Brand Name	Xtandi
Active Ingredient(s)	enzalutamide
Strength	40 mg
Dosage Form	capsule
Inactive Ingredients	caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide
NDC	0469-0125-99
DIN	02407329
Canadian Distributor	Astellas Pharma Canada Inc. 650 675 Cochrane Drive, West Tower, Markham, Ontario, Canada L3R 0B8
NDA Number	NDA203415
US Distributor (NDA Holder)	Astellas Pharma US, Inc. 1 Astellas Wy, Northbrook, IL 60062
Manufacturer (Final Packager)	Not available
API Manufacturer	Not available
Relationship to Sponsor	The Sponsor may have or have had agreements with the U.S. manufacturer for rebates. The Sponsor has no relationship with the foreign manufacturer.

Current FDA-approved Package Insert

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

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

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:

- castration-resistant prostate cancer. (1)
- metastatic castration-sensitive prostate cancer. (1)

DOSAGE AND ADMINISTRATION

XTANDI 160 mg administered orally once daily. (2.1)
Patients receiving XTANDI should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.4)

DOSAGE FORMS AND STRENGTHS

- Capsules: 40 mg (3)
- Tablets: 40 mg, 80 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Seizure occurred in 0.5% of patients receiving XTANDI. In patients with predisposing factors, seizures were reported in 2.2% of patients. Permanently discontinue XTANDI in patients who develop a seizure during treatment. (5.1)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue XTANDI. (5.2)
- Hypersensitivity: Discontinue XTANDI. (5.3)
- Ischemic Heart Disease: Optimize management of cardiovascular risk factors. Discontinue XTANDI for Grade 3-4 events. (5.4)
- Falls and Fractures occurred in 11% and 10% of patients receiving XTANDI, respectively. Evaluate patients for fracture and fall risk, and treat patients with bone-targeted agents according to established guidelines. (5.5)
- Embryo-Fetal Toxicity: XTANDI can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception. (5.6, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. (6.1)

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

DRUG INTERACTIONS

- Strong CYP2C8 Inhibitors: Avoid strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI. (2.3, 7.1)
- Strong CYP3A4 Inducers: Avoid strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI. (2.3, 7.1)
- Avoid coadministration with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. In cases where active metabolites are formed, there may be increased exposure to the active metabolites. (7.2)

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

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI® is indicated for the treatment of patients with:

- castration-resistant prostate cancer (CRPC)
- metastatic castration-sensitive prostate cancer (mCSPC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of XTANDI is 160 mg administered orally once daily with or without food *[see Clinical Pharmacology (12.3)]*. Swallow capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.

2.2 Dosage Modifications for Adverse Reactions

If a patient experiences a ≥ Grade 3 or an intolerable adverse reaction, withhold XTANDI for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted *[see Warnings and Precautions (5.1, 5.2)]*.

2.3 Dosage Modifications for Drug Interactions

Strong CYP2C8 Inhibitors

Avoid the coadministration of strong CYP2C8 inhibitors. If the coadministration of a strong CYP2C8 inhibitor cannot be avoided, reduce the XTANDI dosage to 80 mg once daily. If the coadministration of the strong inhibitor is discontinued, increase the XTANDI dosage to the dosage used prior to initiation of the strong CYP2C8 inhibitor *[see Clinical Pharmacology (12.3)]*.

Strong CYP3A4 Inducers

Avoid the coadministration of strong CYP3A4 inducers. If the coadministration of a strong CYP3A4 inducer cannot be avoided, increase the XTANDI dosage from 160 mg to 240 mg orally once daily. If the coadministration of the strong CYP3A4 inducer is discontinued, decrease the XTANDI dosage to the dosage used prior to initiation of the strong CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

2.4 Important Administration Instructions

Patients receiving XTANDI should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

3 DOSAGE FORMS AND STRENGTHS

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

XTANDI 40 mg tablets are yellow, round, film-coated and debossed with E 40.

XTANDI 80 mg tablets are yellow, oval, film-coated and debossed with E 80.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Seizure

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 1776 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

5.2 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI *[see Adverse Reactions (6.2)]*. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, 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). Discontinue XTANDI in patients who develop PRES.

5.3 Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in seven randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

5.4 Ischemic Heart Disease

In the combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on the XTANDI arm compared to 0.7% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

5.5 Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

5.6 Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Seizure *[see Warnings and Precautions (5.1)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Warnings and Precautions (5.3)]*
- Ischemic Heart Disease *[see Warnings and Precautions (5.4)]*
- Falls and Fractures *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

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

The data in WARNINGS and PRECAUTIONS reflect seven randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, Asian PREVAIL (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N = 3509) or mCSPC (N = 572) treated with XTANDI. Patients received XTANDI 160 mg (N = 4081) or placebo orally once daily (N = 2472) or bicalutamide 50 mg orally once daily (N = 387). All patients continued androgen deprivation therapy (ADT). In these seven trials, the median duration of treatment was 13.8 months (range: < 0.1 to 87.6) in the XTANDI group.

In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the median duration of treatment was 14.3 months (range: < 0.1 to 87.6) in the XTANDI group *[see Clinical Studies (14)]*. In these four trials, the most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension.

AFFIRM: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	51	9.0	44	9.3
Peripheral Edema	15	1.0	13	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26	5.3	24	4.0
Arthralgia	21	2.5	17	1.8
Musculoskeletal Pain	15	1.3	12	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	22	1.1	18	0.3
Vascular Disorders				
Hot Flush	20	0.0	10	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12	0.9	5.5	0.0
Dizziness[3]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[4]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections and Infestations				
Upper Respiratory Tract Infection[5]	11	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[6]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal and Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

1. CTCAE v4
2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

PREVAIL: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	47	3.4	33	2.8
Peripheral Edema	12	0.2	8.2	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	29	2.5	22	3.0
Arthralgia	21	1.6	16	1.1
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.4
Diarrhea	17	0.3	14	0.4
Vascular Disorders				
Hot Flush	18	0.1	7.8	0.0
Hypertension	14	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[3]	11	0.3	7.1	0.0
Headache	11	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[4]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[5]	11	0.6	8.5	0.6
Infections and Infestations				
Upper Respiratory Tract Infection[6]	16	0.0	11	0.0
Lower Respiratory Tract And Lung Infection[7]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal and Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning and Procedural Complications				
Fall	13	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	19	0.3	16	0.7
Investigations				
Weight Decreased	12	0.8	8.5	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0.0	1.4	0.0

1. CTCAE v4

2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes dyspnea, exertional dyspnea, and dyspnea at rest.
6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
7. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

TERRAIN: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

	XTANDI (N = 183)		Bicalutamide (N = 189)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Overall	94	39	94	38
General Disorders				
Asthenic Conditions[2]	32	1.6	23	1.1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	19	2.7	18	1.6
Musculoskeletal Pain[3]	16	1.1	14	0.5
Vascular Disorders				
Hot Flush	15	0	11	0
Hypertension	14	7.1	7.4	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhea	12	0	9.0	1.1
Infections and Infestations				
Upper Respiratory Tract Infection[4]	12	0	6.3	0.5
Investigational				
Weight Loss	11	0.5	7.9	0.5

1. CTCAE v 4
2. Including asthenia and fatigue.
3. Including musculoskeletal pain and pain in extremity.
4. Including nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.

PROSPER: XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm,

mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 4. Adverse Reactions in PROSPER

	XTANDI (N = 930)		Placebo (N = 465)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	9.6	0.2	3.9	0.2
Nervous System Disorders				
Dizziness[2]	12	0.5	5.2	0
Headache	9.1	0.2	4.5	0
Cognitive and Attention Disorders[3]	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	7.7	0
Hypertension	12	4.6	5.2	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	8.6	0
Constipation	9.1	0.2	6.9	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions[4]	40	4.0	20	0.9
Investigations				
Weight Decreased	5.9	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fall	11	1.3	4.1	0.6
Fractures[5]	9.8	2.0	4.9	1.7
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0

1. CTCAE v 4
2. Includes dizziness and vertigo.
3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
4. Includes asthenia and fatigue.
5. Includes all osseous fractures from all sites.

ARCHES: XTANDI versus Placebo in Metastatic CSPC Patients

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analogue concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). The median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo.

Overall, 10 patients (1.7%) receiving XTANDI died from adverse events. The reasons for death in ≥ 2 patients included heart disease (n = 3), sepsis (n = 2) and pulmonary embolism (n = 2). Eight patients (1.4%) receiving placebo died from adverse events. The reasons for death in ≥ 2 patients included heart disease (n = 2) and sudden death (n = 2). Grade 3 or

higher adverse events were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse events as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse events resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common adverse events leading to permanent discontinuation in placebo-treated patients were arthralgia, and fatigue, each in 0.3%.

Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients.

Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	4.9	0.2	2.6	0
Nervous System Disorders				
Cognitive and Memory Impairment[2]	4.5	0.7	2.1	0
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27	0.3	22	0
Hypertension	8.0	3.3	5.6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions[3]	24	1.7	20	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6.3	0.2	4.0	0.2
Injury, Poisoning and Procedural Complications				
Fractures[4]	6.5	1.0	4.2	1.0

1. CTCAE v 4.03.
2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia alzheimer's type, mental impairment, senile dementia and vascular dementia.
3. Includes asthenia and fatigue.
4. Includes Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.

Laboratory Abnormalities

Table 6 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 6. Laboratory Abnormalities

	XTANDI (N = 3173)		Placebo (N = 2282)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hematology				
Neutrophil count decreased	20	0.9	17	0.4
White blood cell decreased	17	0.4	9.8	0.2

	XTANDI (N = 3173)		Placebo (N = 2282)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Chemistry				
Hyperglycemia	83	3.2	75	3.1
Hypermagnesemia	16	0.1	13	0
Hyponatremia	13	1.4	8.6	1.5
Hypercalcemia	6.8	0.1	4.5	0

Hypertension

In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting

Immune System Disorders: hypersensitivity (edema of the face, tongue, lip, or pharynx)

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia

Skin and Subcutaneous Tissue Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XTANDI

Strong CYP2C8 Inhibitors

The coadministration of XTANDI with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of XTANDI. Avoid the coadministration of XTANDI with strong CYP2C8 inhibitors. If the coadministration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Strong CYP3A4 Inducers

The coadministration of XTANDI with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of XTANDI. Avoid the coadministration of XTANDI with strong CYP3A4 inducers. If the coadministration of XTANDI with a strong CYP3A4 inducer cannot be avoided, increase the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

7.2 Effect of XTANDI on Other Drugs

Certain CYP3A4, CYP2C9, or CYP2C19 Substrates

XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of XTANDI decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. Avoid the coadministration of XTANDI with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose *(see Data)*.

Data

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at $\geq$ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

8.2 Lactation

Risk Summary

The safety and efficacy of XTANDI have not been established in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats *(see Data)*.

Data

Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 4081 patients who received XTANDI in seven randomized, controlled clinical trials, 78% were 65 and over, while 35% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

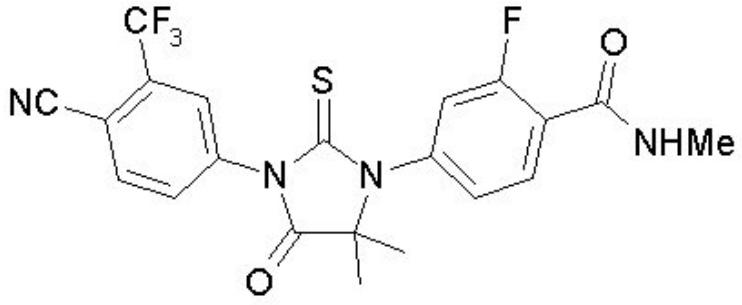
10 OVERDOSAGE

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

11 DESCRIPTION

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

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



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

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

XTANDI is also available as film-coated tablets for oral administration. Each tablet contains 40 mg or 80 mg of enzalutamide. The inactive ingredients are hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate. The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Once daily dosing of 160 mg enzalutamide in addition to ADT reduced PSA levels to undetectable levels (< 0.2 ng/mL) in 68% of patients with mCSPC (ARCHES).

Based on the efficacy results of AFFIRM after once daily dosing of 160 mg enzalutamide, no exposure-response relationship for the efficacy endpoint of overall survival could be identified. In addition, there was no clinically meaningful exposure-response relationship for adverse effects (e.g. fatigue, flushing, headache, or hypertension) within the limited exposure range for 160 mg/day.

Cardiac Electrophysiology

At the recommended dosage, XTANDI does not cause large mean increases (i.e., > 20 msec) in the QT interval.

12.3 Pharmacokinetics

Enzalutamide achieves steady-state by Day 28 and its AUC accumulates approximately 8.3-fold relative to a single dose. At steady-state, the mean (%CV) maximum concentration (C_{max}) for enzalutamide and N-desmethyl enzalutamide are 16.6 μg/mL (23%) and 12.7 μg/mL (30%), respectively, and the mean (%CV) minimum concentrations (C_{min}) are 11.4 μg/mL (26%) and 13.0 μg/mL (30%), respectively.

Enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 (0.2 times the approved recommended dosage) to 360 mg (2.25 times the approved recommended dosage).

Absorption

The median T_{max} is 1 hour (0.5 to 3 hours) following a single 160 mg dose of capsules and 2 hours (0.5 to 6 hours) following a single 160 mg dose of tablets.

Effect of Food

There was no clinically meaningful effect on enzalutamide or N-desmethyl enzalutamide pharmacokinetics following the administration of XTANDI with a high-fat meal (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat).

Distribution

The mean (%CV) volume of distribution after a single oral dose is 110 L (29%).

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

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism.

