inhibitors may increase the plasma exposure of enzalutamide and should be avoided if possible. In patients who must be co-administered a strong CYP2C8 inhibitor, reduce the Xtandi dose to 80 mg once daily.

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

Elderly patients: No dose adjustment is necessary for elderly patients (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Patients with hepatic impairment: No dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child-Pugh Class A or B; see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). The effect of severe hepatic impairment (Child-Pugh Class C) on enzalutamide pharmacokinetics has not been studied, and therefore is not recommended in patients with severe hepatic impairment (Child-Pugh Class C; see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Patients with renal impairment: No dose adjustment is necessary for patients with mild or moderate renal impairment (calculated creatinine clearance (CrCL) values ≥ 30 ml/min; see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**). The effect of severe renal impairment on enzalutamide pharmacokinetics has not been studied. Caution is advised in patients with severe renal impairment or end-stage renal disease (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Missed Dose

If a patient misses taking Xtandi at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose.

Administration

Xtandi capsules should be swallowed whole with water, and can be taken with or without food.

OVERDOSAGE

There is no antidote for Xtandi. 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. It is unlikely that enzalutamide will be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis, owing to its large volume of distribution and low unbound free fraction.

Patients may be at increased risk of seizures following an overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors and as a result, inhibits translocation of androgen receptors and association of androgen receptors with DNA. The active metabolite (M2) exhibited similar *in vitro* activity to enzalutamide. Enzalutamide treatment decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model. In preclinical studies, enzalutamide lacked androgen receptor agonist activity in cell growth assays using LNCaP cells expressing clinically relevant mutant ARs (T877A and/or W741C).

Pharmacodynamic Effects

In the phase 3 clinical study of patients who failed prior chemotherapy with docetaxel (AFFIRM), 54% of patients treated with Xtandi, versus 1.5% of patients who received placebo, had at least a 50% decline from baseline in PSA levels.

Cardiac Electrophysiology

A comprehensive ECG assessment was embedded in the placebo-controlled phase 3 AFFIRM study. ECGs were collected at baseline and prior to dosing on weeks 2, 5, 9, 13, 17, 21, and 25 and every 12 weeks thereafter. Enzalutamide 160 mg QD was associated with statistically significant, QTc prolongation. During steady-state treatment, the placebo-adjusted mean increase from baseline in the QTcF interval ranged from 3.0 to 6.5 milliseconds between weeks 5 and 25. The magnitude of QTc prolongation at maximal concentrations of enzalutamide was predicted to be 6.0 ms, with a one-sided upper 95% confidence interval bound of 7.0 ms, using pharmacokinetic/pharmacodynamic modeling.

Blood Pressure

Serial blood pressure assessments were performed in the placebo-controlled phase 3 AFFIRM study. Statistically significant mean differences from placebo in systolic blood pressure were observed at most time points during steady-state treatment (weeks 5, 9, 17, 21, and 25), with point estimates in the range of 2-4 mm Hg and one-sided 95% CI upper bounds up to 7.4 mm Hg. Statistically significant mean differences from placebo in diastolic blood pressure were observed at weeks 5, 9, 13, 17, and 21, with point estimates ranging from approximately 1-4 mm Hg and one-sided 95% CI upper bounds as high as 5.2 mm Hg.

Pharmacokinetics

Table 5: Arithmetic Mean ± SD (CV%) Pharmacokinetic Parameters of Xtandi in Adult Subjects							
Study Number	**Dosage Regimen**	**Subject Population**	**C_{max} (μg/mL)**	**AUC (μg•h/mL) ‡**	**$t_{1/2}$ (h)**	**CL/F (L/h)**	**V/F (L)**
MDV3100-05	160 mg§ single dose (fasted)	Healthy volunteers (n=27)	5.25 ± 1.06 (20%)	292 ± 88 (30%)	94.3 ± 30.0 (32%)	0.600 ± 0.193 (32%)	76.4 ± 21.9 (29%)
	160 mg§ single dose (fed)	Healthy volunteers (n=30)	3.74 ± 1.15 (31%)	285 ± 73 (26%)	87.4 ± 24.7 (28%)	0.599 ± 0.160 (27%)	71.9 ± 16.6 (23%)
S-3100-1-01	150 mg† single dose	CRPC patients (n=3)	3.36 ± 0.78 (23%)	334 ± 50 (15%)	143.7 ± 34.8 (24%)	0.456 ± 0.064 (14%)	92.4 ± 11.8 (13%)
	150 mg† once daily (day 84)	CRPC patients (n=23)	14.46 ± 3.29 (23%)	300 ± 68 (23%)	Not applicable	0.530 ± 0.149 (28%)	Not applicable
9785-CL-0009	160 mg§ (fasted) [matched subjects]	CRPC patients with MHI (n=8)	3.68 ± 2.09 (57%)	303 ± 126 (41%)	196 ± 185 (94%)	0.604 ± 0.229 (38%)	142 ± 105 (74%)
		CRPC patients with NHF (n=8)	3.83 ± 0.822 (22%)	225 ± 50.7 (23%)	108 ± 53.3 (49%)	0.753 ± 0.213 (28%)	109 ± 40.9 (38%)

‡ AUC_{inf} and AUC_{τ} (steady state) were calculated in single dose and multiple dose studies, respectively;
§ Administered as 4 x 40 mg soft gelatin capsules;
† Administered as 5 x 30 mg hard gelatin capsules.
CRPC: Castration resistant prostate cancer; MHI: moderate hepatic impairment; NHF: normal hepatic function

The pharmacokinetics of enzalutamide have been evaluated in metastatic castration-resistant prostate cancer patients and in healthy male volunteers.

Absorption: Following oral administration of Xtandi 160 mg in patients with metastatic castration-resistant prostate cancer, the median time to reach maximum plasma enzalutamide (t_{max}) was 1.02 h (range 0.52 h to 3.02 h). With the daily dosing regimen, steady state is achieved after approximately 28 days, and enzalutamide accumulates approximately 8.3-fold relative to a single dose. At steady state, the active metabolite M2 circulates at approximately the same plasma concentration as enzalutamide; the mean C_{max} values for enzalutamide and M2 were 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively. The steady-state C_{min} values of enzalutamide (11.4 µg/mL) and M2 (13.0 µg/mL) in individual patients remained constant during more than one year of chronic therapy, demonstrating time-linear pharmacokinetics once steady-state is achieved. The plasma concentration of the inactive metabolite M1 was approximately 75% that of enzalutamide at steady state. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). No major deviations from dose proportionality are observed over the dose range 30 to 360 mg.

Based on a mass balance study in healthy volunteers, oral absorption of enzalutamide is estimated to be at least 84.2%. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP.

Food has no clinically significant effect on the extent of absorption (Table 5). However, the peak plasma enzalutamide concentration (C_{max}) was 30% higher when administered to subjects in the fasted state. In clinical trials, Xtandi was administered without regard to food.

Distribution: The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution.

Studies in rodents indicate that enzalutamide and M2 can cross the blood brain barrier.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite (M2) is 95% bound to plasma proteins. There is no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen, and salicylic acid) *in vitro*.

Metabolism: Enzalutamide is extensively metabolized. There are two major metabolites in human plasma: N-desmethyl enzalutamide (M2, active) and a carboxylic acid derivative (M1, inactive).

In vitro studies show that enzalutamide is metabolized by CYP2C8 and to a lesser extent by CYP3A4/5, both of which play a role in the formation of the active metabolite (M2). Enzalutamide is not metabolized *in vitro* by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C18, CYP2C19, CYP2D6, or CYP2E1.

Following a single oral dose of 160 mg ^{14}C-enzalutamide to healthy volunteers, a total of 7 Phase I metabolites were identified in plasma, urine, and feces. These metabolites were formed via demethylation, oxidation, and hydrolysis reactions. No Phase II conjugation products were observed. Enzalutamide, N-desmethyl enzalutamide (M2, active) and a carboxylic acid derivative (M1, inactive) accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-$AUC_{0\text{-}inf}$.

Excretion: Clearance of enzalutamide is primarily via renal excretion of hepatic metabolites. Following a single oral dose of 160 mg ^{14}C-enzalutamide to healthy volunteers, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as M1, with trace amounts of enzalutamide and M2), and 13.6% is recovered in feces (0.39% of dose as unchanged enzalutamide).

The mean apparent clearance (CL/F) of enzalutamide is between 0.520 and 0.564 L/h in patients and 0.596 to 0.753 L/h in healthy volunteers.

The mean $t_{1/2}$ of enzalutamide in patients is 5.8 days, while the mean $t_{1/2}$ of enzalutamide is shorter in healthy volunteers, averaging 2.9 to 4.8 days. The $t_{1/2}$ of M1 and M2 in patients has not been evaluated. The mean $t_{1/2}$ for M1 in healthy volunteers ranges from 7.8 to 9.3 days, and the mean $t_{1/2}$ for M2 in healthy volunteers ranges from 7.5 to 8.8 days, respectively. The $t_{1/2}$ does not appear to be affected by dose.