The mean apparent clearance (CL/F) of enzalutamide after a single dose is 0.56 L/h (0.33 to 1.02 L/h). The mean terminal half-life ($t_{1/2}$) for enzalutamide after a single oral dose is 5.8 days (2.8 to 10.2 days). The mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Metabolism

Enzalutamide is metabolized by CYP2C8 and CYP3A4. CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Carboxylesterase 1 metabolizes N-desmethyl enzalutamide and enzalutamide to the inactive carboxylic acid metabolite.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of enzalutamide were observed based on age (41 to 92 years), race (White, Chinese, and Japanese), body weight (46 kg to 163 kg), mild to moderate renal impairment (CLcr $\geq$ 30 mL/min) and hepatic impairment (Child-Pugh A, B, and C). Severe renal impairment and end stage renal disease (CLcr $<$ 30 mL/min) have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP2C8 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg with gemfibrozil (strong CYP2C8 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}.

Effect of CYP3A4 and CYP2C8 Inducers on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}.

Effect of CYP3A4 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of itraconazole (strong CYP3A4 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}.

Effect of XTANDI on Other Drugs:

The coadministration of XTANDI 160 mg orally once daily with midazolam (a sensitive CYP3A4 substrate) decreased midazolam AUC by 86% and C_{max} by 77%.

Coadministration of XTANDI 160 mg orally once daily with warfarin (a sensitive CYP2C9 substrate) decreased S-warfarin AUC by 56% and C_{max} by 17%.

Coadministration of XTANDI 160 mg orally once daily with omeprazole (a sensitive CYP2C19 substrate) decreased omeprazole AUC by 72% and C_{max} by 62%.

Coadministration of XTANDI 160 mg orally once daily with digoxin (a P-glycoprotein substrate) increased digoxin AUC by 33% and C_{max} by 17%.

No clinically meaningful changes in exposure of pioglitazone (a sensitive CYP2C8 substrate), caffeine (a sensitive CYP1A2 substrate), dextromethorphan (a sensitive CYP2D6 substrate), or rosuvastatin (a BCRP substrate) were observed following coadministration with XTANDI.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Enzalutamide induces CYP2B6 at clinically achievable concentrations.

Transporter Systems: Enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for P-glycoprotein or BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

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

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES

The efficacy of XTANDI in patients with CRPC (N = 4692) or mCSPC (N = 1150) was demonstrated in five randomized, multicenter clinical trials. All patients received concomitant GnRH therapy or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate glucocorticoids.

AFFIRM (NCT00974311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

In AFFIRM, a total of 1199 patients who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a previous history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible *[see Warnings and Precautions (5.1)]*.

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

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis at the time of 520 deaths in patients on the XTANDI arm compared to patients on the placebo arm (Table 7 and Figure 1).

Table 7. Overall Survival of Patients Treated with Either XTANDI or Placebo in AFFIRM

	XTANDI (N = 800)	**Placebo (N = 399)**
Number of Deaths (%)	308 (38.5)	212 (53.1)
Median Survival, months (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[1]	p < 0.0001	
Hazard Ratio (95% CI)[2]	0.63 (0.53, 0.75)	

NR = Not reached.

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

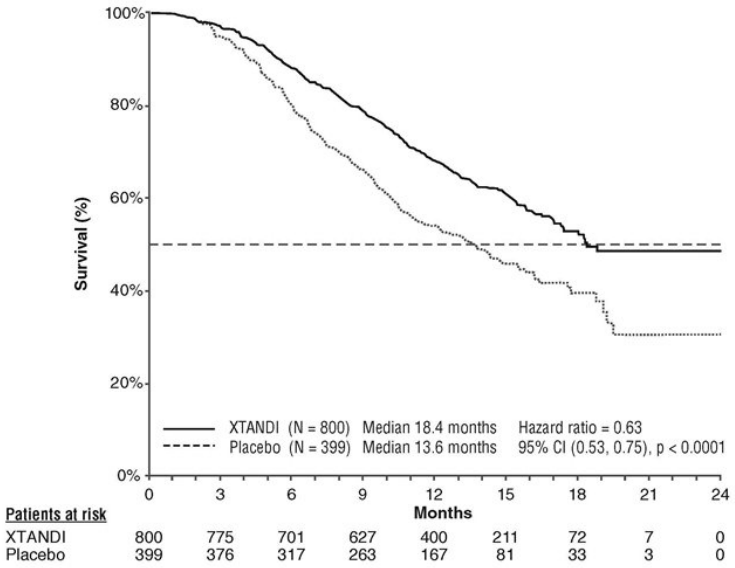


Figure 1. Kaplan-Meier Curves of Overall Survival in AFFIRM

PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

In PREVAIL, 1717 chemotherapy-naïve patients 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 with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), 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 a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 42-93) and the racial distribution was 77% White, 10% Asian, 2% Black and 11% Other. The ECOG performance status score was 0 for 68% of patients, and 1 for 32% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 67% of patients, and 2-3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours at study entry). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Twelve percent of patients had visceral (lung and/or liver) disease involvement. During the study, 27% of patients on the XTANDI arm and 30% of patients on the placebo arm received glucocorticoids for varying reasons.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis, conducted after 540 deaths, in patients treated with XTANDI compared to those treated with placebo (Table 8). Forty percent of XTANDI-treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 8, Figure 2). At the updated analysis, 52% of XTANDI-treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. XTANDI was used as a subsequent therapy in 2% of XTANDI-treated patients and 29% of placebo-treated patients.

Table 8. Overall Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 872)	Placebo (N = 845)
Pre-specified Interim Analysis[1]		
Number of Deaths (%)	241 (28)	299 (35)
Median Survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[2]	p < 0.0001	
Hazard Ratio (95% CI)[3]	0.71 (0.60, 0.84)	
Updated Survival Analysis[4]		
Number of Deaths (%)	368 (42)	416 (49)
Median Survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
Hazard Ratio (95% CI)[3]	0.77 (0.67, 0.88)	

NR = Not reached.

1. The data cut-off date is 16 Sep 2013.
2. P-value is derived from an unstratified log-rank test.
3. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.
4. The data cut-off date is 1 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥ 765.

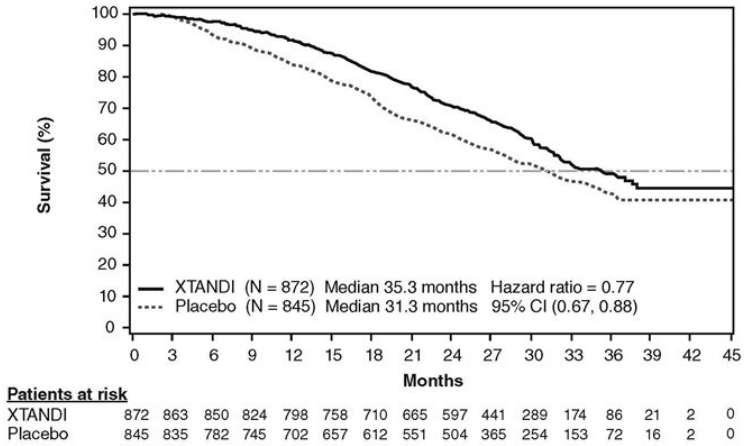


Figure 2. Kaplan-Meier Curves of Overall Survival in PREVAIL

A statistically significant improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with placebo (Table 9, Figure 3).

Table 9. Radiographic Progression-free Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 832)	Placebo (N = 801)
Number of Progression or Deaths (%)	118 (14)	320 (40)
Median rPFS (months) (95% CI)	NR (13.8, NR)	3.7 (3.6, 4.6)
P-value[1]	p < 0.0001	
Hazard Ratio (95% CI)[2]	0.17 (0.14, 0.21)	

NR = Not reached.

Note: As of the cut-off date for the rPFS analysis, 1633 patients had been randomized.

1. P-value is derived from an unstratified log-rank test.
2. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

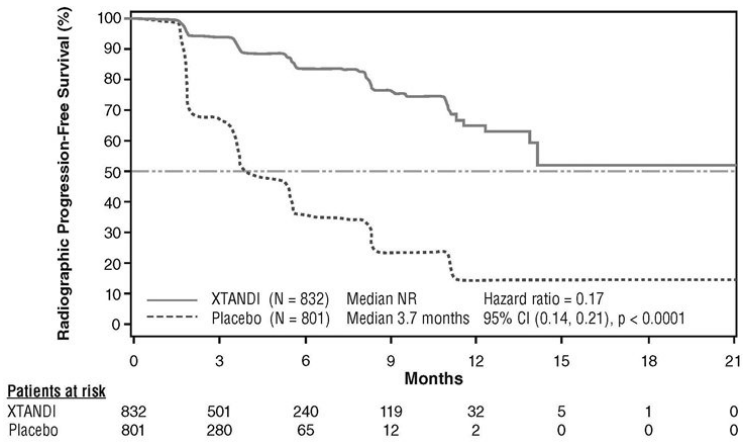


Figure 3. Kaplan-Meier Curves of Radiographic Progression-free Survival in PREVAIL

Time to initiation of cytotoxic chemotherapy was prolonged after XTANDI treatment, with a median of 28.0 months for patients on the XTANDI arm versus a median of 10.8 months for patients on the placebo arm [HR = 0.35 (95% CI: 0.30, 0.40), p < 0.0001].

The median time to first skeletal-related event was 31.1 months for patients on the XTANDI arm versus 31.3 months for patients on the placebo arm [HR = 0.72 (95% CI: 0.61, 0.84), p < 0.0001]. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

TERRAIN (NCT01288911): XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN was conducted in 375 chemotherapy-naïve patients who were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate to severe pain from prostate cancer were excluded. Patients could have received prior bicalutamide, but those whose disease had progressed on prior antiandrogen therapy (e.g., bicalutamide) were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event), the initiation of subsequent antineoplastic agent, unacceptable toxicity, or withdrawal. Radiographic disease progression was assessed by Independent Central Review (ICR) using the Prostate Cancer Clinical Trials Working Group 2 criteria and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. Radiographic progression-free survival (rPFS) was defined as the time from randomization to the first objective evidence of radiographic progression as assessed by ICR or death, whichever occurred first.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 48-96) and the racial distribution was 93% White, 5% Black, 1% Asian and 1% Other. The ECOG performance status score was 0 for 74% of patients and 1 for 26% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 58% of patients, and 2-3 (mildly symptomatic) in 36% of patients as defined by the Brief Pain Inventory Short Form Question 3 (worst pain over past 24 hours at study entry). Ninety-eight percent of patients had objective evidence of disease progression at study entry. Forty-six percent of patients had received prior treatment with bicalutamide while no patients received prior treatment with XTANDI.

An improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with bicalutamide (Table 10, Figure 4).

Table 10. Radiographic Progression-free Survival of Patients in TERRAIN

	XTANDI (N = 184)	Bicalutamide (N = 191)
Number of Progression or Deaths (%)	72 (39)	74 (39)
Median rPFS (months) (95% CI)	19.5 (11.8, NR)	13.4 (8.2, 16.4)
Hazard Ratio (95% CI)[1]	0.60 (0.43, 0.83)	

NR = Not reached.

1. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

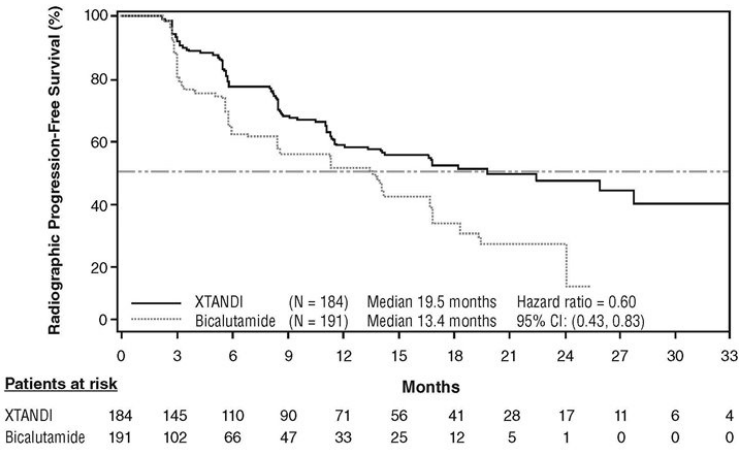


Figure 4. Kaplan-Meier Curves of Radiographic Progression-free Survival in TERRAIN

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC

PROSPER enrolled 1401 patients with non-metastatic CRPC who were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 933) or placebo orally once daily (N = 468). All patients in the PROSPER trial received a gonadotropin-releasing hormone (GnRH) analog or had a prior bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) and the use of bone-targeting agents. Patients were required to have a PSA doubling time ≤ 10 months, PSA ≥ 2 ng/mL, and confirmation of non-metastatic disease by blinded independent central review (BICR). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 74 years (range 50-95) and 23% were 80 years of age or older. The racial distribution was 71% White, 16% Asian, and 2% Black. A majority of patients had a Gleason score of 7 or higher (77%). The median PSADT was 3.7 months. Fifty-four percent (54%) of patients received prior treatment for prostate cancer with either surgery or radiation. Sixty-three percent (63%) of patients received prior treatment with an anti-androgen; 56% of patients received bicalutamide and 11% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The major efficacy outcome of the study was metastasis-free survival (MFS), defined as the time from randomization to whichever of the following occurred first 1) loco-regional and/or distant radiographic progression per BICR or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression. A statistically significant improvement in MFS and OS was demonstrated in patients randomized to receive XTANDI compared with patients randomized to receive placebo. Consistent MFS results were observed when considering only distant radiographic progression events or deaths regardless of the cut-off date. Consistent MFS results were also observed in pre-specified and stratified patient sub-groups of PSADT (< 6 months or ≥ 6 months) and use of a prior bone-targeting agent (yes or no). The efficacy results from PROSPER are summarized in Table 11, Figure 5 and Figure 6.

Table 11. Summary of Efficacy Results in PROSPER (Intent-to-treat Population)

	XTANDI (N = 933)	Placebo (N = 468)
Metastasis-free survival		
Number of Events (%)	219 (23.5)	228 (48.7)
Median, months (95% CI)[1]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard Ratio (95% CI)[2]	0.29 (0.24, 0.35)	
P-value[2]	p < 0.0001	
Overall survival[3]		
Number of Events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[1]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard Ratio (95% CI)[2]	0.73 (0.61, 0.88)	
P-value[2]	p = 0.0011	

NR = Not reached.

1. Based on Kaplan-Meier estimates.
2. Hazard ratio from a Cox regression model (with treatment as the only covariate) and p-value from a log-rank test are stratified by PSA doubling time and prior or concurrent use of a bone targeting agent.
3. The pre-specified final analysis of OS occurred 27 months after the MFS analysis.

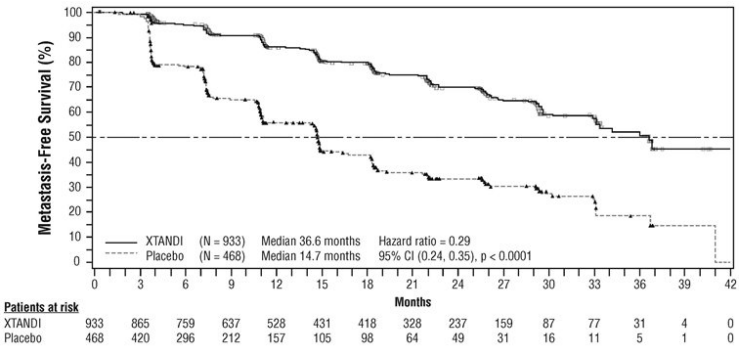


Figure 5. Kaplan-Meier Curves of Metastasis-free Survival in PROSPER

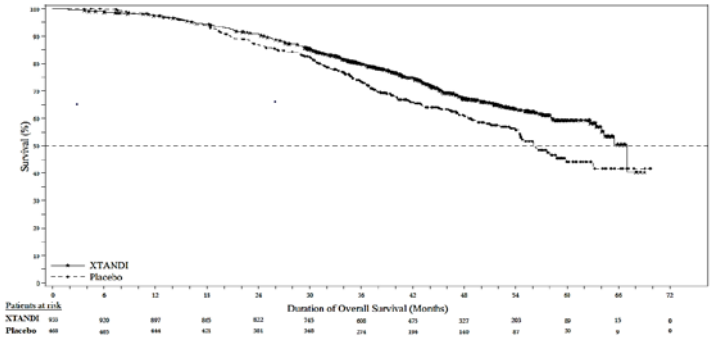


Figure 6. Kaplan-Meier Curves of Overall Survival in PROSPER

The primary efficacy outcome was also supported by a statistically significant delay in time to first use of new antineoplastic therapy (TTA) for patients in the XTANDI arm compared to those in the placebo arm. The median TTA was 39.6 months for patients on XTANDI and was 17.7 months for patients on placebo (HR = 0.21; 95% CI: [0.17, 0.26], p < 0.0001).

ARCHES (NCT02677896): XTANDI versus Placebo in Metastatic CSPC

ARCHES enrolled 1150 patients with mCSPC who were randomized 1:1 to receive XTANDI orally at a dose of 160 mg once daily (N = 574) or placebo orally once daily (N = 576). All patients in the trial received a GnRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Treatment with concurrent docetaxel was not allowed. Patients continued treatment until radiographic disease progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 70 years (range: 42-92) and 30% were 75 years of age or older. The racial distribution was 81% White, 14% Asian, and 1% Black. Sixty-six percent (66%) of patients had a Gleason score of ≥ 8. Thirty-seven percent (37%) of patients had a low volume of disease and 63% of patients had a high volume of disease. Eighty-two percent (82%) of patients had no prior docetaxel treatment; 2% of patients had 1 to 5 cycles of docetaxel and 16% of patients had 6 prior cycles of docetaxel treatment. Twelve percent (12%) of patients received concomitant bone-targeted agents (bisphosphonates or RANKL inhibitors) which included both prostate and non-prostate cancer indications. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 78% of patients and 1 for 22% of patients at study entry.

The major efficacy outcome measure was radiographic progression-free survival (rPFS) based on blinded independent central review (BICR). Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy and OS were additional efficacy endpoints.

XTANDI demonstrated a statistically significant improvement in rPFS and OS compared to placebo. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. Efficacy results for rPFS and OS from ARCHES are summarized in Table 12, Figure 7 and Figure 8.

Table 12. Efficacy Results in ARCHES (Intent-to-Treat Analysis)

	XTANDI (N = 574)	**Placebo (N = 576)**
Radiographic Progression-free Survival[1]		
Number of events (%)	89 (15.5)	198 (34.4)
Radiographic disease progression	77 (13.4)	185 (32.1)
Death within 24 weeks after treatment discontinuation	12 (2.1)	13 (2.3)
Median, months (95% CI)[2]	NR	19.4 (16.6, NR)
Hazard ratio (95% CI)[3]	0.39 (0.30, 0.50)	
P-value[4]	p < 0.0001	
Overall Survival		
Number of events (%)	154 (26.8)	202 (35.1)
Median, months (95% CI)[2]	NR (NR, NR)	NR (49.7, NR)
Hazard ratio (95% CI)[3]	0.66 (0.53, 0.81)	
P-value[4]	p < 0.0001	

NR = Not reached.

1. Based on BICR.
2. Based on Kaplan-Meier estimates.
3. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).
4. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no).

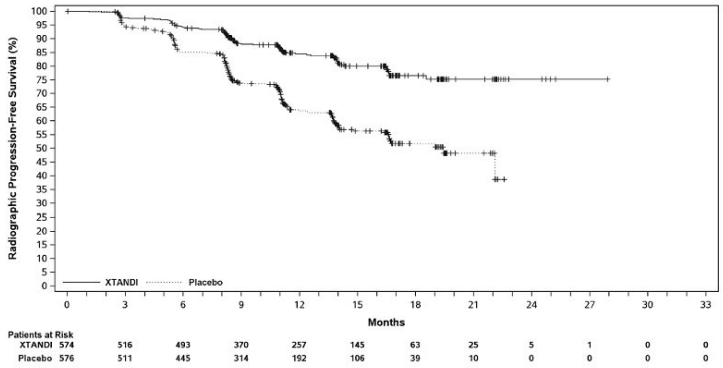


Figure 7. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)

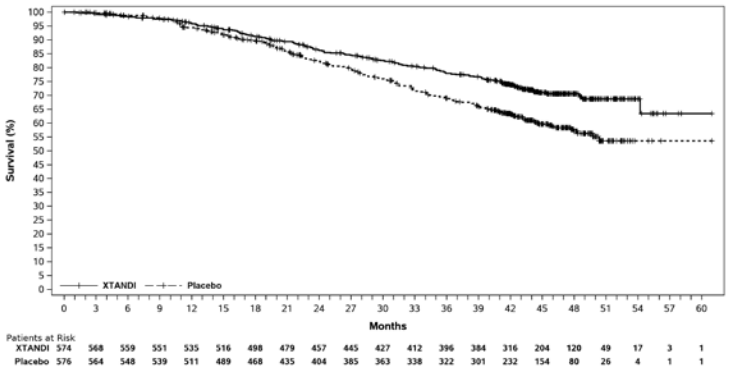


Figure 8. Kaplan-Meier Curves of Overall Survival in ARCHES

A statistically significant improvement was also reported on the XTANDI arm compared to placebo in time to initiation of a new antineoplastic therapy (HR = 0.28 [95% CI: 0.20, 0.40]; $p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 0469-0125-99)

XTANDI (enzalutamide) 40 mg tablets are supplied as yellow, round, film-coated tablets debossed with E 40, and are available in the following package size:

- Bottles of 120 tablets with child resistant closures (NDC 0469-0625-99)

XTANDI (enzalutamide) 80 mg tablets are supplied as yellow, oval, film-coated tablets debossed with E 80, and are available in the following package size:

- Bottles of 60 tablets with child resistant closures (NDC 0469-0725-60)

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

Swallow capsules or tablets whole. Do not chew, dissolve or open the capsules. Do not cut, crush, or chew the tablets.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Seizure

- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure *[see Warnings and Precautions (5.1)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Inform patients to contact their healthcare provider right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision *[see Warnings and Precautions (5.2)]*.

Hypersensitivity

- Inform patients that XTANDI may be associated with hypersensitivity reactions that include swelling of the face, lip, tongue, or throat *[see Warnings and Precautions (5.3)]*. Advise patients who experience these types of symptoms of hypersensitivity to discontinue XTANDI and promptly contact their healthcare provider.

Ischemic Heart Disease

- Inform patients that XTANDI has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur *[see Warnings and Precautions (5.4)]*.

Falls and Fractures

- Inform patients that XTANDI is associated with an increased incidence of dizziness/vertigo, falls, and fractures. Advise patients to report these adverse reactions to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Hypertension

- Inform patients that XTANDI is associated with an increased incidence of hypertension *[see Adverse Reactions (6.1)]*.

Dosing and Administration

- Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule or tablet should be swallowed whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their healthcare provider.
- Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day *[see Dosage and Administration (2.1)]*.

Embryo-Fetal Toxicity

- Inform patients that XTANDI can be harmful to a developing fetus and can cause loss of pregnancy.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions (5.6)]*.

Infertility

- Inform male patients that XTANDI may impair fertility *[see Use in Specific Populations (8.3)]*.

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

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017
337921-XTA-USA

Rx Only

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

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that:

- no longer responds to a hormone therapy or surgical treatment to lower testosterone
  OR
- has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone.

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

Before taking XTANDI, tell your healthcare provider about all your medical conditions, including if you:

- have a history of seizures, brain injury, stroke, or brain tumors.
- have a history of heart disease.
- have high blood pressure.
- have abnormal amounts of fat or cholesterol in your blood (dyslipidemia).
- are pregnant or plan to become pregnant. XTANDI can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- have a partner who is pregnant or may become pregnant.
  - Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with XTANDI and for 3 months after the last dose of XTANDI.
  - Males must use a condom during sex with a pregnant female.
- are breastfeeding or plan to breastfeed. It is not known if XTANDI passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.
Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI 1 time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI each day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?
XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES.
- **Allergic Reactions.** Allergic reactions have happened in people who take XTANDI. Stop taking XTANDI and get medical help right away if you develop swelling of the face, tongue, lip or throat.
- **Heart disease.** Blockage of the arteries in the heart (ischemic heart disease) that can lead to death has happened in some people during treatment with XTANDI. Your healthcare provider will monitor you for signs and symptoms of heart problems during your treatment with XTANDI. Call your healthcare provider or go to the nearest emergency room right away if you get chest pain or discomfort at rest or with activity or shortness of breath during your treatment with XTANDI.
- **Falls and fractures.** XTANDI treatment may increase your risk for falls and fractures. Falls were not caused by loss of consciousness (fainting) or seizures. Your healthcare provider will monitor your risks for falls and fractures during treatment with XTANDI.

Your healthcare provider will stop treatment with XTANDI if you have serious side effects.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- hot flashes
- constipation
- joint pain
- decreased appetite
- diarrhea
- high blood pressure

XTANDI may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of XTANDI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

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

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

General information about the safe and effective use of XTANDI.

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

You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

What are the ingredients in XTANDI?

XTANDI capsules

Active ingredient: enzalutamide

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

XTANDI tablets

Active ingredient: enzalutamide

Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

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

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017

337921-XTA-USA

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Sep 2022

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

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that:

- no longer responds to a hormone therapy or surgical treatment to lower testosterone
  OR
- has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone.

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

Before taking XTANDI, tell your healthcare provider about all your medical conditions, including if you:

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- have a history of heart disease.
- have high blood pressure.
- have abnormal amounts of fat or cholesterol in your blood (dyslipidemia).
- are pregnant or plan to become pregnant. XTANDI can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- have a partner who is pregnant or may become pregnant.
  - Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with XTANDI and for 3 months after the last dose of XTANDI.
  - Males must use a condom during sex with a pregnant female.
- are breastfeeding or plan to breastfeed. It is not known if XTANDI passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.
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- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
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- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES.
- **Allergic Reactions.** Allergic reactions have happened in people who take XTANDI. Stop taking XTANDI and get medical help right away if you develop swelling of the face, tongue, lip or throat.
- **Heart disease.** Blockage of the arteries in the heart (ischemic heart disease) that can lead to death has happened in some people during treatment with XTANDI. Your healthcare provider will monitor you for signs and symptoms of heart problems during your treatment with XTANDI. Call your healthcare provider or go to the nearest emergency room right away if you get chest pain or discomfort at rest or with activity or shortness of breath during your treatment with XTANDI.
- **Falls and fractures.** XTANDI treatment may increase your risk for falls and fractures. Falls were not caused by loss of consciousness (fainting) or seizures. Your healthcare provider will monitor your risks for falls and fractures during treatment with XTANDI.

Your healthcare provider will stop treatment with XTANDI if you have serious side effects.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
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- hot flashes
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- joint pain
- decreased appetite
- diarrhea
- high blood pressure

XTANDI may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

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You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

What are the ingredients in XTANDI?

XTANDI capsules

Active ingredient: enzalutamide

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

XTANDI tablets

Active ingredient: enzalutamide

Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

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

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017

337921-XTA-USA

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Sep 2022

Proposed Package Insert

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

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

---------- INDICATIONS AND USAGE ----------
XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:
- castration-resistant prostate cancer. (1)
- metastatic castration-sensitive prostate cancer. (1)

---------- DOSAGE AND ADMINISTRATION ----------
XTANDI 160 mg administered orally once daily. (2.1)
Patients receiving XTANDI should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.4)

---------- DOSAGE FORMS AND STRENGTHS ----------
- Capsules: 40 mg (3)

---------- CONTRAINDICATIONS ----------
None. (4)

---------- WARNINGS AND PRECAUTIONS ----------
- Seizure occurred in 0.5% of patients receiving XTANDI. In patients with predisposing factors, seizures were reported in 2.2% of patients. Permanently discontinue XTANDI in patients who develop a seizure during treatment. (5.1)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue XTANDI. (5.2)
- Hypersensitivity: Discontinue XTANDI. (5.3)
- Ischemic Heart Disease: Optimize management of cardiovascular risk factors. Discontinue XTANDI for Grade 3-4 events. (5.4)
- Falls and Fractures occurred in 11% and 10% of patients receiving XTANDI, respectively. Evaluate patients for fracture and fall risk, and treat patients with bone-targeted agents according to established guidelines. (5.5)
- Embryo-Fetal Toxicity: XTANDI can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception. (5.6, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Strong CYP2C8 Inhibitors: Avoid strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI. (2.3, 7.1)
- Strong CYP3A4 Inducers: Avoid strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI. (2.3, 7.1)
- Avoid coadministration with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. In cases where active metabolites are formed, there may be increased exposure to the active metabolites. (7.2)

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

Revised: 9/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI® is indicated for the treatment of patients with:

- castration-resistant prostate cancer (CRPC)
- metastatic castration-sensitive prostate cancer (mCSPC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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

2.2 Dosage Modifications for Adverse Reactions

If a patient experiences a ≥ Grade 3 or an intolerable adverse reaction, withhold XTANDI for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted *[see Warnings and Precautions (5.1, 5.2)]*.