Special Populations and Conditions

Pediatrics (≤ 18 years of age): The pharmacokinetics of enzalutamide has not been evaluated in pediatric patients.

Geriatrics (≥ 65 years of age): Of the 1671 patients in the two phase 3 clinical trials who received Xtandi, 1261 patients (75%) were 65 years and over and 516 patients (31%) were 75 years and over. Based on the population pharmacokinetic analysis for age, no dose adjustment is necessary in the elderly.

Gender: The pharmacokinetics of enzalutamide has not been evaluated in women.

Race: The majority of patients in the randomized clinical trial were Caucasian (~85%). Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Hepatic Insufficiency: The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (n=6) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 14 matched control subjects with normal hepatic function. Following a single oral 160 mg dose of Xtandi, the enzalutamide plus M2 AUC increased by 1.13-fold in subjects with mild hepatic impairment, and 1.18-fold in subjects with moderate hepatic impairment, compared to healthy control subjects. Overall, the results indicate that no dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment.

Patients with baseline severe hepatic impairment (Child-Pugh C) were excluded from clinical trials.

Renal Insufficiency: No formal renal impairment study for Xtandi has been completed. Patients with serum creatinine > 177 µmol/l (2 mg/dl) were excluded from clinical trials. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 ml/min (estimated by the Cockcroft and Gault formula). Xtandi has not been evaluated in patients with severe renal impairment (CrCL < 30 ml/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent hemodialysis or continuous ambulatory peritoneal dialysis.

Genetic Polymorphism: No formal study has been completed to assess the effect of genetic polymorphisms on exposure or response.

STORAGE AND STABILITY

Store Xtandi (enzalutamide capsules) at controlled room temperature 15°C - 30°C.

SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Xtandi (enzalutamide capsules) is supplied as a liquid filled, white to off-white, oblong, soft gelatin capsule imprinted in black ink with “ENZ”. Each capsule contains 40 mg of enzalutamide and the inactive ingredients caprylocaproyl macrogolglycerides, butylhydroxyanisole and butylhydroxytoluene.

The ingredients of the capsule shell are gelatin, sorbitol sorbitan solution, glycerol, titanium dioxide (E171), and purified water.

The ingredients of the ink are: ethanol, ethyl acetate, propylene glycol, iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, and ammonia solution concentrated.

Xtandi capsules are available in the following package sizes:

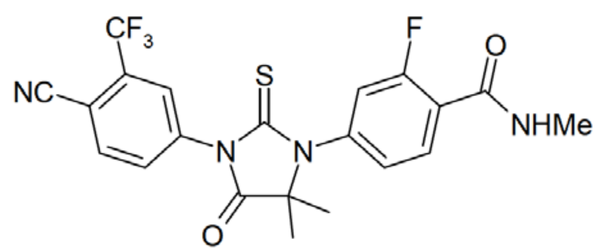
- Bottles of 120 capsules
- Blister Cartons of 112 capsules (4 capsules per cavity, 28 capsules per wallet)

Do not use beyond expiration date indicated on the package.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	enzalutamide
Chemical names:	
IUPAC	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide
Alternate names	4-{3-[4-Cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide
	3-(4-Cyano-3-trifluoromethylphenyl)-1-[3-fluoro-4-(methylcarbamoyl)phenyl]-5,5-dimethyl-2-thioxoimidazolin-4-one
	Benzamide, 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxo-1-imidazolidinyl]-2-fluoro-*N*-methyl
Molecular formula	$C_{21}H_{16}F_4N_4O_2S$
Molecular mass	464.44
Structural formula	
Physicochemical properties:	Enzalutamide is a white to off white solid that is insoluble in water. No salts are formed from pH 2 to 10. One crystalline form and four solvates have been observed.

CLINICAL TRIALS

The efficacy of Xtandi (enzalutamide) was established in two randomized placebo-controlled multicentre phase 3 clinical studies [PREVAIL, AFFIRM] of patients with progressive metastatic prostate cancer who had failed androgen deprivation therapy [Gonadotropin-releasing hormone (GnRH) analogue or after bilateral orchiectomy]. All patients continued on a GnRH analogue or had prior bilateral orchiectomy.

Chemotherapy-naïve mCRPC that Progressed on Androgen Deprivation Therapy (PREVAIL)

Study demographics and trial design

In the PREVAIL study, a total of 1717 patients with asymptomatic or mildly symptomatic metastatic castration-resistant prostate cancer who had not received prior chemotherapy were randomized 1:1 to receive either Xtandi orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients were allowed, but not required, to continue or initiate corticosteroids (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class 1 or 2), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression) and the initiation of either a cytotoxic chemotherapy or an investigational agent, or until unacceptable toxicity or withdrawal.

Changes in PSA serum concentration independently do not always predict clinical benefit. PSA rise without evidence of confirmed radiographic progression or a skeletal-related event was strongly discouraged as a criterion to start a new systemic anti-neoplastic therapy during the first 12 weeks of therapy and was discouraged as a criterion to start a new systemic anti-neoplastic therapy throughout the study.

Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). In addition to the co-primary endpoints, benefit was also assessed using secondary endpoints as follows: time to initiation of cytotoxic chemotherapy, best overall soft tissue response, time to first skeletal-related event, PSA response (≥ 50% decrease from baseline), and time to PSA progression.

Radiographic progression was assessed with the use of sequential imaging studies as defined by Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (for bone lesions) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms (see Table 6). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Approximately 45% of patients had measurable soft tissue disease at study entry, and 12% of patients had visceral (lung and/or liver) metastases.

Table 6: PREVAIL Key Demographics and Baseline Disease Characteristics		
Baseline Characteristic	**Xtandi (N = 872)**	**Placebo (N = 845)**
Age (years)		
Mean (SD)	71.3 (8.5%)	71.2 (8.42%)
Min, Max	43.0, 93.0	42.0, 93.0
Race		
White	669 (76.7%)	655 (77.5%)
Other, multiple, or unknown	95 (10.9%)	94 (11.1)
Asian	85 (9.7%)	82 (9.7%)
Black	21 (2.4%)	13 (1.5%)
American Indian or Alaska Native	1 (0.1%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	1 (0.1%)	1 (0.1%)
Time from initial diagnosis or first treatment of prostate cancer to randomization		
N	872	844
Median (months)	62.7	64.6
Baseline ECOG performance status (n [%])		
0	584 (67.0%)	585 (69.2%)
1	288 (33.0%)	260 (30.8%)
Distribution of disease at screening[a]		
Bone	741 (85.0%)	690 (81.7%)
Lymph node	437 (50.1%)	434 (51.4%)
Visceral disease (lung or liver)	98 (11.2%)	106 (12.5%)
Other soft tissue	113 (13.0%)	105 (12.4%)
Baseline mean pain score[b]		
N	859	840
0 to 1	569 (66.2%)	567 (67.5%)
2 to 3	275 (32.0%)	262 (31.2%)
> 3	15 (1.7%)	11 (1.3%)

Table 6: PREVAIL Key Demographics and Baseline Disease Characteristics		
Baseline Characteristic	**Xtandi (N = 872)**	**Placebo (N = 845)**
Number of bone metastases at screening		
0	131 (15.0%)	155 (18.3%)
1	97 (11.1%)	85 (10.1%)
2 to 4	213 (24.4%)	186 (22.0%)
5 to 9	146 (16.7%)	147 (17.4%)
10 to 20	140 (16.1%)	122 (14.4%)
> 20	145 (16.6%)	150 (17.8%)
Baseline serum PSA (ng/mL)		
N	872	844
Mean (SD)	140.7 (284.22)	137.9 (298.61)
Min, max	0.1, 3182.0	0.3, 3637.0
Baseline use of corticosteroids (> 7 days) (n [%])[c]	35 (4.0%)	36 (4.3%)

[a] Patients can be summarized for more than 1 category but are counted only once for each category

[b] Protocol defined by as a score of < 4 on question 3 on the Brief Pain Inventory Short Form (BPI) [worst prostate cancer-related pain over past 24 hours] assessed both at screening and again before randomization at baseline visit

[c] Includes all oral steroid use on the date of first dose of study drug. Excludes steroids taken for indications not associated with prostate cancer and continuous steroids taken for less than 7 days.

ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.

Study results

At the pre-specified interim analysis for overall survival, treatment with Xtandi demonstrated a statistically significant improvement in overall survival compared to treatment with placebo with a 29.4% reduction in risk of death [HR=0.706, (95% CI: 0.596; 0.837), p < 0.0001]. At the interim analysis, 27.6% (241 of 872) of patients treated with Xtandi, compared with 35.4% (299 of 845) of patients treated with placebo, had died. Estimated median overall survival was 32.4 months (95% CI: 30.1, not reached) in the Xtandi-treated patients and was 30.2 months (95% CI: 28.0, not reached) in the placebo-treated patients (Figure 1, Table 7). In addition, 40.4% of Xtandi-treated patients and 70.5% of placebo-treated patients received subsequent therapies with a demonstrated survival benefit. Median follow-up time based on reverse Kaplan-Meier estimates were 22.2 months for Xtandi-treated patients and 22.4 months for placebo-treated patients.

Table 7: PREVAIL Duration of Overall Survival – Co-primary Analysis (ITT Population)		
Parameter	**Xtandi (N = 872)**	**Placebo (N = 845)**
Death	241 (27.6%)	299 (35.4%)
Median survival (95% CI)	32.4 (30.1, NYR)	30.2 (28.0, NYR)
P-value (unstratified)	< 0.0001	
Hazard ratio (95% CI)[a]	0.706 (0.596, 0.837)	

[a] The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring Xtandi.

ITT, intent-to-treat; NYR, not yet reached.

The treatment effect was apparent after the first three months of treatment and maintained through the follow-up period (Figure 1). Subgroup survival analysis showed a consistent survival benefit for treatment with Xtandi (Figure 2).

Figure 1: Kaplan-Meier Overall Survival Curves of Patients Treated with Either Xtandi or Placebo in the PREVAIL Study (Intent-to-Treat Analysis)

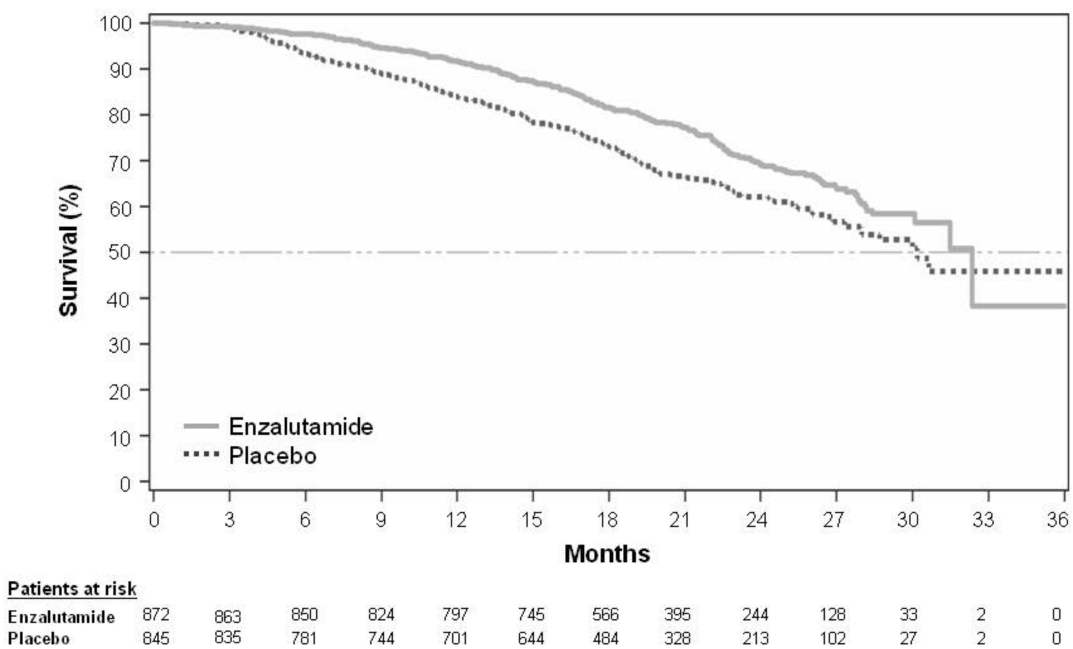
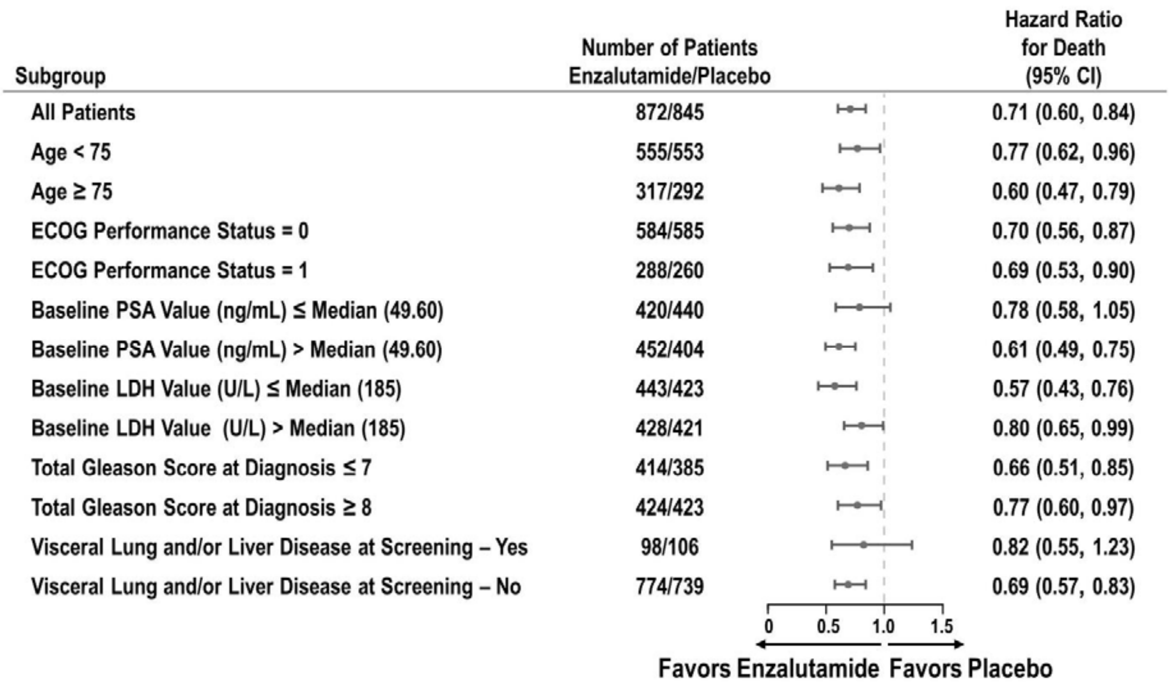


Figure 2: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval in the PREVAIL Study (Intent-to-Treat Analysis)



At the pre-specified rPFS analysis, a statistically significant improvement was demonstrated between the treatment groups with an 81.4% reduction in risk of radiographic progression or death [HR = 0.186 (95% CI: 0.149, 0.231), p < 0.0001]. One hundred and eighteen (14%) Xtandi-treated patients and 321 (40%) of placebo-treated patients had an event. The median rPFS was not reached (95% CI: 13.8, not reached) in the Xtandi-treated group and was 3.9 months (95% CI: 3.7, 5.4) in the placebo-treated group (Figure 3, Table 8). Consistent rPFS benefit was observed across all pre-specified patient subgroups (Figure 4). Median follow-up time based on reverse Kaplan-Meier estimates were 5.4 months for Xtandi-treated patients and 3.6 months for placebo-treated patients.

Table 8: PREVAIL, Duration of Radiographic Progression-Free Survival – Co-primary Analysis Based on Independent Central Review (ITT Population)

Radiographic Progression-Free Survival Follow-Up	Xtandi (N = 832)	Placebo (N = 801)
rPFS Events[a]	118 (14.2%)	321 (40.1%)
Duration of rPFS (months)[b,c]		
Median duration of rPFS (months)[b,c] (95% CI)	NYR (13.8, NYR)	3.9 (3.7, 5.4)
P-value (unstratified)	< 0.0001	
Hazard ratio (95% CI)[d]	0.186 (0.149, 0.231)	

[a] Based on the earliest contributing event (radiographic progression or death due to any cause within 168 days after treatment discontinuation).

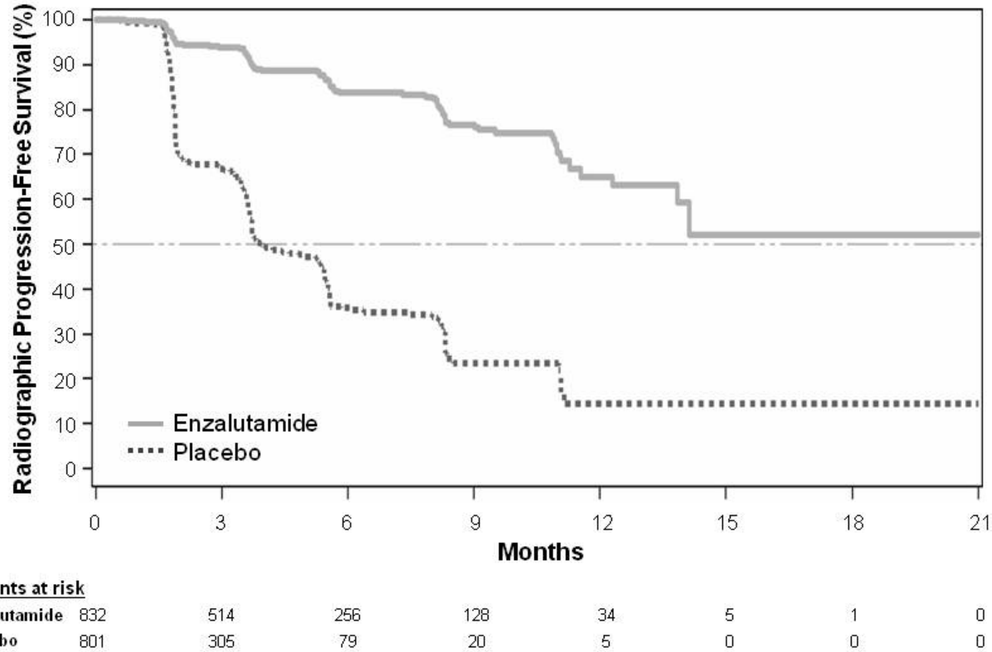
[b] Patients who were not known to have had an rPFS event at the time of analysis data cutoff are censored at date of last assessment showing no objective evidence of radiographic progression prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, skeletal-related event, treatment discontinuation, and 2 or more consecutive missed tumor assessments.