2.3 Dosage Modifications for Drug Interactions

Strong CYP2C8 Inhibitors

Avoid the coadministration of strong CYP2C8 inhibitors. If the coadministration of a strong CYP2C8 inhibitor cannot be avoided, reduce the XTANDI dosage to 80 mg once daily. If the coadministration of the strong inhibitor is discontinued, increase the XTANDI dosage to the dosage used prior to initiation of the strong CYP2C8 inhibitor *[see Clinical Pharmacology (12.3)]*.

Strong CYP3A4 Inducers

Avoid the coadministration of strong CYP3A4 inducers. If the coadministration of a strong CYP3A4 inducer cannot be avoided, increase the XTANDI dosage from 160 mg to 240 mg orally once daily. If the coadministration of the strong CYP3A4 inducer is discontinued, decrease the XTANDI dosage to the dosage used prior to initiation of the strong CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

2.4 Important Administration Instructions

Patients receiving XTANDI should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

3 DOSAGE FORMS AND STRENGTHS

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

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Seizure

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 1776 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

5.2 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI *[see Adverse Reactions (6.2)]*. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, 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). Discontinue XTANDI in patients who develop PRES.

5.3 Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in seven randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

5.4 Ischemic Heart Disease

In the combined data of four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on the XTANDI arm compared to 0.7% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

5.5 Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

5.6 Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

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

- Seizure *[see Warnings and Precautions (5.1)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Warnings and Precautions (5.3)]*
- Ischemic Heart Disease *[see Warnings and Precautions (5.4)]*
- Falls and Fractures *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trial Experience

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

The data in WARNINGS and PRECAUTIONS reflect seven randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, Asian PREVAIL (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N = 3509) or mCSPC (N = 572) treated with XTANDI. Patients received XTANDI 160 mg (N = 4081) or placebo orally once daily (N = 2472) or bicalutamide 50 mg orally once daily (N = 387). All patients continued androgen deprivation therapy (ADT). In these seven trials, the median duration of treatment was 13.8 months (range: < 0.1 to 87.6) in the XTANDI group.

In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the median duration of treatment was 14.3 months (range: < 0.1 to 87.6) in the XTANDI group *[see Clinical Studies (14)]*. In these four trials, the most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension.

AFFIRM: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic CRPC who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	51	9.0	44	9.3
Peripheral Edema	15	1.0	13	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26	5.3	24	4.0
Arthralgia	21	2.5	17	1.8
Musculoskeletal Pain	15	1.3	12	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhea	22	1.1	18	0.3
Vascular Disorders				
Hot Flush	20	0.0	10	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12	0.9	5.5	0.0
Dizziness[3]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[4]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections and Infestations				
Upper Respiratory Tract Infection[5]	11	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection[6]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal and Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

1. CTCAE v4
2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

PREVAIL: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	47	3.4	33	2.8
Peripheral Edema	12	0.2	8.2	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	29	2.5	22	3.0
Arthralgia	21	1.6	16	1.1
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.4
Diarrhea	17	0.3	14	0.4
Vascular Disorders				
Hot Flush	18	0.1	7.8	0.0
Hypertension	14	7.2	4.1	2.3
Nervous System Disorders				
Dizziness[3]	11	0.3	7.1	0.0
Headache	11	0.2	7.0	0.4
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[4]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[5]	11	0.6	8.5	0.6
Infections and Infestations				
Upper Respiratory Tract Infection[6]	16	0.0	11	0.0
Lower Respiratory Tract And Lung Infection[7]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal and Urinary Disorders				
Hematuria	8.8	1.3	5.8	1.3
Injury, Poisoning and Procedural Complications				
Fall	13	1.6	5.3	0.7
Non-Pathological Fracture	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	19	0.3	16	0.7
Investigations				
Weight Decreased	12	0.8	8.5	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0.0	1.4	0.0

1. CTCAE v4

2. Includes asthenia and fatigue.
3. Includes dizziness and vertigo.
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
5. Includes dyspnea, exertional dyspnea, and dyspnea at rest.
6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.
7. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection.

TERRAIN: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

	XTANDI (N = 183)		Bicalutamide (N = 189)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Overall	94	39	94	38
General Disorders				
Asthenic Conditions[2]	32	1.6	23	1.1
Musculoskeletal and Connective Tissue Disorders				
Back Pain	19	2.7	18	1.6
Musculoskeletal Pain[3]	16	1.1	14	0.5
Vascular Disorders				
Hot Flush	15	0	11	0
Hypertension	14	7.1	7.4	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhea	12	0	9.0	1.1
Infections and Infestations				
Upper Respiratory Tract Infection[4]	12	0	6.3	0.5
Investigational				
Weight Loss	11	0.5	7.9	0.5

1. CTCAE v 4
2. Including asthenia and fatigue.
3. Including musculoskeletal pain and pain in extremity.
4. Including nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis.

PROSPER: XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomized 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm,

mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 4. Adverse Reactions in PROSPER

	XTANDI (N = 930)		Placebo (N = 465)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	9.6	0.2	3.9	0.2
Nervous System Disorders				
Dizziness[2]	12	0.5	5.2	0
Headache	9.1	0.2	4.5	0
Cognitive and Attention Disorders[3]	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	7.7	0
Hypertension	12	4.6	5.2	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	8.6	0
Constipation	9.1	0.2	6.9	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions[4]	40	4.0	20	0.9
Investigations				
Weight Decreased	5.9	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fall	11	1.3	4.1	0.6
Fractures[5]	9.8	2.0	4.9	1.7
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0

1. CTCAE v 4
2. Includes dizziness and vertigo.
3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.
4. Includes asthenia and fatigue.
5. Includes all osseous fractures from all sites.

ARCHES: XTANDI versus Placebo in Metastatic CSPC Patients

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analogue concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). The median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo.

Overall, 10 patients (1.7%) receiving XTANDI died from adverse events. The reasons for death in ≥ 2 patients included heart disease (n = 3), sepsis (n = 2) and pulmonary embolism (n = 2). Eight patients (1.4%) receiving placebo died from adverse events. The reasons for death in ≥ 2 patients included heart disease (n = 2) and sudden death (n = 2). Grade 3 or

higher adverse events were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse events as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse events resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common adverse events leading to permanent discontinuation in placebo-treated patients were arthralgia, and fatigue, each in 0.3%.

Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients.

Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	4.9	0.2	2.6	0
Nervous System Disorders				
Cognitive and Memory Impairment[2]	4.5	0.7	2.1	0
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27	0.3	22	0
Hypertension	8.0	3.3	5.6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions[3]	24	1.7	20	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6.3	0.2	4.0	0.2
Injury, Poisoning and Procedural Complications				
Fractures[4]	6.5	1.0	4.2	1.0

1. CTCAE v 4.03.
2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia alzheimer's type, mental impairment, senile dementia and vascular dementia.
3. Includes asthenia and fatigue.
4. Includes Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.

Laboratory Abnormalities

Table 6 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 6. Laboratory Abnormalities

	XTANDI (N = 3173)		Placebo (N = 2282)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hematology				
Neutrophil count decreased	20	0.9	17	0.4
White blood cell decreased	17	0.4	9.8	0.2

	XTANDI (N = 3173)		Placebo (N = 2282)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Chemistry				
Hyperglycemia	83	3.2	75	3.1
Hypermagnesemia	16	0.1	13	0
Hyponatremia	13	1.4	8.6	1.5
Hypercalcemia	6.8	0.1	4.5	0

Hypertension

In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting

Immune System Disorders: hypersensitivity (edema of the face, tongue, lip, or pharynx)

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia

Skin and Subcutaneous Tissue Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XTANDI

Strong CYP2C8 Inhibitors

The coadministration of XTANDI with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of XTANDI. Avoid the coadministration of XTANDI with strong CYP2C8 inhibitors. If the coadministration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

Strong CYP3A4 Inducers

The coadministration of XTANDI with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of XTANDI. Avoid the coadministration of XTANDI with strong CYP3A4 inducers. If the coadministration of XTANDI with a strong CYP3A4 inducer cannot be avoided, increase the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

7.2 Effect of XTANDI on Other Drugs

Certain CYP3A4, CYP2C9, or CYP2C19 Substrates

XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of XTANDI decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. Avoid the coadministration of XTANDI with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose *(see Data)*.

Data

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at $\geq$ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

8.2 Lactation

Risk Summary

The safety and efficacy of XTANDI have not been established in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats *(see Data)*.

Data

Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of 4081 patients who received XTANDI in seven randomized, controlled clinical trials, 78% were 65 and over, while 35% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

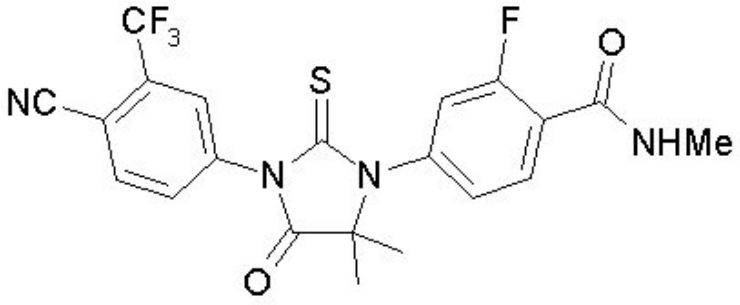
10 OVERDOSAGE

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

11 DESCRIPTION

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

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



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

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

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Once daily dosing of 160 mg enzalutamide in addition to ADT reduced PSA levels to undetectable levels (< 0.2 ng/mL) in 68% of patients with mCSPC (ARCHES).

Based on the efficacy results of AFFIRM after once daily dosing of 160 mg enzalutamide, no exposure-response relationship for the efficacy endpoint of overall survival could be identified. In addition, there was no clinically meaningful exposure-response relationship for adverse effects (e.g. fatigue, flushing, headache, or hypertension) within the limited exposure range for 160 mg/day.

Cardiac Electrophysiology

At the recommended dosage, XTANDI does not cause large mean increases (i.e., > 20 msec) in the QT interval.

12.3 Pharmacokinetics

Enzalutamide achieves steady-state by Day 28 and its AUC accumulates approximately 8.3-fold relative to a single dose. At steady-state, the mean (%CV) maximum concentration (C_{max}) for enzalutamide and N-desmethyl enzalutamide are 16.6 μg/mL (23%) and 12.7 μg/mL (30%), respectively, and the mean (%CV) minimum concentrations (C_{min}) are 11.4 μg/mL (26%) and 13.0 μg/mL (30%), respectively.

Enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 (0.2 times the approved recommended dosage) to 360 mg (2.25 times the approved recommended dosage).

Absorption

The median T_{max} is 1 hour (0.5 to 3 hours) following a single 160 mg dose of capsules and 2 hours (0.5 to 6 hours) following a single 160 mg dose of tablets.

Effect of Food

There was no clinically meaningful effect on enzalutamide or N-desmethyl enzalutamide pharmacokinetics following the administration of XTANDI with a high-fat meal (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat).

Distribution

The mean (%CV) volume of distribution after a single oral dose is 110 L (29%).

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

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism.

The mean apparent clearance (CL/F) of enzalutamide after a single dose is 0.56 L/h (0.33 to 1.02 L/h). The mean terminal half-life ($t_{1/2}$) for enzalutamide after a single oral dose is 5.8 days (2.8 to 10.2 days). The mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Metabolism

Enzalutamide is metabolized by CYP2C8 and CYP3A4. CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Carboxylesterase 1 metabolizes N-desmethyl enzalutamide and enzalutamide to the inactive carboxylic acid metabolite.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of enzalutamide were observed based on age (41 to 92 years), race (White, Chinese, and Japanese), body weight (46 kg to 163 kg), mild to moderate renal impairment (CLcr $\geq$ 30 mL/min) and hepatic impairment (Child-Pugh A, B, and C). Severe renal impairment and end stage renal disease (CLcr $<$ 30 mL/min) have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP2C8 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg with gemfibrozil (strong CYP2C8 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}.

Effect of CYP3A4 and CYP2C8 Inducers on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}.

Effect of CYP3A4 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of itraconazole (strong CYP3A4 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}.

Effect of XTANDI on Other Drugs:

The coadministration of XTANDI 160 mg orally once daily with midazolam (a sensitive CYP3A4 substrate) decreased midazolam AUC by 86% and C_{max} by 77%.

Coadministration of XTANDI 160 mg orally once daily with warfarin (a sensitive CYP2C9 substrate) decreased S-warfarin AUC by 56% and C_{max} by 17%.

Coadministration of XTANDI 160 mg orally once daily with omeprazole (a sensitive CYP2C19 substrate) decreased omeprazole AUC by 72% and C_{max} by 62%.

Coadministration of XTANDI 160 mg orally once daily with digoxin (a P-glycoprotein substrate) increased digoxin AUC by 33% and C_{max} by 17%.