[c] Based on Kaplan-Meier estimates.

[d] The hazard ratio is based on a Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favoring Xtandi.

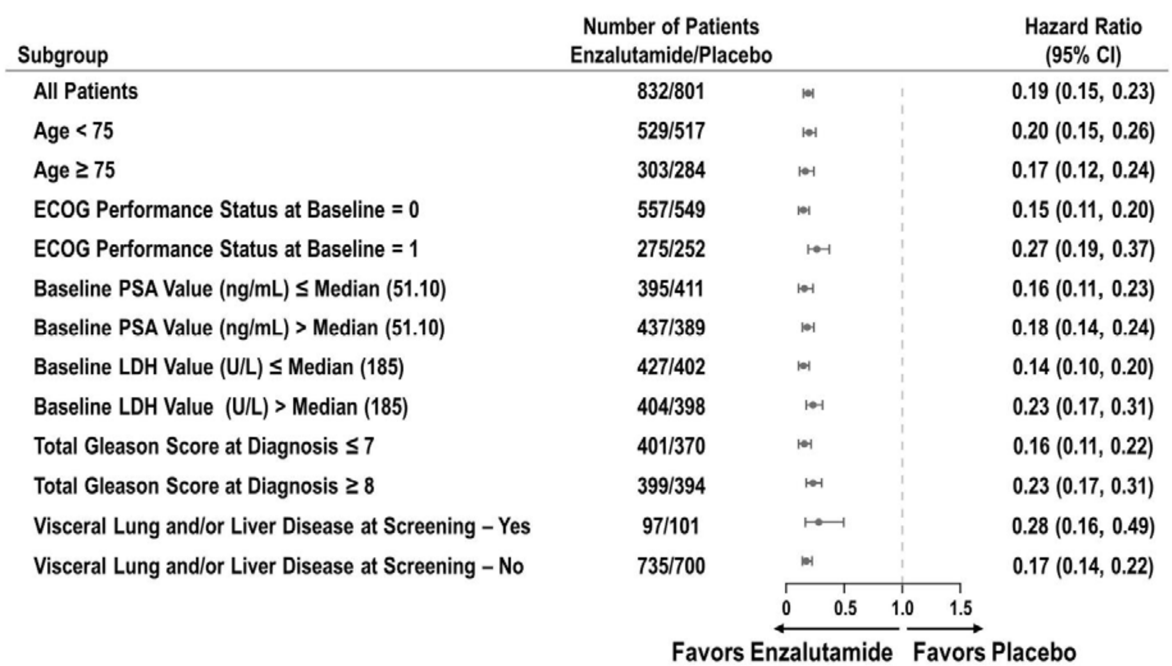
ITT, intent-to-treat; NYR, not yet reached; rPFS, radiographic progression-free survival.

Figure 3: Kaplan-Meier Curves of Radiographic Progression-Free Survival in Patients Treated with Either Xtandi or Placebo in the PREVAIL Study (Intent-to-Treat Analysis*)



* At the time of the primary analysis there were 1633 patients randomized.

Figure 4: Radiographic Progression-Free Survival by Subgroup: Hazard Ratio and 95% Confidence Interval in the PREVAIL Study (Intent-to-Treat Analysis)



In addition to the co-primary efficacy endpoints, statistically significant improvements were also demonstrated in prospectively defined secondary endpoints, see Table 9.

Table 9: Summary of Secondary Endpoint Results (PREVAIL)

Endpoint	Xtandi	Placebo	Hazard Ratio [95% CI]	P-Value
Secondary Efficacy Endpoints				
Time To Initiation Of Cytotoxic Chemotherapy[a]	28.0 months	10.8 months	0.349 (0.303, 0.403)	< 0.0001
Best Overall Soft Tissue Response	58.8%	5.0%	53.85% (48.53, 59.17%)	< 0.0001
Complete response	19.7%	1.0%		
Partial response	39.1%	3.9%		
Time to First Skeletal-Related Event (median)[a,b]	31.1 months	31.3 months	0.718 (0.610, 0.844)	< 0.0001
Time to PSA Progression[a,c]	11.2 months	2.8 months	0.169 (0.147, 0.195)	< 0.0001
PSA Response Rate ≥ 50% Decrease	78.0%	3.5%	N/A	< 0.0001

a Based on Kaplan-Meier estimates.
b Skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathological bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain from prostate cancer.
c Based on PSA progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria.

Best overall soft tissue response was analyzed for the ITT population with measurable soft tissue disease at baseline, defined by the presence of at least 1 target lesion according to RECIST v 1.1 as assessed by the investigator. Response categories are based on target, non-target, and new lesions. Confirmation of response was not required. The trial used the same modality of imaging (CT or MRI) throughout the trial for each institution.

PSA response ≥ 50% decreased from baseline was evaluated in 854 patients (97.9%) in the Xtandi treatment group and 777 patients (92.0%) in the placebo treatment group who had both baseline and at least 1 post-baseline PSA assessment during the study (ITT evaluable population). Confirmation required a subsequent assessment that was consecutive and conducted at least 3 weeks later.

mCRPC Patients with Prior Docetaxel Treatment (AFFIRM)

Study demographics and trial design

In the AFFIRM study, a total of 1199 patients with metastatic castration-resistant prostate cancer who had previously received docetaxel were randomized 2:1 to receive either Xtandi orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed, but not required to continue or initiate corticosteroids (47.8% vs. 45.6% were administered corticosteroids in Xtandi and placebo arms, respectively). In addition, 51.0% vs. 49.6% of patients in the Xtandi and placebo arms, respectively, were using bisphosphonates at baseline.

Patients were excluded if having a history of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrollment (Day 1 visit), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arteriovenous malformation, head trauma with loss of consciousness requiring hospitalization). Patients were also excluded if they had clinically significant cardiovascular disease, significant renal impairment, hepatic impairment, or histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features were excluded from the study.

Patients randomized to either arm were to continue treatment until either:

1. Disease progression (defined as radiographic progression or the occurrence of a skeletal-related event) and initiation of a new systemic antineoplastic treatment
2. Death
3. Unacceptable toxicity
4. Withdrawal

Increases in PSA, especially during the first 12 weeks of therapy, were not considered disease progression.

The primary efficacy endpoint for the AFFIRM study was overall survival defined as time from randomization to death from any cause.

The following key secondary efficacy endpoints were evaluated:

- Radiographic progression-free survival, defined as the time to the earliest objective evidence of radiographic progression or death due to any cause. Radiographic disease progression is defined by RECIST v 1.1 for soft tissue disease, or the appearance of two or more new lesions on bone scan, as per PCWG2 criteria, with a confirmatory scan 6 or more weeks only after the first assessment (13 weeks after initial dose).

- Time to PSA progression, defined as the time from randomization to PSA progression. PSA progression was assessed for each patient in the study using the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria. PSA progression could only be declared on or after the Week 13 assessment and required a confirmation that was consecutive and conducted at least 3 weeks later.

- Time to first skeletal related event, where skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

Additional efficacy endpoints included PSA response rate (≥ 50% or ≥ 90% reduction from baseline), and the response rate for quality of life as measured by Functional Assessment of Cancer Therapy – Prostate [FACT-P]. Patients were defined as having a positive quality of life response if they had a 10-point improvement in their global FACT-P score, compared with baseline, on 2 consecutive measurements obtained at least 3 weeks apart.

The patient demographics and baseline disease characteristics were balanced between the treatment arms (see Table 10).