No clinically meaningful changes in exposure of pioglitazone (a sensitive CYP2C8 substrate), caffeine (a sensitive CYP1A2 substrate), dextromethorphan (a sensitive CYP2D6 substrate), or rosuvastatin (a BCRP substrate) were observed following coadministration with XTANDI.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Enzalutamide induces CYP2B6 at clinically achievable concentrations.

Transporter Systems: Enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for P-glycoprotein or BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

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

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES

The efficacy of XTANDI in patients with CRPC (N = 4692) or mCSPC (N = 1150) was demonstrated in five randomized, multicenter clinical trials. All patients received concomitant GnRH therapy or had prior bilateral orchiectomy. Patients were allowed, but not required, to continue or initiate glucocorticoids.

AFFIRM (NCT00974311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

In AFFIRM, a total of 1199 patients who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a previous history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible *[see Warnings and Precautions (5.1)]*.

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

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis at the time of 520 deaths in patients on the XTANDI arm compared to patients on the placebo arm (Table 7 and Figure 1).

Table 7. Overall Survival of Patients Treated with Either XTANDI or Placebo in AFFIRM

	XTANDI (N = 800)	**Placebo (N = 399)**
Number of Deaths (%)	308 (38.5)	212 (53.1)
Median Survival, months (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[1]	p < 0.0001	
Hazard Ratio (95% CI)[2]	0.63 (0.53, 0.75)	

NR = Not reached.

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

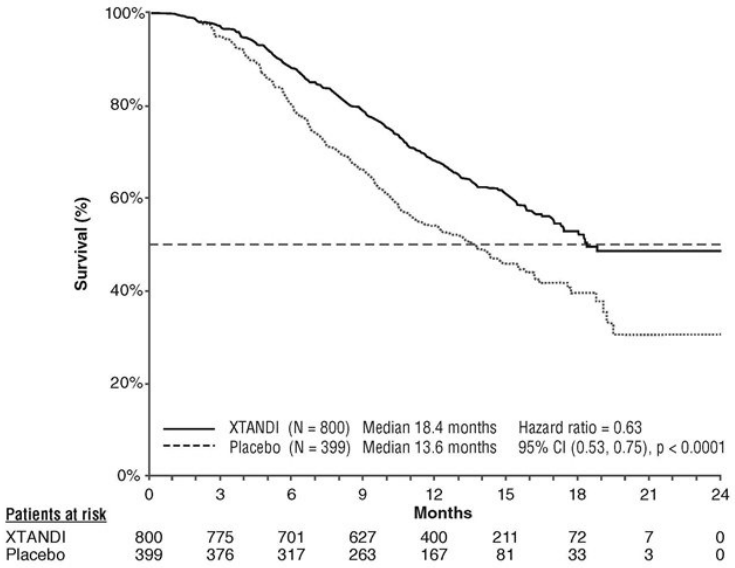


Figure 1. Kaplan-Meier Curves of Overall Survival in AFFIRM

PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

In PREVAIL, 1717 chemotherapy-naïve patients 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 with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), 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 a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 42-93) and the racial distribution was 77% White, 10% Asian, 2% Black and 11% Other. The ECOG performance status score was 0 for 68% of patients, and 1 for 32% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 67% of patients, and 2-3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours at study entry). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Twelve percent of patients had visceral (lung and/or liver) disease involvement. During the study, 27% of patients on the XTANDI arm and 30% of patients on the placebo arm received glucocorticoids for varying reasons.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis, conducted after 540 deaths, in patients treated with XTANDI compared to those treated with placebo (Table 8). Forty percent of XTANDI-treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 8, Figure 2). At the updated analysis, 52% of XTANDI-treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. XTANDI was used as a subsequent therapy in 2% of XTANDI-treated patients and 29% of placebo-treated patients.

Table 8. Overall Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 872)	Placebo (N = 845)
Pre-specified Interim Analysis[1]		
Number of Deaths (%)	241 (28)	299 (35)
Median Survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[2]	p < 0.0001	
Hazard Ratio (95% CI)[3]	0.71 (0.60, 0.84)	
Updated Survival Analysis[4]		
Number of Deaths (%)	368 (42)	416 (49)
Median Survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
Hazard Ratio (95% CI)[3]	0.77 (0.67, 0.88)	

NR = Not reached.

1. The data cut-off date is 16 Sep 2013.
2. P-value is derived from an unstratified log-rank test.
3. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.
4. The data cut-off date is 1 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥ 765.

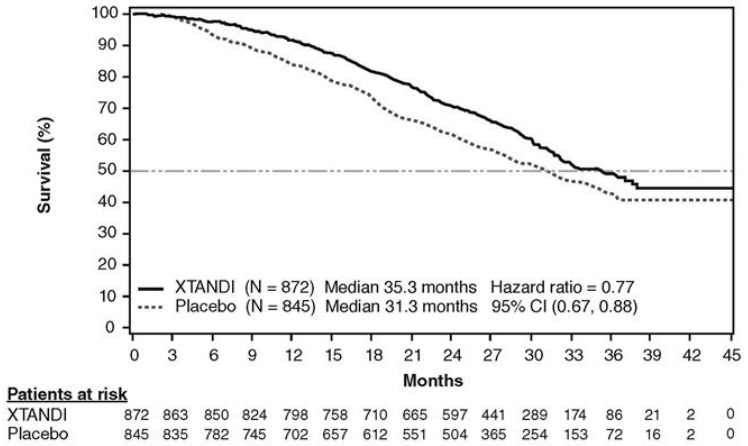


Figure 2. Kaplan-Meier Curves of Overall Survival in PREVAIL

A statistically significant improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with placebo (Table 9, Figure 3).

Table 9. Radiographic Progression-free Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 832)	Placebo (N = 801)
Number of Progression or Deaths (%)	118 (14)	320 (40)
Median rPFS (months) (95% CI)	NR (13.8, NR)	3.7 (3.6, 4.6)
P-value[1]	p < 0.0001	
Hazard Ratio (95% CI)[2]	0.17 (0.14, 0.21)	

NR = Not reached.

Note: As of the cut-off date for the rPFS analysis, 1633 patients had been randomized.

1. P-value is derived from an unstratified log-rank test.
2. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

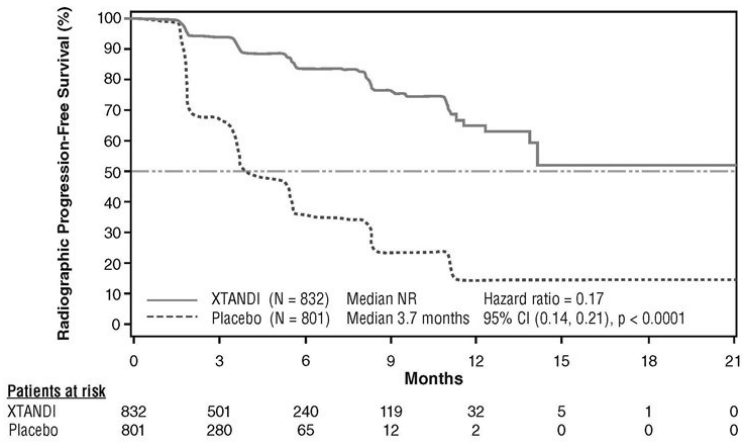


Figure 3. Kaplan-Meier Curves of Radiographic Progression-free Survival in PREVAIL

Time to initiation of cytotoxic chemotherapy was prolonged after XTANDI treatment, with a median of 28.0 months for patients on the XTANDI arm versus a median of 10.8 months for patients on the placebo arm [HR = 0.35 (95% CI: 0.30, 0.40), $p < 0.0001$].

The median time to first skeletal-related event was 31.1 months for patients on the XTANDI arm versus 31.3 months for patients on the placebo arm [HR = 0.72 (95% CI: 0.61, 0.84), $p < 0.0001$]. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

TERRAIN (NCT01288911): XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN was conducted in 375 chemotherapy-naïve patients who were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate to severe pain from prostate cancer were excluded. Patients could have received prior bicalutamide, but those whose disease had progressed on prior antiandrogen therapy (e.g., bicalutamide) were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event), the initiation of subsequent antineoplastic agent, unacceptable toxicity, or withdrawal. Radiographic disease progression was assessed by Independent Central Review (ICR) using the Prostate Cancer Clinical Trials Working Group 2 criteria and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. Radiographic progression-free survival (rPFS) was defined as the time from randomization to the first objective evidence of radiographic progression as assessed by ICR or death, whichever occurred first.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 48-96) and the racial distribution was 93% White, 5% Black, 1% Asian and 1% Other. The ECOG performance status score was 0 for 74% of patients and 1 for 26% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 58% of patients, and 2-3 (mildly symptomatic) in 36% of patients as defined by the Brief Pain Inventory Short Form Question 3 (worst pain over past 24 hours at study entry). Ninety-eight percent of patients had objective evidence of disease progression at study entry. Forty-six percent of patients had received prior treatment with bicalutamide while no patients received prior treatment with XTANDI.

An improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with bicalutamide (Table 10, Figure 4).

Table 10. Radiographic Progression-free Survival of Patients in TERRAIN

	XTANDI (N = 184)	Bicalutamide (N = 191)
Number of Progression or Deaths (%)	72 (39)	74 (39)
Median rPFS (months) (95% CI)	19.5 (11.8, NR)	13.4 (8.2, 16.4)
Hazard Ratio (95% CI)[1]	0.60 (0.43, 0.83)	

NR = Not reached.

1. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

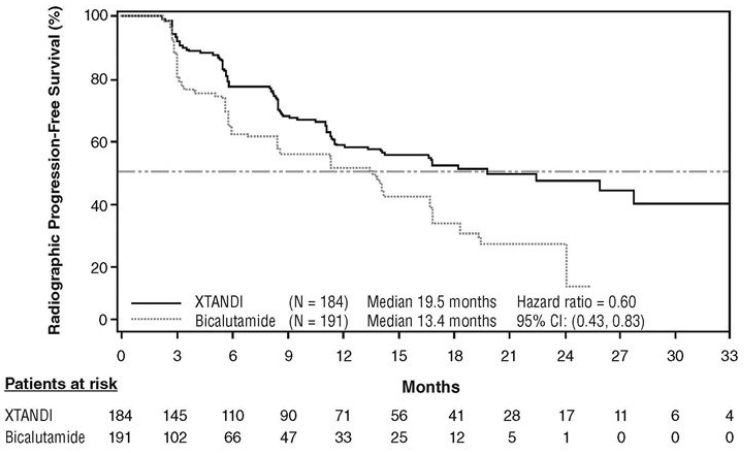


Figure 4. Kaplan-Meier Curves of Radiographic Progression-free Survival in TERRAIN

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC

PROSPER enrolled 1401 patients with non-metastatic CRPC who were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 933) or placebo orally once daily (N = 468). All patients in the PROSPER trial received a gonadotropin-releasing hormone (GnRH) analog or had a prior bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) and the use of bone-targeting agents. Patients were required to have a PSA doubling time ≤ 10 months, PSA ≥ 2 ng/mL, and confirmation of non-metastatic disease by blinded independent central review (BICR). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 74 years (range 50-95) and 23% were 80 years of age or older. The racial distribution was 71% White, 16% Asian, and 2% Black. A majority of patients had a Gleason score of 7 or higher (77%). The median PSADT was 3.7 months. Fifty-four percent (54%) of patients received prior treatment for prostate cancer with either surgery or radiation. Sixty-three percent (63%) of patients received prior treatment with an anti-androgen; 56% of patients received bicalutamide and 11% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The major efficacy outcome of the study was metastasis-free survival (MFS), defined as the time from randomization to whichever of the following occurred first 1) loco-regional and/or distant radiographic progression per BICR or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression. A statistically significant improvement in MFS and OS was demonstrated in patients randomized to receive XTANDI compared with patients randomized to receive placebo. Consistent MFS results were observed when considering only distant radiographic progression events or deaths regardless of the cut-off date. Consistent MFS results were also observed in pre-specified and stratified patient sub-groups of PSADT (< 6 months or ≥ 6 months) and use of a prior bone-targeting agent (yes or no). The efficacy results from PROSPER are summarized in Table 11, Figure 5 and Figure 6.

Table 11. Summary of Efficacy Results in PROSPER (Intent-to-treat Population)

	XTANDI (N = 933)	Placebo (N = 468)
Metastasis-free survival		
Number of Events (%)	219 (23.5)	228 (48.7)
Median, months (95% CI)[1]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard Ratio (95% CI)[2]	0.29 (0.24, 0.35)	
P-value[2]	p < 0.0001	
Overall survival[3]		
Number of Events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[1]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard Ratio (95% CI)[2]	0.73 (0.61, 0.88)	
P-value[2]	p = 0.0011	

NR = Not reached.

1. Based on Kaplan-Meier estimates.
2. Hazard ratio from a Cox regression model (with treatment as the only covariate) and p-value from a log-rank test are stratified by PSA doubling time and prior or concurrent use of a bone targeting agent.
3. The pre-specified final analysis of OS occurred 27 months after the MFS analysis.