Table 10: Summary of Patient Demographics and Baseline Characteristics for the Phase 3 AFFIRM Study

	Xtandi (160 mg/day) N = 800	Placebo N = 399
Age (years)		
Mean (SD)	68.8 (7.96)	68.6 (8.39)
Min, Max	41.0, 92.0	49.0, 89.0
Race		
Asian	5 (0.6%)	8 (2.0%)
Black	27 (3.4%)	20 (5.0%)
White	745 (93.1%)	366 (91.7%)
Other	23 (2.9%)	5 (1.3%)
Baseline ECOG Performance Status		
0	298 (37.3%)	156 (39.1%)
1	432 (54.0%)	211 (52.9%)
2	70 (8.8%)	32 (8.0%)
Baseline PSA (ng/mL)		
Mean (SD)	415.6 (930.76)	389.4 (1105.72)
Median	107.7	128.3
Min, Max	0.2, 11794.1	0.0, 19000.0
Average Pain Score as Assessed by Brief Pain Inventory†		
< 4	574 (71.8%)	284 (71.2%)
≥ 4	226 (28.3%)	115 (28.8%)
Type of Disease Progression at Study Entry		
PSA progression only	326 (40.8%)	164 (41.2%)
Radiographic progression‡	470 (58.8%)	234 (58.8%)
Missing	4	1
Distribution of Disease at Screening		
Bone	730 (92.2%)	364 (91.5%)
Lymph node	442 (55.8%)	219 (55.0%)
Visceral liver	92 (11.6%)	34 (8.5%)
Visceral lung	122 (15.4%)	59 (14.8%)
Other soft tissue	147 (18.6%)	70 (17.6%)
Missing	8	1

† Mean of patient's reported worst pain over the previous 24 hours calculated for seven days prior to randomization. Randomization was stratified by baseline ECOG performance status score (0–1 vs. 2) and mean Brief Pain Inventory – Short Form Question #3 score averaged over the 7 days prior to randomization;

‡ Bone and or soft tissue

Study results

The pre-specified interim analysis was conducted after 520 deaths were observed. A statistically significant 4.8 month improvement in median overall survival was observed with treatment with Xtandi versus placebo (18.4 months and 13.6 months respectively), (Table 11 and Figure 5). The stratified hazard ratio for death for Xtandi-treated patients was 0.631 (95% CI: 0.529, 0.752; $p < 0.0001$), a 37% reduction in the risk of patient death.

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with Xtandi remained alive, compared to those treated with placebo (Figure 5). The median duration of follow-up was 14.4 months.

Table 11: Overall Survival of Patients Treated with Either Xtandi or Placebo in the AFFIRM Study (Intent-to-Treat Analysis)

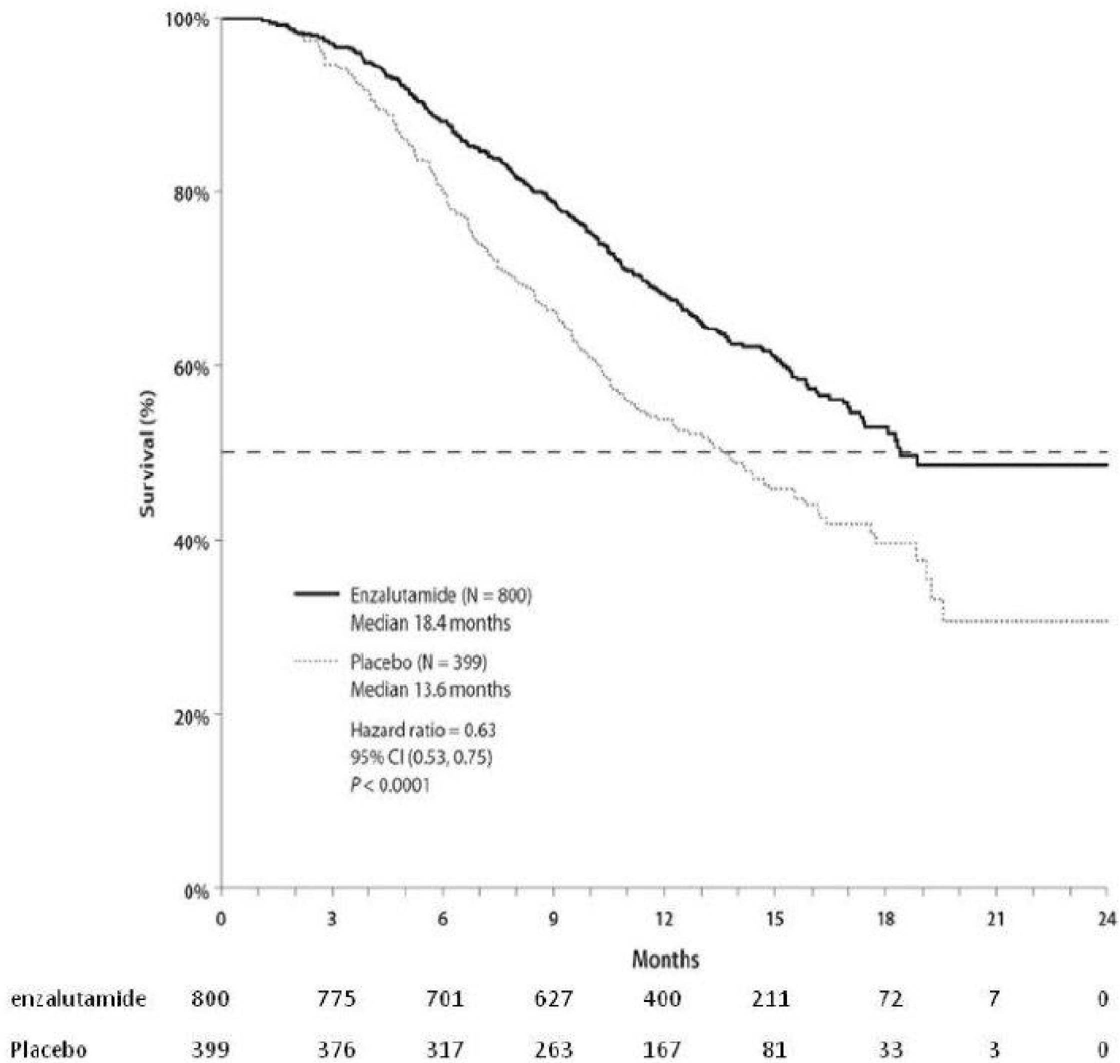
Parameter	Xtandi (N=800)	Placebo (N=399)
Deaths (%)	308 (38.5%)	212 (53.1%)
Median survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value†	< 0.0001	
Hazard ratio (95% CI)‡	0.631 (0.529, 0.752)	

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

‡ Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours Xtandi

NR: not reached.

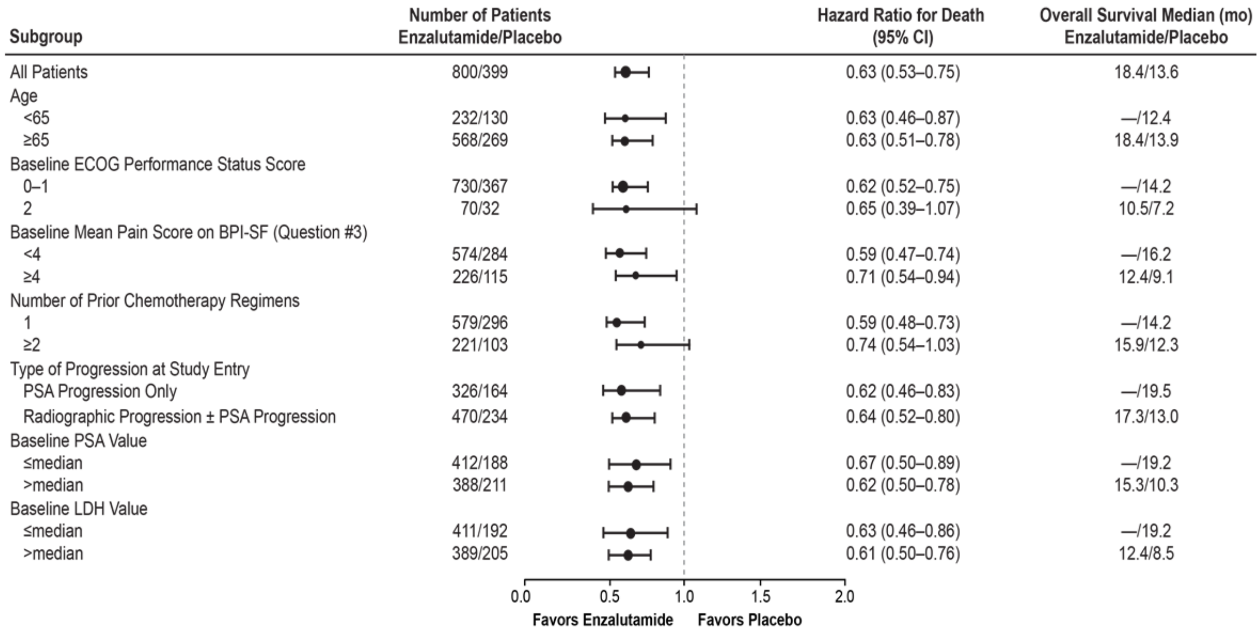
Figure 5: Kaplan-Meier Overall Survival Curves of Patients Treated with Either Xtandi or Placebo in the AFFIRM Study (Intent-to-Treat Analysis)



The median duration of therapy on Xtandi was 8.3 months vs. 3.0 months for placebo.

Subgroup survival analysis demonstrated a consistent favorable survival benefit for treatment with Xtandi (see Figure 6).

Figure 6: Overall Survival by Subgroup – Hazard Ratio and 95% Confidence Interval in the AFFIRM Study



The benefit observed for Xtandi in overall survival was supported by significant improvements in all secondary endpoints (see Table 12).

Table 12: Summary of Secondary Endpoint Results (AFFIRM)				
Endpoint	**Xtandi**	**Placebo**	**Hazard Ratio [95% CI]**	**P-Value**
Key Secondary Efficacy Endpoints				
Time to PSA Progression (median)	8.3 months	3.0 months	0.248 [0.204, 0.303]	< 0.0001
Radiographic Progression-Free Survival (median)	8.3 months	2.9 months	0.404 [0.350, 0.466]	< 0.0001
Time to First Skeletal-Related Event (median)	16.7 months	13.3 months	0.688 [0.566, 0.835]	0.0001
Other Secondary Efficacy Endpoints[a]				
FACT-P Response Rate[b]	43.2%	18.3%	NA	< 0.0001
PSA Response Rate				
≥ 50% Decrease	54.0%	1.5%	NA	< 0.0001
≥ 90% Decrease	24.8%	0.9%		< 0.0001

[a] No corrections for multiplicity were made for these efficacy endpoints.

[b] The evaluable population consists of 85.9% (651/758) of patients in the Xtandi group with a Global FACT-P score at baseline and 66.8% (257/385) of patients in the placebo group with a Global FACT-P score at baseline. The disparity in the evaluable population for FACT-P analysis was due to a higher number of placebo patients who discontinued study treatment early due to disease progression.

DETAILED PHARMACOLOGY

Animal Pharmacology

Decreased activity, tremor and/or convulsions were observed in mice following a single oral dose of enzalutamide ≥ 400 mg/kg. Enzalutamide treatment was also associated with convulsions in mice upon oral dosing of ≥ 200 mg/kg for 7 days. A low incidence of convulsions was observed in the pivotal repeat dose toxicity studies in rats and dogs (1 individual animal in the highest dose group per study). *In vitro*, enzalutamide and its metabolites bind and inhibit the GABA-gated chloride channel, an off-target mechanism associated with the onset of seizure in animals. Enzalutamide and M2 were also found to cross the blood-brain barrier in rodents.

Table 13: Non-clinical Studies Related to the Convulsion Potential of Enzalutamide

	Studies	Observation
In vitro	Chloride channel binding	Enzalutamide binds to the GABA-gated chloride channel: IC_{50} = 2.6 µM (1.2 µg/mL) K_i = 2.1 µM (1.0 µg/mL)
		M2 binds to the GABA-gated chloride channel: IC_{50} = 7.1 µM (3.2 µg/mL) K_i = 5.9 µM (2.7 µg/mL)
	Inhibition of GABA-gated chloride channel activity in whole cells	Enzalutamide inhibits the GABA-gated chloride channel IC_{50} = 3.0 µM (1.4 µg/mL)
		M2 inhibits the GABA-gated chloride channel IC_{50} = 2.3 µM (1.04 µg/mL)
In vivo	Brain penetration studies in rodents	Enzalutamide and M2 crossed the blood-brain barrier in rats and mice. Based on the brain-to-plasma ratios in rats, enzalutamide and M2 concentrations in brain are approximately the same as those in the plasma.
	2-week oral gavage bridging toxicity study in rats	Enzalutamide treatment was associated with a convulsion in a single rat at a dose of 100 mg/kg.
	Single-dose study in mice	Enzalutamide treatment was associated with convulsions in mice at a dose ≥ 400 mg/kg
	Repeat-dose oral toxicity study in mice	Enzalutamide treatment was associated with a convulsion in a single female mouse (1/5 per group) at a dose of 300 mg/kg on Day 2
	Convulsion model in mice	Enzalutamide treatment was associated with a dose-dependent incidence of convulsions in mice at doses ≥ 200 mg/kg
	4-week dog toxicity study	Enzalutamide treatment in 28-day dog toxicity study was associated with a single convulsion on Day 28 in a dog receiving 60 mg/kg/day.
	39-week dog toxicity study	Enzalutamide treatment was associated with convulsions on Day 13 in one dog receiving 45 mg/kg/day. Dosing (45 mg/kg/day) in this animal was re-started at day 17; no convulsions occurred for the remainder of the study duration.

IC_{50}, concentration required for 50% inhibition; GABA, gamma aminobutyric acid.

Nonclinical Pharmacokinetics

The absorption, distribution, metabolism and excretion of [^{14}C]-enzalutamide was studied in rats and dogs. Enzalutamide was extensively metabolized in these species via the same Phase I reactions observed in humans, mainly via demethylation, oxidation and hydrolysis. The two major metabolites in human plasma also circulate in rat and dog plasma; however, the exposure

(C_{max} and AUC_{24h}) of M2 in these species was ≤ 15% that of humans. In rodents, M2 is hydrolyzed to M1 by plasma esterases. Enzalutamide was eliminated mainly as metabolites in the feces of rats and in the urine of dogs. M1 was the major metabolite in excreta. Phase I metabolites were the precursors to Phase II products, such as glutathione, glucuronide, and taurine conjugates that were observed in animal bile. Acyl glucuronides and their rearrangement isomers have been detected in bile of both rats and dogs; whether enzalutamide is metabolized to form acyl glucuronides in humans is not known.

Tissue distribution studies in rodents have shown that enzalutamide and M2 readily cross the blood-brain barrier, whereas M1 poorly penetrates the brain.

Human Pharmacology- *In Vitro*

A summary of the *in vitro* evaluations with human biomaterials and enzalutamide and major human metabolites M1 and M2 are presented in the table below, along with the primary study conclusions.

Table 14: Overview of *In Vitro* Evaluations of Enzalutamide and Metabolites

Type of Study	Results and Conclusion
Caco-2 permeability	Mean permeability flux values for enzalutamide in the absorptive apical-to-basolateral (A→B) direction were ≥ 31 × 10^{-6} cm/s at all concentrations, more than twice the apparent permeability of propranolol. Bidirectional permeability indicated that transport is passive. Enzalutamide is a high permeability compound that crosses Caco-2 cell monolayers by passive diffusion
Protein binding in human plasma	Enzalutamide, M1, and M2 are highly protein bound in plasma. Enzalutamide: 97%–98%. M1: 98%, M2: 95%
Protein binding in solutions	Albumin is the main binding protein in human plasma. Albumin: 97%, High density lipoprotein: 75% to 77%, Low density lipoprotein: 70% to 75%, α_1-acid glycoprotein: 44% to 52% γ-globulin: 10% to 19%
Red blood cell distribution	Enzalutamide was preferentially retained in the plasma component of blood. Whole blood-to-plasma ^{14}C-AUC_{inf} ratio: 0.55
Metabolism with human recombinant CYP enzymes[†]	Mean recovery of enzalutamide after a 2 hour incubation with CYP2C8, CYP3A4, and CYP3A5 ranged from 67.0% to 81.8% suggesting slow metabolism. CYP2C8, CYP3A4, and CYP3A5 may play a role in the metabolism of enzalutamide.
Metabolism with human liver microsomes and human plasma	Incubation of enzalutamide (4.64 µg/mL) with microsomes produced metabolites M2 and a N-hydroxymethyl derivative of enzalutamide (M6); whereas, no metabolites were observed in enzalutamide incubations with human plasma or phosphate buffer. Incubation with M6 (10 µM) with microsomes, human plasma, or phosphate buffer resulted in M2 formation. Enzalutamide is metabolized to M2 and M6 in the presence of human microsomes, and M6 degrades to M2 in a reaction that does not require metabolic enzymes.
Induction of CYP enzymes in human primary hepatocytes	Enzalutamide or M2 increased mRNA expression and enzyme activity of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. M1 increased mRNA expression of CYP2C8 but did not increase enzyme activity. Enzalutamide, M1 or M2 increased mRNA expression of UGT1A1 and UGT1A4. Enzalutamide, M1 or M2 did not increase mRNA expression of CYP1A2. Enzalutamide has the potential to induce CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, UGT1A1 and UGT1A4 in the clinical setting.