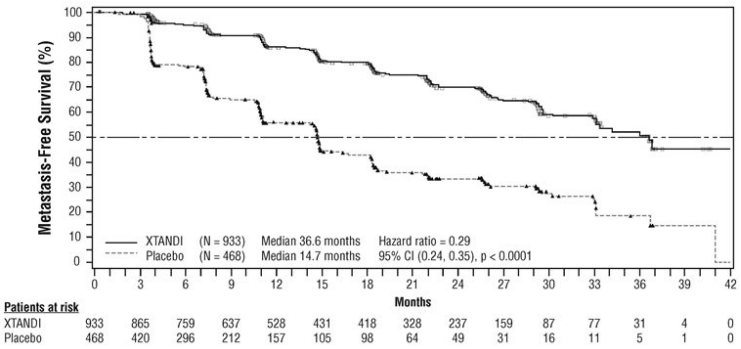


Figure 5. Kaplan-Meier Curves of Metastasis-free Survival in PROSPER

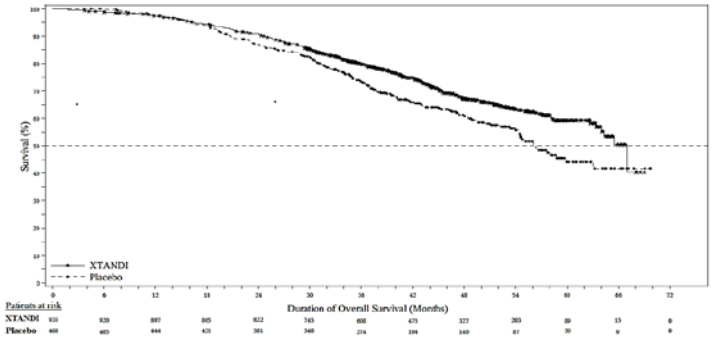


Figure 6. Kaplan-Meier Curves of Overall Survival in PROSPER

The primary efficacy outcome was also supported by a statistically significant delay in time to first use of new antineoplastic therapy (TTA) for patients in the XTANDI arm compared to those in the placebo arm. The median TTA was 39.6 months for patients on XTANDI and was 17.7 months for patients on placebo (HR = 0.21; 95% CI: [0.17, 0.26], p < 0.0001).

ARCHES (NCT02677896): XTANDI versus Placebo in Metastatic CSPC

ARCHES enrolled 1150 patients with mCSPC who were randomized 1:1 to receive XTANDI orally at a dose of 160 mg once daily (N = 574) or placebo orally once daily (N = 576). All patients in the trial received a GnRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles). High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Treatment with concurrent docetaxel was not allowed. Patients continued treatment until radiographic disease progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 70 years (range: 42-92) and 30% were 75 years of age or older. The racial distribution was 81% White, 14% Asian, and 1% Black. Sixty-six percent (66%) of patients had a Gleason score of ≥ 8. Thirty-seven percent (37%) of patients had a low volume of disease and 63% of patients had a high volume of disease. Eighty-two percent (82%) of patients had no prior docetaxel treatment; 2% of patients had 1 to 5 cycles of docetaxel and 16% of patients had 6 prior cycles of docetaxel treatment. Twelve percent (12%) of patients received concomitant bone-targeted agents (bisphosphonates or RANKL inhibitors) which included both prostate and non-prostate cancer indications. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 78% of patients and 1 for 22% of patients at study entry.

The major efficacy outcome measure was radiographic progression-free survival (rPFS) based on blinded independent central review (BICR). Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy and OS were additional efficacy endpoints.

XTANDI demonstrated a statistically significant improvement in rPFS and OS compared to placebo. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. Efficacy results for rPFS and OS from ARCHES are summarized in Table 12, Figure 7 and Figure 8.

Table 12. Efficacy Results in ARCHES (Intent-to-Treat Analysis)

	XTANDI (N = 574)	**Placebo (N = 576)**
Radiographic Progression-free Survival[1]		
Number of events (%)	89 (15.5)	198 (34.4)
Radiographic disease progression	77 (13.4)	185 (32.1)
Death within 24 weeks after treatment discontinuation	12 (2.1)	13 (2.3)
Median, months (95% CI)[2]	NR	19.4 (16.6, NR)
Hazard ratio (95% CI)[3]	0.39 (0.30, 0.50)	
P-value[4]	p < 0.0001	
Overall Survival		
Number of events (%)	154 (26.8)	202 (35.1)
Median, months (95% CI)[2]	NR (NR, NR)	NR (49.7, NR)
Hazard ratio (95% CI)[3]	0.66 (0.53, 0.81)	
P-value[4]	p < 0.0001	

NR = Not reached.

1. Based on BICR.
2. Based on Kaplan-Meier estimates.
3. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).
4. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no).

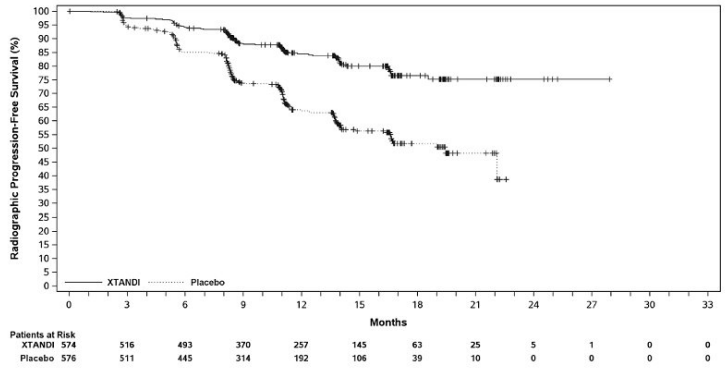


Figure 7. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)

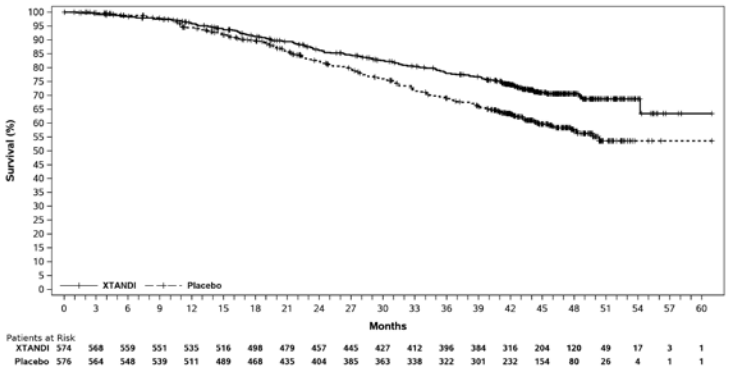


Figure 8. Kaplan-Meier Curves of Overall Survival in ARCHES

A statistically significant improvement was also reported on the XTANDI arm compared to placebo in time to initiation of a new antineoplastic therapy (HR = 0.28 [95% CI: 0.20, 0.40]; $p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 42067-300-12)

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

Swallow capsules whole. Do not chew, dissolve or open the capsules.

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of Catalent Pharma Solutions, LLC
for Astellas Pharma US, Inc.,under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Seizure

- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure *[see Warnings and Precautions (5.1)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Inform patients to contact their healthcare provider right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision *[see Warnings and Precautions (5.2)]*.

Hypersensitivity

- Inform patients that XTANDI may be associated with hypersensitivity reactions that include swelling of the face, lip, tongue, or throat *[see Warnings and Precautions (5.3)]*. Advise patients who experience these types of symptoms of hypersensitivity to discontinue XTANDI and promptly contact their healthcare provider.

Ischemic Heart Disease

- Inform patients that XTANDI has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur *[see Warnings and Precautions (5.4)]*.

Falls and Fractures

- Inform patients that XTANDI is associated with an increased incidence of dizziness/vertigo, falls, and fractures. Advise patients to report these adverse reactions to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Hypertension

- Inform patients that XTANDI is associated with an increased incidence of hypertension *[see Adverse Reactions (6.1)]*.

Dosing and Administration

- Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
  The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their healthcare provider.
- Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day *[see Dosage and Administration (2.1)]*.

Embryo-Fetal Toxicity

- Inform patients that XTANDI can be harmful to a developing fetus and can cause loss of pregnancy.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions (5.6)]*.

Infertility

- Inform male patients that XTANDI may impair fertility *[see Use in Specific Populations (8.3)]*.

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

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017
337921-XTA-USA

Rx Only

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

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that:

- no longer responds to a hormone therapy or surgical treatment to lower testosterone
  OR
- has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone.

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

Before taking XTANDI, tell your healthcare provider about all your medical conditions, including if you:

- have a history of seizures, brain injury, stroke, or brain tumors.
- have a history of heart disease.
- have high blood pressure.
- have abnormal amounts of fat or cholesterol in your blood (dyslipidemia).
- are pregnant or plan to become pregnant. XTANDI can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- have a partner who is pregnant or may become pregnant.
  - Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with XTANDI and for 3 months after the last dose of XTANDI.
  - Males must use a condom during sex with a pregnant female.
- are breastfeeding or plan to breastfeed. It is not known if XTANDI passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works. You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.
Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI 1 time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules. The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI each day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES.
- **Allergic Reactions.** Allergic reactions have happened in people who take XTANDI. Stop taking XTANDI and get medical help right away if you develop swelling of the face, tongue, lip or throat.
- **Heart disease.** Blockage of the arteries in the heart (ischemic heart disease) that can lead to death has happened in some people during treatment with XTANDI. Your healthcare provider will monitor you for signs and symptoms of heart problems during your treatment with XTANDI. Call your healthcare provider or go to the nearest emergency room right away if you get chest pain or discomfort at rest or with activity or shortness of breath during your treatment with XTANDI.
- **Falls and fractures.** XTANDI treatment may increase your risk for falls and fractures. Falls were not caused by loss of consciousness (fainting) or seizures. Your healthcare provider will monitor your risks for falls and fractures during treatment with XTANDI.

Your healthcare provider will stop treatment with XTANDI if you have serious side effects.

The most common side effects of XTANDI include:

- weakness or feeling more tired than usual
- back pain
- hot flashes
- constipation
- joint pain
- decreased appetite
- diarrhea
- high blood pressure

XTANDI may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of XTANDI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

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

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

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

General information about the safe and effective use of XTANDI.

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

You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

What are the ingredients in XTANDI?

XTANDI capsules

Active ingredient: enzalutamide

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

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

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

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017

337921-XTA-USA

XTANDI is a registered trademark of Astellas Pharma Inc.

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

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Sep 2022

Annotated Label Comparisons

PI Comparisons FDA VS. FLCPDIP
Differences
Updated information Adverse Reactions Contact
How Supplied/Storage and Handling added SIP804 language
Patient Information added SIP804 language
Listed new NDC #
Added Importation language & Importer name & address
Listed only drug strength purchased for program

FDA

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

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

---------- DOSAGE FORMS AND STRENGTHS ----------

- Capsules: 40 mg (3)
- Tablets: 40 mg, 80 mg (3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. (6.1)

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

2.1 Recommended Dosage

The recommended dosage of XTANDI is 160 mg administered orally once daily with or without food *[see Clinical Pharmacology (12.3)]*. Swallow capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.

3 DOSAGE FORMS AND STRENGTHS

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

XTANDI 40 mg tablets are yellow, round, film-coated and debossed with E 40.

XTANDI 80 mg tablets are yellow, oval, film-coated and debossed with E 80.

FLSIP 804

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

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

---------- DOSAGE FORMS AND STRENGTHS ----------

- Capsules: 40 mg (3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients are asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact LifeScience Logistics at 1-855-738-6171 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

2.1 Recommended Dosage

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

3 DOSAGE FORMS AND STRENGTHS

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

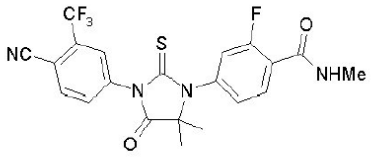
The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

FDA

11 DESCRIPTION

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

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



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

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

XTANDI is also available as film-coated tablets for oral administration. Each tablet contains 40 mg or 80 mg of enzalutamide. The inactive ingredients are hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate. The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 0469-0125-99)

XTANDI (enzalutamide) 40 mg tablets are supplied as yellow, round, film-coated tablets debossed with E 40, and are available in the following package size:

- Bottles of 120 tablets with child resistant closures (NDC 0469-0625-99)

XTANDI (enzalutamide) 80 mg tablets are supplied as yellow, oval, film-coated tablets debossed with E 80, and are available in the following package size:

- Bottles of 60 tablets with child resistant closures (NDC 0469-0725-60)

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

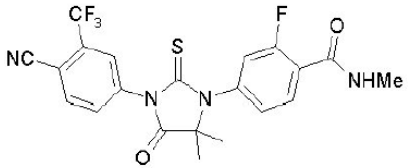
Swallow capsules or tablets whole. Do not chew, dissolve or open the capsules. Do not cut, crush, or chew the tablets.

FLSIP 804

11 DESCRIPTION

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

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



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

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

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 42067-300-12)

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

Swallow capsules whole. Do not chew, dissolve or open the capsules.

The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

This drug was imported from Canada without the authorization of Catalent Pharma Solutions, LLC for Astellas Pharma US, Inc.,under the State of Florida Section 804 Importation Program.
Imported by: LifeScience Logistics, 310 N. Galloway Rd., Lakeland, FL 33815

FDA

Dosing and Administration

- Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule or tablet should be swallowed whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their healthcare provider.
- Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day *[see Dosage and Administration (2.1)]*.

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

How should I take XTANDI?
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI 1 time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI each day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the ingredients in XTANDI?
XTANDI capsules
Active ingredient: enzalutamide
Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide.
XTANDI tablets
Active ingredient: enzalutamide
Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.
The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

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

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10017

337921-XTA-USA

XTANDI is a registered trademark of Astellas Pharma Inc.
For more information go to www.Xtandi.com or call 1-800-727-7003.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Sep 2022

FLSIP 804

Dosing and Administration

- Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
  The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their healthcare provider.
- Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day *[see Dosage and Administration (2.1)]*.

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

How should I take XTANDI?
- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI 1 time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow XTANDI capsules whole. Do not chew, dissolve, or open the capsules. The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI each day.

If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

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The 40 mg and 80 mg tablets are not being imported by LifeScience Logistics.