Table 14: Overview of *In Vitro* Evaluations of Enzalutamide and Metabolites	
Type of Study	**Results and Conclusion**
Inhibition of CYP enzymes in human liver microsomes	Enzalutamide, M1, and/or M2 are inhibitors of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Enzalutamide showed time-dependent inhibition of CYP1A2 with a pattern suggesting that a metabolite formed *in vitro* (other than M1 or M2) may be a more potent inhibitor of this enzyme than enzalutamide itself. M2 showed weak time-dependent inhibition of CYP3A4/5. Enzalutamide has the potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in the clinical setting.
P-glycoprotein (MDR1 transporter) interactions	Enzalutamide and M2 are inhibitors of P-gp at lower concentrations ($IC_{50:}$ 0.775 µg/mL and 0.491 µg/mL, respectively), and inducers at higher concentrations (4.64 µg/mL and 4.50 µg/mL, respectively). Enzalutamide and M2 are not substrates of P-gp. M1 is not an inhibitor, inducer, nor substrate of P-gp. Enzalutamide has the potential to affect exposures to drugs that are substrates for the efflux transporter P-gp.
Breast Cancer Resistant Protein (BCRP) interactions	Enzalutamide, M1 and M2 are inhibitors of BCRP. Enzalutamide has the potential to affect exposures to drugs that are substrates of BCRP.
Organic anion transporters	M1 is a substrate of human organic anion transporters 3 (hOAT3) but not a substrate of hOAT1. Organic anion transporters 3 (OAT3) inhibitors have the potential to affect the exposure of M1.

† 12 human recombinant CYP isoforms: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP3A5

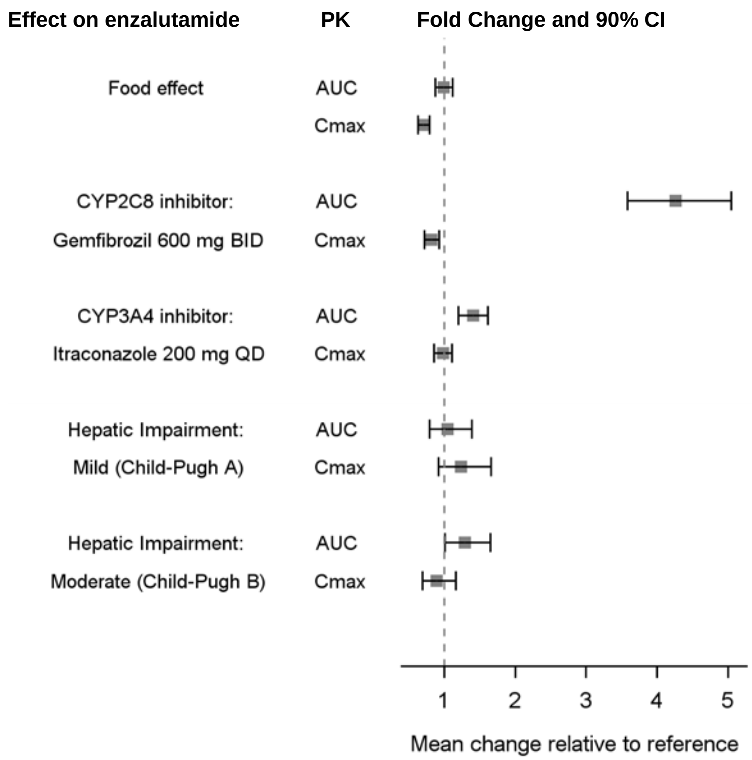
AUC, area under the curve; CYP, cytochrome P450; IC_{50}, concentration required for 50% inhibition; mRNA, messenger ribonucleic acid; P-gp, permeability-glycoprotein; µg/mL, micrograms per milliliter; µM, micromolar; cm/s, centimeters per second

<u>Human Pharmacology – *In Vivo*</u>

See **DRUG INTERACTIONS** and **ACTION AND CLINICAL PHARMACOLOGY** sections.

The results of studies evaluating the Effect of Intrinsic/Extrinsic Factors on the PK of Enzalutamide are shown in Figure 7.

Figure 7: Effect of Intrinsic/Extrinsic Factors on the PK of Enzalutamide



See **Drug-Drug Interactions**

In patients, the inter-subject variability, expressed as CV%, on the enzalutamide PK parameters AUCτ, C_{min}, and C_{max} ranged from 23.0% to 29.3%. The inter-subject variability of the M2 PK parameters AUCτ, C_{min} and C_{max} ranged from 29.7% to 30.9%. In a dose-escalation study, intra-subject variability on the enzalutamide PK parameter C_{min} ranged between 3% and 59% after once daily administration.

TOXICOLOGY

Safety pharmacology

In safety pharmacology studies, enzalutamide and its active metabolite M2, caused a concentration-dependent inhibition of hERG potassium currents in HEK293 cells with IC_{50} values of 15.7 µM (7.3 µg/mL) and 18.6 µM (8.4 µg/mL), respectively. No treatment-related electrocardiographic effects were detected when enzalutamide was administered at single oral doses of 5, 15, or 30 mg/kg in a Latin square crossover conscious dog telemetry study (N=4), but maximal plasma concentrations in the dogs were less than the human C_{max} at the therapeutic dose.

Repeated dose studies in mice

In mice dosed with 30 and 60 mg/kg/day enzalutamide for 4 weeks, changes related to the pharmacological activity included decreased weights of the epididymis, seminal vesicles and prostate. Decreased cytoplasmic vacuoles in the zona fasciculata were observed in all enzalutamide dosed groups. Increased liver weight was observed in both sexes at 30 and 60 mg/kg/day and histopathology revealed hypertrophy of centrilobular hepatocytes. Thickening of mucosa in the forestomach was found in both sexes at 60 mg/kg/day, while ulcer and focal hyperplasia in the mucosa in the forestomach occurred only in the 60 mg/kg/day females. Two male animals dosed with 60 mg/kg/day died. All treatment-related changes observed at the end of the administration period were essentially reversible after a 4-week withdrawal of the test article. The doses used in mice (10, 30 and 60 mg/kg) resulted in systemic exposures (combined sex AUC) of 0.4, 1.0 and 1.4 times, respectively, the AUC in patients.

Repeated dose studies in rats
Morphological and/or histopathological changes were observed in the reproductive and hormone-sensitive organs of rats in all enzalutamide dose groups in the 26-week repeated dose study. These changes included atrophy of the prostate and seminal vesicles, enlarged pituitary glands in females marked by hyperplasia on pars distalis, mammary gland atrophy in males and mammary gland hyperplasia in females. Effects on the pituitary and mammary glands persisted beyond the eight-week recovery period. Systemic exposure (combined sex AUC) at the doses used (10, 30 and 100 mg/kg/day) were 0.7, 1.4 and 1.8 times, respectively, the AUC in patients.

Repeated dose studies in dogs
In the 39-week study in dogs, atrophy of the prostate, epididymides and seminiferous tubules and hypertrophy and/or hyperplasia of the Leydig cells in the testes were observed in all enzalutamide dose groups. In one male animal in the 45 mg/kg/day group, convulsions were observed before dosing on Day 13. Dosing in this animal was re-initiated on Day 17 and no recurrence of convulsions was observed in this animal or in any of the other animals up to the end of the study period. All changes to the reproductive organs were either partially or fully reversed after a thirteen-week recovery period. Systemic exposure (combined sex AUC) at the doses used (5, 15 and 45 mg/kg/day) were 0.4, 0.8 and 1.1 times, respectively, the AUC in patients.

Reproductive Toxicology

In a developmental toxicity study in mice, enzalutamide (10 and 30 mg/kg/day) caused embryo-fetal lethality (increased post-implantation loss and decreased number of live fetuses). Also at 10 and 30 mg/kg/day, there was a higher incidence of fetuses with external abnormalities (shortened anogenital distance). At 30 mg/kg/day, cleft palate and absent palatine bone were increased. The doses (1, 10, and 30 mg/kg/day) tested in mice resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the AUC in patients.

In the developmental toxicity study in rabbits, there were no treatment-related effects in any dam up to 10 mg/kg/day, although a preliminary study showed maternal and fetal toxicity at a dose of 30 mg/kg. No treatment-related effects were noted on the viability, growth, external, visceral, or skeletal morphology or the degree of ossification of embryos/fetuses up to 10 mg/kg/day. The No Observed Adverse Effect Level was considered to be 10 mg/kg/day for maternal general toxicity, maternal reproductive function and embryo-fetal development. At the tested doses (0.3, 3 and 10 mg/kg/day), the systemic exposures (AUC) were approximately 0.016, 0.1 and 0.36 times, respectively, the AUC in patients.

Overall, enzalutamide induced embryo-fetal deaths and/or external and skeletal abnormalities in mice and rabbits. These findings are consistent with the pharmacological activity of enzalutamide. For this reason, Xtandi is contraindicated in pregnancy.

Carcinogenesis and Genotoxicity

Enzalutamide was devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation (Ames) assay, *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay and in the *in vivo* mouse micronucleus assay. Metabolites M1 and M2 were not mutagenic in the bacterial Ames assay. M1 but not M2 showed mutagenic and clastogenic potential in the *in vitro* mouse lymphoma thymidine kinase assay at concentrations that also caused extensive cell death (≥ 50 µg/mL). Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

REFERENCES

1. Beer T.M., Armstrong A.J., Rathkopf D.E., *et al* Enzalutamide in Metastatic Prostate Cancer before Chemotherapy. N Engl J Med Jun 01, 2014: 1-10.
2. Chen Y., Clegg N.J., Scher H.I. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. Lancet Oncol 2009; 10:981-991.
3. Scher H.I, Beer T.M., Higano C.S et al. Antitumour activity of enzalutamide in castration-resistant prostate cancer: a phase 1–2 study. Lancet 2010; 375:1437-46.
4. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in Prostate Cancer after chemotherapy. N Engl J Med Aug, 15 2012: 1-11.
5. Tran C, Ouk S, Clegg NJ et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. Science 2009; 324(5928):787-790.