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

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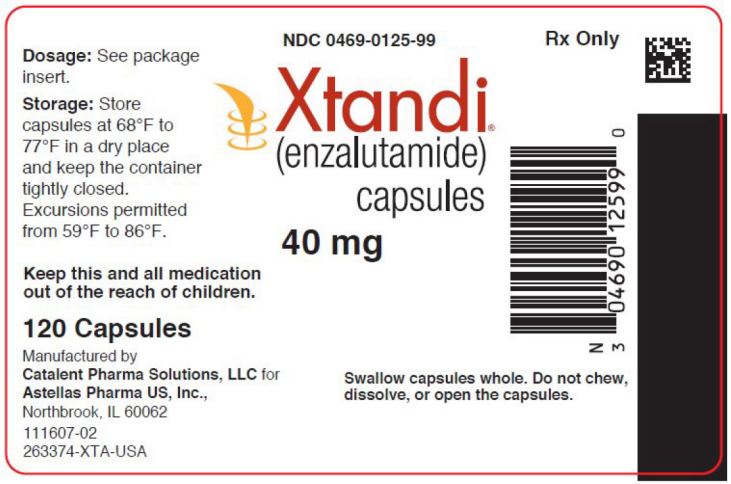
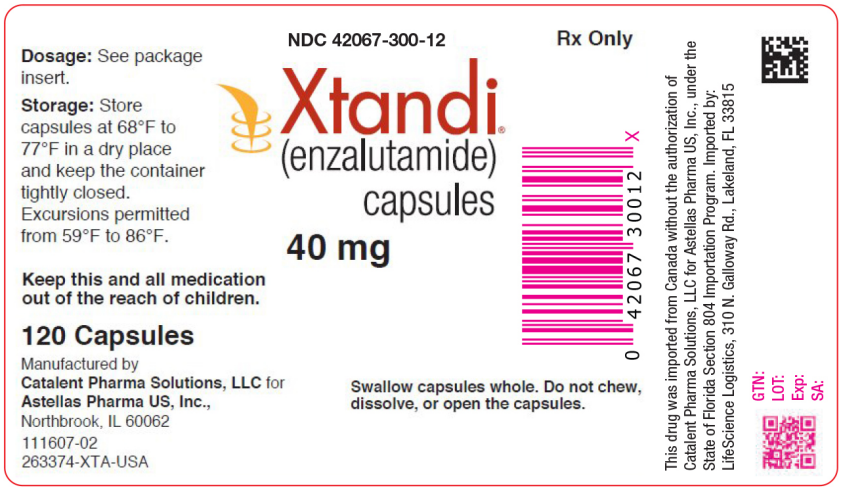
Proposed Package Label



Label Comparisons FDA VS. FLCPDIP
Differences
NDC
GTN
Bar Codes FPO with Associated NDCs
SIP804 Importation Language
Label SIZE due to production process & adding SIP804 language
Importer Name & Address
Brand logos FPO low resolution. Native art files requested upon SIP804 approval.



Comparisons
FDA to FLSIP

Recent FDA Approved Label	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	Applicant Holder Address	US Active Ingredients	Date Labeling Prepared for FLSIP	FLSIP Proprietary Name	FLSIP Generic Name	FLSIP Strength	LSL NDC	Relabeler Name	Applicant Holder Name	Applicant Holder Address	Active Ingredients	FDA Comments
May-23	Xtandi	Enzalutamide	40 mg	0469-0125-99	213674	ASTELLAS Pharma US, Inc.	Northbrook, IL 60062	Enzalutamide	Aug-23	Xtandi	Enzalutamide	40 mg	42067-300-12	LifeScience Logistics, LLC	ASTELLAS Pharma US, Inc.	Northbrook, IL 60062	Enzalutamide	none

Comparisons
Canada to FDA

Active Ingredient	Canadian Submission Number	Canadian Proprietary Name	Canadian Generic Name	DIN	Date Labeling Approved	Company Name	Address	Canadian Strength	Dosage Form	# of active Ingred.	Canadian Ingredients	US Proprietary Name	US Generic Name	US Strength	NDC	NDA or ANDA	Applicant Holder Name	US Active Ingredients	Comments for FDA
Enzalutamide	263476	Xtandi	Enzalutamide	02407329	March-23	Arteillar Pharma Canada Inc	650 675 Cochrane Dr Wort Tauer Markham Ontario Canada L3R0B8	40 mg	capsule, oral	1	Enzalutamide	Xtandi	Enzalutamide	40 mg	0469-0125-99	213674	ASTELLAS	Enzalutamide	n/a

Canadian Monograph

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrXtandi®

Enzalutamide capsules

40 mg

Anti-androgen (L02BB04)

Astellas Pharma Canada, Inc.

Markham, ON

L3R 0B8

Date of Initial Authorization:
May 28, 2013

Date of Revision:
MAR 14, 2023

Submission Control Number: 263476

RECENT MAJOR LABEL CHANGES

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Xtandi® (enzalutamide capsules) is indicated for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

Xtandi® (enzalutamide capsules) is indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC).

Xtandi has not been studied in patients with NM-CRPC at low risk of developing metastatic disease (see **Clinical Trials**). The benefit and risk profile in these patients is unknown.

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.

1.1 Pediatrics (< 18 years of age)

The safety and efficacy of enzalutamide has not been established for patients less than 18 years of age.

1.2 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**).

2 CONTRAINDICATIONS

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

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).

4 DOSAGE AND ADMINISTRATION

4.1 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.

4.2 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 (120 mg or 80 mg), if warranted.

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

Patients with hepatic impairment: No dose adjustment is necessary for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C. An increased drug half-life, however, has been observed in patients with severe hepatic impairment; see **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 **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 **CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

4.4 Administration

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

Do not chew, dissolve or open the capsules.

4.5 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.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
Oral	Each capsule contains 40 mg of enzalutamide and the inactive ingredients	butylhydroxyanisole, butylhydroxytoluene and caprylocaproyl macrogolglycerides.

Xtandi (enzalutamide capsules) is supplied as a liquid-filled, white-to-off-white, oblong, soft gelatin capsule imprinted in black ink with “ENZ”.

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.

7 WARNINGS AND PRECAUTIONS

General

Xtandi contains sorbitol (see **DOSAGE FORMS, STRENGTHS, 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

Daily oral dosing of rats for two years with enzalutamide at 10, 30, and 100 mg/kg/day increased the incidence of neoplastic findings that were considered related to the primary pharmacology of enzalutamide. Enzalutamide did not show carcinogenic potential (absence of neoplastic findings) in a 6-month study in transgenic rasH2 mice and 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 **NON-CLINICAL TOXICOLOGY, Carcinogenesis and Genotoxicity**).

Cardiovascular

Ischemic Heart Disease: In randomized placebo-controlled phase 3 studies, higher incidences of ischemic heart disease were reported in patients treated with Xtandi (see **ADVERSE REACTIONS, Cardiovascular**). Ischemic events led to death in 0.4% of patients on the Xtandi arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue Xtandi for Grade 3-4 ischemic heart disease.

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 > 170 mm Hg and/or diastolic blood pressure > 105 mm Hg) were excluded from the Phase 3 clinical trials (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 **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 *Torsades 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 Phase 3 clinical trials (see **CLINICAL PHARMACOLOGY, Blood Pressure**). In the Phase 3 trials, the overall incidence of any hypertension-related events was higher in the Xtandi group compared to the placebo group (12.0% vs. 5.0%). 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.

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed.

Hepatic/Biliary/Pancreatic

Mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C) had no significant effects on the pharmacokinetics of enzalutamide (see **CLINICAL PHARMACOLOGY, Special Populations and Conditions**). Patients with baseline severe hepatic impairment (Child-Pugh C) were excluded from both the AFFIRM and PREVAIL trials.

Immune

Hypersensitivity reactions manifested by symptoms including, but not limited to face, tongue, lip and pharyngeal oedema have been observed with enzalutamide (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**). Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue Xtandi and promptly seek medical care. Permanently discontinue Xtandi for serious hypersensitivity reactions.

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.

Patients with cardiac history should be assessed for active cardiac disease before starting therapy with Xtandi.

Patients with NM-CRPC should be monitored for disease progression radiographically at the discretion of their treating physician in addition to serum Prostate Specific Antigen (PSA), as 104 out of 219 patients treated with Xtandi in the PROSPER trial reported radiographic progression without PSA progression.

Musculoskeletal

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

Falls and Fall-related Injuries: In Phase 3 clinical trials, adverse events of falls were reported in 10.0% Xtandi-treated patients and 3.8% placebo-treated patients. A fall of Grade 3 or greater was reported in 1.1% of patients in the Xtandi-treated group and in 0.4% of patients in the placebo group. Non-pathological fractures associated with falls were reported in 10.2% of patients treated with Xtandi and in 4.4% of patients in the placebo arms. Additionally, in AFFIRM and PREVAIL, 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: In the Phase 3 clinical studies (AFFIRM, PREVAIL, PROSPER and ARCHES) (see **CLINICAL TRIALS**), seizure occurred in 0.9% (7/800), 0.1% (1/871) and 0.3% (3/930), 0.3% (2/572) respectively in patients treated with a daily dose of Xtandi 160 mg. Three patients treated with placebo in the Phase 3 clinical studies experienced a seizure 0.1% (3/2282). Patients experiencing a seizure were discontinued from therapy, and all seizures resolved.

In a single-arm Phase 4 trial to assess incidence of seizure in patients with predisposing factors for seizure, 8 of 366 (2.2%) patients treated with Xtandi (160 mg per day) experienced a seizure. The median duration of treatment was 9.3 months. Use of enzalutamide has been associated with seizure. Xtandi should be used with caution in patients with history of seizures or other predisposing risk factors for seizures. Permanently discontinue Xtandi in patients who develop a seizure during treatment.

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 the Phase 3 clinical trials. The AFFIRM trial excluded the use of concomitant medications that may lower the seizure threshold, whereas the PREVAIL and PROSPER trials 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 **NON-CLINICAL TOXICOLOGY, 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.

Mental Impairment Disorders: In the 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. 1.7%).

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.

Renal

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 **CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Reproductive Health: Female and Male Potential

- **Sexual Function/Reproduction**

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 **NON-CLINICAL TOXICOLOGY**). Considering the pharmacological consequences of androgen receptor inhibition, an effect on male fertility cannot be excluded in humans.

7.1 Special Populations

7.1.1 Pregnant Women

Animal studies demonstrated that enzalutamide can cause fetal harm when administered during pregnancy (see **NON-CLINICAL 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**; **NON-CLINICAL 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.

7.1.2 Breast-feeding

Xtandi is not indicated for use in women and is contraindicated in women who are lactating. It is unknown whether enzalutamide or its metabolites are present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk (see **NON-CLINICAL TOXICOLOGY, Nonclinical Pharmacokinetics**).

7.1.3 Pediatrics (< 18 years of age)

The safety and efficacy of Xtandi has not been established for patients less than 18 years of age.

7.1.4 Geriatrics (≥ 65 years of age)

Of the 3173 patients in Phase 3 trials who received Xtandi, 79% of patients were 65 years and over and 36% 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.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse reactions in this section were defined as treatment-emergent adverse events if the incidences in the Xtandi group were greater than those in the placebo group.

In the Phase 3 clinical trials, the most common adverse reactions (≥ 10%) seen with Xtandi were arthralgia, back pain, constipation, decreased appetite, dizziness/vertigo, diarrhea, fatigue/asthenia, hot flush, and hypertension. The rate of serious adverse events was 32.3% for Xtandi and 25.7% for placebo. Patients treated with Xtandi also had a higher incidence of Grade 3 or higher serious adverse events (of any causality) than patients treated with placebo (28.2% vs 22.2%). Adverse events as the primary reason that led to treatment discontinuation were reported for 8.4% of Xtandi-treated patients and 6.2% of placebo-treated patients.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

ARCHES Study: Xtandi versus Placebo in Metastatic Castration-Sensitive Prostate Cancer Patients

The ARCHES trial enrolled 1150 patients with metastatic castration-sensitive prostate cancer (mCSPC). Patients received either Xtandi at a dose of 160 mg once daily (N = 572) or placebo (N = 574). The median duration of treatment at the time of analysis was 12.8 months with Xtandi and 11.6 months with placebo.

Table 2 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the Xtandi arm than the placebo arm.

Table 2 – Adverse Reactions[a] in ARCHES

System Organ Class/ MedDRA Preferred Term, MedDRA v21.0	Xtandi N = 572		Placebo N = 574	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
General disorders and administration site conditions				
Asthenic Conditions[b]	138 (24.1%)	10 (1.7%)	112 (19.5%)	9 (1.6%)
Vascular disorders				
Hot Flush	155 (27.1%)	2 (0.3%)	128 (22.3%)	0
Hypertension	46 (8.0%)	19 (3.3%)	32 (5.6%)	10 (1.7%)
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain	36 (6.3%)	1 (0.2%)	23 (4.0%)	1 (0.2%)
Injury, Poisoning and Procedural Complications				
Fractures[c]	37 (6.5%)	6 (1.0%)	24 (4.2%)	6 (1.0%)

a. 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.
b. Includes asthenia and fatigue.
c. Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.

PROSPER Study: Non-Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy

The PROSPER trial enrolled 1401 patients with non-metastatic CRPC. Patients were randomized 2:1 and received either Xtandi at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months with Xtandi and 11.1 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 (e.g. prednisone).

Grade 3 or higher adverse reactions were reported among 31.4% of Xtandi-treated patients and 23.4% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of Xtandi-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse reaction leading to treatment discontinuation was fatigue, which occurred in 1.6% of the Xtandi-treated patients compared to none for the placebo-treated patients.

Overall, 32 patients (3.4%) receiving Xtandi died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1).

Table 3 shows adverse reactions occurring at an incidence of ≥ 2% in patients randomized to Xtandi in the PROSPER study.