PART III: CONSUMER INFORMATION

PrXtandi®
(enzalutamide capsules)

This leaflet is part III of a three-part "Product Monograph" published when Xtandi was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Xtandi. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Xtandi is used to treat prostate cancer that has spread to other parts of the body in patients who are receiving drugs to lower the testosterone level or have had surgical removal of the testicles. These patients may have also received prior cancer treatment with docetaxel.

What it does:
Xtandi blocks the activity of androgens (like testosterone), which can slow the growth of prostate cancer.

When it should not be used:
- If you are allergic to enzalutamide or to any of the ingredients in the formulation (see **What the nonmedicinal ingredients are**).
- If you are or may become pregnant.
- If you are breast-feeding.

What the medicinal ingredient is:
enzalutamide

What the nonmedicinal ingredients are:
caprylocaproyl macrogolglycerides, butylhydroxyanisole (E320), butylhydroxytoluene (E321)

Capsule Shell: gelatin, sorbitol sorbitan solution, glycerol, titanium dioxide (E171), purified water

Printing ink: ethanol, ethyl acetate, propylene glycol, iron oxide black (E172), polyvinyl acetate phthalate, purified water, isopropyl alcohol, macrogol 400, ammonia solution concentrated

What dosage forms it comes in:
Xtandi is available as a 40 mg white to off-white, oblong, liquid filled, soft capsule. The letters "ENZ" are printed in black on each capsule.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Xtandi should only be prescribed by a doctor experienced with the treatment of prostate cancer.
Clinically significant adverse events:
- Seizures (see **Seizures** section, below).
- Posterior Reversible Encephalopathy Syndrome (PRES, see **PRES** section below)

Be careful if you are engaging in activities that require mental concentration or where sudden loss of consciousness could cause serious harm to others (e.g., driving or operating tools or machines).

BEFORE you use Xtandi talk to your doctor or pharmacist:

- If you have history of seizures or are at a high risk of seizures (see below paragraph on situations in which you may have a higher risk of seizures).
- If you have problems with your liver or kidneys.
- If you have any heart disorder, including an irregular heartbeat, an abnormal electrical signal called "prolongation of the QT interval" or a known history of QT interval prolongation.
- If you have high blood pressure. Xtandi can raise blood pressure. Your doctor will measure your blood pressure before starting treatment with Xtandi and periodically during treatment.
- If you have a personal history of fainting spells.
- If you have electrolyte disturbances (e.g. low blood potassium or magnesium levels) or conditions that could lead to electrolyte disturbances (e.g. vomiting, diarrhea, dehydration, eating disorder).
- About all medicines (including natural health products) you have recently taken or are currently taking.

You should not start or stop Xtandi before you talk to your healthcare provider that prescribed you Xtandi.

Men who are sexually active with a pregnant woman must use a condom during and for three 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 three months after treatment.

Xtandi should not be given to patients less than 18 years of age.

Seizures
Xtandi has been shown to cause seizures in about 9 of every 1,000 people who had received prior cancer treatment with docetaxel, and in about 1 of every 1,000 people who had not received chemotherapy.

Posterior Reversible Encephalopathy Syndrome (PRES)
Reversible swelling in the rear part of the brain that can be associated with high blood pressure and can lead to headache, loss of speech or vision, confusion and/or seizure.

Tell your doctor, pharmacist or nurse

if you are taking any of the following medicines. When taken at the same time as Xtandi, these medicines may increase the risk of a seizure:

- Certain medicines used to treat asthma and other respiratory diseases (e.g. aminophylline, theophylline)
- Medicines used to treat certain psychiatric disorders such as depression and schizophrenia (e.g. clozapine, olanzapine, risperidone, ziprasidone, bupropion, lithium, chlorpromazine, mesoridazine, thioridazine, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine, venlafaxine)
- Certain medicines for the treatment of pain (e.g. meperidine)

Some situations in which you may have a higher risk of seizures include:

- If you had earlier episodes of seizures
- If you drink very large amounts of alcohol either regularly or from time to time
- If you have had a serious head injury or a history of head trauma
- If you have had certain kinds of stroke
- If you have had a brain tumour or metastases of cancer in the brain
- If you are taking a medicine that can cause seizures or medicines that can lower the susceptibility for having seizures

If you have a seizure during treatment: Stop taking Xtandi and see your doctor, pharmacist or nurse as soon as possible.

INTERACTIONS WITH THIS MEDICATION

Certain medicines may interact with Xtandi. These include drugs used to:

- Treat bacterial infections (e.g. clarithromycin)
- Treat anxiety or depression (e.g. diazepam)
- Treat psychosis (e.g. diazepam, haloperidol, midazolam)
- Treat gout (colchicine)
- Lower cholesterol (e.g. atorvastatin, simvastatin)
- Treat heart conditions and lower blood pressure (e.g. bisoprolol, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil)
- Treat serious disease related to inflammation (e.g. dexamethasone, prednisone)
- Prevent the rejection of organ transplants (e.g. cyclosporine, tacrolimus)
- Treat HIV infection (e.g. indinavir, ritonavir)
- Treat epilepsy (e.g. phenobarbitone, phenytoin)
- Prevent blood clots (e.g. acenocoumarol, dabigatran etexilate, warfarin)
- Treat cancer (e.g. cabazitaxel, irinotecan, sunitinib)
- Treat pain (e.g. fentanyl, tramadol)
- Treat thyroid conditions (e.g. levothyroxine)

Tell your doctor, pharmacist or nurse if you are taking any of the medicines listed above. You should check with your doctor, pharmacist, or nurse before taking any other medications with Xtandi. The dose of any other medicines that you are taking may need to be changed.

PROPER USE OF THIS MEDICATION

Usual dose:
The usual dose is 160 mg per day (4 capsules). The dose should be taken at the same time each day. Swallow the capsules whole with water. This medicine can be taken with or without food.

Overdose:
If you take more drug than prescribed, stop taking Xtandi and contact your doctor. You may be at increased risk for seizure.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

- If you forget to take Xtandi at the usual time, take your usual dose as soon as you remember.
- If you forget to take Xtandi for the whole day, take your usual dose the following day.
- If you forget to take Xtandi for more than one day, talk to your doctor without delay.

Do not take a double dose to make up for the dose you forgot.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Xtandi can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Very Common side effects (affects more than 1 in 10 people):

- Fatigue
- High blood pressure
- Headache
- Hot flush

Common side effects (affects less than 1 in 10 people):

- Falls
- Bone fractures
- Feeling anxious
- Forgetfulness
- Inability to remember and to solve problems
- Reduced concentration
- Disturbance in attention
- Dry skin, itching
- Breast enlargement in men

- Bruise
- Nose bleed
- Shingles
- Dizziness
- Flu like symptoms
- Drowsiness
- Uncontrollable urge to move a part of the body, usually the leg (restless leg syndrome)

Uncommon side effects (affects less than 1 in 100 people):

- Hallucinations
- Bleeding in digestive tract
- Infection
- Seizure
- Low white blood cell count

Reported from post-marketing with unknown frequency:

- Posterior Reversible Encephalopathy Syndrome (PRES): symptoms include seizure, worsening headache, consciousness impairment (including confusion, tiredness, or coma), blindness or other vision problems.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations, or fainting, you should seek immediate medical attention.

Approximately 9 in every 1,000 people taking Xtandi are at risk of having a seizure, if they have received prior docetaxel therapy whereas the risk is approximately 1 in every 1,000 people who have not received prior docetaxel therapy. Seizures are more likely if you take more than the recommended dose of this medicine, if you take some other medicines, or if you are at higher than usual risk of seizures (see **Warnings and Precautions**).

Tell your doctor or pharmacist if you have any side effects while taking Xtandi. This includes any side effects not listed above.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Uncommon (may affect 0.1% to 1% of people)			
Seizure		✓	✓
Reported from post-marketing (unknown frequency)			
Reversible swelling in the rear part of the brain that can be associated with high blood pressure and can lead to headache, loss of speech or vision, confusion and/or seizure		✓	✓

This is not a complete list of side effects. For any unexpected effects while taking Xtandi, contact your doctor or pharmacist.

HOW TO STORE IT

Store between 15°C - 30°C. Keep out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **- Fax toll-free to 1-866-678-6789, or**
  - **- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.astellas.ca

or by contacting the sponsor, Astellas Pharma Canada, Inc., at: 1-888-338-1824

This leaflet was prepared by Astellas Pharma Canada, Inc.

Last revised: April 15, 2015