Table 3 – Adverse Reactions[a] Occurring at an Incidence of ≥ 2% in Patients Randomized to Xtandi in the PROSPER Study

	Xtandi N = 930		Placebo N = 465	
System Organ Class/ MedDRA Preferred Term, MedDRA v16.1	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General disorders and administration site conditions				
Asthenic Conditions[b]	372 (40.0%)	37 (4.0%)	91 (19.6%)	4 (0.9%)
Vascular disorders				
Hot Flush	121 (13.0%)	1 (0.1%)	36 (7.7%)	0 (0.0%)
Hypertension	111 (11.9%)	43 (4.6%)	24 (5.2%)	10 (2.2%)
Nervous system disorders				
Dizziness[c]	108 (11.6%)	5 (0.5%)	24 (5.2%)	0 (0.0%)
Headache	85 (9.1%)	2 (0.2%)	21 (4.5%)	0 (0.0%)
Mental Impairment Disorders[d]	43 (4.6%)	1 (0.1%)	7 (1.5%)	0 (0.0%)
Investigations				
Weight decreased	55 (5.9%)	2 (0.2%)	7 (1.5%)	0 (0.0%)
Injury, poisoning and procedural complications				
Fall	106 (11.4%)	12 (1.3%)	19 (4.1%)	3 (0.6%)
Metabolism and nutrition disorders				
Decreased appetite	89 (9.6%)	2 (0.2%)	18 (3.9%)	1 (0.2%)
Gastrointestinal disorders				
Constipation	85 (9.1%)	2 (0.2%)	32 (6.9%)	2 (0.4%)

a. 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.
b. Includes asthenia and fatigue.
c. Includes dizziness and vertigo.
d. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention.

PREVAIL Study: Chemotherapy-naïve 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 4 shows adverse reactions occurring at an incidence of ≥ 2% in patients randomized to Xtandi in the PREVAIL study.

Table 4 – Adverse Reactions[a] 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[b]	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[c]	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

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 (%)
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%)

a. 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.
b. Includes asthenia and fatigue.
c. 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 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 5 shows adverse reactions occurring at an incidence of ≥ 2% in patients randomized to Xtandi in the AFFIRM study.

Table 5 – Adverse Reactions[a] Occurring at an Incidence of ≥ 2% in Patients Randomized to Xtandi in the AFFIRM Study

System Organ Class/ MedDRA Preferred Term, MedDRA v11.0	Xtandi N = 800		Placebo N = 399	
	All Grades (%)	Grade 3[b] (%)	All Grades (%)	Grade 3[b] (%)
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

	Xtandi N = 800		Placebo N = 399	
System Organ Class/ MedDRA Preferred Term, MedDRA v11.0	**All Grades (%)**	**Grade 3[b] (%)**	**All Grades (%)**	**Grade 3[b] (%)**
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%)

a. 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.
b. Grade 4 and 5 events were not observed.

Cardiovascular

In randomized placebo-controlled phase 3 studies (AFFIRM, PREVAIL, PROSPER and ARCHES), ischemic heart disease was observed in 2.9 % of patients treated with enzalutamide compared to 1.3% of patients treated with placebo. Grade 3-5 ischemic events occurred in 1.8% of patients on the Xtandi arm compared to 0.7% on the placebo arm. Cardiac failure was observed in 1.7% of patients treated with enzalutamide compared to 0.8% treated with placebo. The following preferred terms were observed in at least 2 patients: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, and arteriosclerosis coronary artery.

8.3 Less Common Clinical Trial Adverse Reactions

In the 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 (including hallucination, hallucination tactile and hallucination visual)
Infections and Infestations: Infections and sepsis with fatal outcome
Nervous System Disorders: Seizure
Gastrointestinal Disorders: Gastrointestinal bleeding

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 6 below shows laboratory values of interest from the Phase 3 placebo-controlled trials (AFFIRM, PREVAIL, PROSPER and ARCHES).

Table 6 – Selected Laboratory Abnormalities in Patients Receiving Xtandi in Phase 3 Studies (AFFIRM, PREVAIL, PROSPER, ARCHES)

Parameter	Xtandi N = 3173		Placebo N = 2282	
	All Grades N (%)	Grade 3-4 N (%)	All Grades N (%)	Grade 3-4 N (%)
Hematologic Parameters				
Neutrophils (low)	13 (0.4%)	5 (0.2%)	6 (0.3%)	3 (0.1%)
Chemistry Parameters				
AST	32 (1.0%)	7 (0.2%)	30 (1.3%)	4 (0.2%)
ALT	31 (1.0%)	9 (0.3%)	33 (1.4%)	6 (0.3%)
Bilirubin	5 (0.2%)	2 (0.1%)	3 (0.1%)	0
ALT: alanine aminotransferase; AST: aspartate aminotransferase.				

8.5 Post-Market Adverse Reactions

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

Gastrointestinal disorders: diarrhea, nausea, vomiting
Immune disorders: face, tongue, lip, or pharyngeal oedema
Nervous system disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia
Skin and subcutaneous tissue disorders: rash, severe skin reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

9 DRUG INTERACTIONS

9.2 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 **CLINICAL PHARMACOLOGY**).

9.4 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**).

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.

CYP2C8 and CYP3A4 inducers: In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of Xtandi was administered alone or after multiple oral doses of rifampin 600 mg once daily (moderate CYP2C8 and strong CYP3A4 inducer). Rifampin decreased the $AUC_{0\text{-}inf}$ of enzalutamide plus M2 by 37% with no effect on C_{max}. No dose adjustment is necessary when Xtandi is co-administered with inducers of CYP2C8 or CYP3A4. However, the concomitant use of strong CYP3A4 inducers with enzalutamide is not recommended.

Potential for Xtandi to affect exposures to other medicinal products

Substrates of CYP3A4, CYP2B6, CYP2C9, CYP2C19, UGT1A1 or UGT1A4: 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)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anti-epileptics (e.g. carbamazepine, clonazepam, phenobarbital, phenytoin, primidone, valproic acid)
- Antigout agents (e.g. colchicine)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, dabigatran etexilate, warfarin, clopidogrel)
- Benzodiazepines (e.g. diazepam, midazolam)
- Beta blockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine*, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- 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)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

*not marketed in Canada

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

Substrates of CYP1A2 or CYP2D6: In a drug-drug interaction study in patients with prostate cancer (N = 14), a single oral dose of 100 mg caffeine (CYP1A2 substrate) and 30 mg dextromethorphan (CYP2D6 substrate) was administered before and concomitantly with enzalutamide (after at least 49 days of dosing at 160 mg daily). Xtandi did not cause clinically meaningful changes in exposure to the CYP1A2 or CYP2D6 substrates.

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 a drug-drug interaction study in patients with prostate cancer, a single oral dose of the P-gp substrate digoxin was administered before and concomitantly with enzalutamide (after at least 55 days of dosing at 160 mg daily). At steady-state, enzalutamide caused a small increase in the exposure to digoxin (17% and 33% increase in C_{max} and AUC_{inf}, respectively). 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.

Substrates of MRP2: In vitro, enzalutamide and its major metabolites are inhibitors of multidrug resistance-associated protein 2 (MRP2). The effects of enzalutamide on MRP2 substrates have not been evaluated *in vivo*. Xtandi may increase the plasma concentrations of co-administered medicinal products that are MRP2 substrates. Thus, oral medicinal products with a narrow therapeutic range that are 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.

Substrates of BCRP: No dose adjustment is necessary when a breast cancer resistant protein (BCRP) substrate is co-administered with Xtandi. In a drug-drug interaction study in patients with prostate cancer, a single oral dose of the BCRP substrate rosuvastatin was administered before and concomitantly with enzalutamide (after at least 55 days of dosing at 160 mg daily). At steady-state, enzalutamide did not cause a clinically meaningful change in exposure to the BCRP substrate rosuvastatin.

Substrates of OAT1 or OCT2: In vitro data indicate that enzalutamide and its major metabolites do not inhibit organic anion transporter 1 (OAT1) or OCT2 at clinically relevant concentrations.

Substrates of OAT3, OCT1, OATP1B1 or OATP1B3: 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 *Torsades de pointes* (see **CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

9.5 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.

9.6 Drug-Herb Interactions

Products that contain St. John's wort might induce CYP3A, which may lead to decreased plasma concentrations of enzalutamide.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 tumour 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).

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

Table 7 – 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)[a]	$t_{1/2}$ (h)	CL/F (L/h)	V/F (L)
MDV3100-05	160 mg[b] 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[b] 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[c] 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[c] 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[b] (fasted) [matched subjects]	Subjects with MHI (n = 8)	3.68 ± 2.09 (57%)	303 ± 126 (41%)	196 ± 185 (94%)	0.604 ± 0.229 (38%)	142 ± 105 (74%)
		Subjects 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%)

a. AUC_{inf} and AUC_{τ} (steady-state) were calculated in single dose and multiple dose studies, respectively;
b. Administered as 4 x 40 mg soft gelatin capsules;
c. 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 7). 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.

In addition, *in vitro* data show that M2 is metabolized to M1 by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the M1. Carboxylesterase 2 does not appear to play a role in the metabolism of either enzalutamide or M2.

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-$AUC_{0\text{-}inf}$.

Elimination

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 2601 patients in the Phase 3 clinical trials who received Xtandi, 2070 patients (80%) were 65 years and over and 958 patients (37%) were 75 years and over. Based on the population pharmacokinetic analysis for age, no dose adjustment is necessary in the elderly.

- **Sex**

The pharmacokinetics of enzalutamide has not been evaluated in women.

- **Genetic Polymorphism**

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

- **Ethnic Origin**

The majority of patients in the randomized clinical trials were Caucasian (~> 74%). 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.

In a separate study, subjects with severe hepatic impairment (Child-Pugh C; n = 8) and matched healthy control subjects with normal hepatic function (n = 8) were evaluated. Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide plus M2 in subjects with severe hepatic impairment increased by 1.04-fold and decreased by 0.58-fold, respectively, compared to healthy control subjects. An increased drug half-life was observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. Patients with baseline severe hepatic impairment (Child-Pugh C) were excluded from both the AFFIRM and PREVAIL trials.
Overall, the results indicate that no dose adjustment is necessary for patients with baseline mild, moderate or severe hepatic impairment.

- **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.

11 STORAGE, STABILITY AND DISPOSAL

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

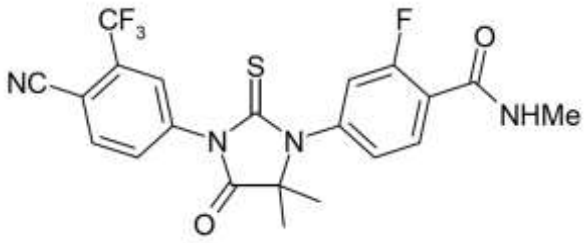
12 SPECIAL HANDLING INSTRUCTIONS

Xtandi should not be handled by persons other than the patient or his caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, enzalutamide may harm a developing fetus. Women who are or may become pregnant should not handle damaged or opened Xtandi capsules without protection (e.g. gloves). Do not dissolve or open the capsules.

PART II: SCIENTIFIC INFORMATION

13 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.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of Xtandi (enzalutamide) was established in four randomized placebo-controlled multicentre Phase 3 clinical studies (PREVAIL, AFFIRM, PROSPER, ARCHES) of patients with progressive non-metastatic (PROSPER) or metastatic prostate cancer (AFFIRM, PREVAIL) who had failed androgen

deprivation therapy [Gonadotropin-releasing hormone (GnRH) analogue or after bilateral orchiectomy] and patients with metastatic castration-sensitive prostate cancer (ARCHES). All patients continued on a GnRH analogue or had prior bilateral orchiectomy.

Metastatic Castration-Sensitive Prostate Cancer (ARCHES)

The ARCHES study enrolled 1150 patients with mCSPC randomized 1:1 to receive treatment orally once daily with Xtandi 160 mg (N = 574) or placebo (N = 576). All patients in the trial received a GnRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles). Treatment with concurrent docetaxel was not allowed. Patients were required to have confirmation of metastatic prostate cancer by positive bone scan or metastatic lesions on CT or MRI scan. Patients continued treatment until radiographic disease progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

Radiographic progression-free survival (rPFS) was the primary endpoint defined as the time from randomization to the first objective evidence of radiographic disease progression or death (any cause from time of randomization through 24 weeks after study drug discontinuation), whichever occurred first. Key secondary efficacy endpoints assessed in the study were time to PSA progression, time to start of new antineoplastic therapy, PSA undetectable rate (decline to < 0.2 µg/L), objective response rate (RECIST 1.1) based on independent review, time to deterioration of urinary symptoms, and overall survival.

The demographic and baseline disease characteristics were balanced between the two treatment arms (Table 8).

Table 8 – ARCHES Key Demographics and Baseline Disease Characteristics (ITT Population)

Baseline Characteristic	**Xtandi** (N = 574)	**Placebo** (N = 576)
Age category (years), n (%)		
< 65	148 (25.8)	152 (26.4)
65 to < 75	256 (44.6%)	255 (44.3%)
≥ 75	170 (29.6%)	169 (29.3%)
Age (years)		
Mean (SD)	69.5 (8.0%)	69.5 (5.4%)
Median (minimum, maximum)	70.0 (46, 92)	70.0 (42, 92)
Race, n (%)		
White	466 (81.2%)	460 (79.9%)
Black or African American	8 (1.4%)	8 (1.9%)
Asian	75 (13.1%)	80 (13.9%)
Other	2 (0.3%)	3 (0.5%)

Baseline Characteristic	Xtandi (N = 574)	Placebo (N = 576)
Missing	23 (4.0%)	25 (4.3%)
Ethnicity, n (%)		
Hispanic or Latino	46 (8.0%)	37 (6.4%)
Not Hispanic or Latino	504 (87.8%)	514 (89.2%)
Missing	24 (4.2%)	25 (4.3%)
Weight (kg)		
N	573	575
Mean (SD)	81.25 (16.17)	81.26 (16.22)
Median (minimum, maximum)	80.00 (42.7, 163.0)	80.00 (39.1, 157.5)
Body mass index (kg/m^2)		
N	567	570
Mean (SD)	27.20 (4.44)	27.21 (4.61)
Median (minimum, maximum)	26.65 (16.7, 45.2)	26.91 (16.4, 48.8)
ECOG performance status at study entry, n (%)		
0	448 (78.0)	443 (76.9)
1	125 (21.8)	133 (23.1)
Baseline serum PSA[a] (ng/mL)		
N	572	574
Mean (SD)	75.37 (356.36)	104.78 (834.48)
Median (minimum, maximum)	5.36 (0.0, 4823.5)	5.07 (0.0, 19000.0)
Total Gleason score at initial diagnosis, n (%)		
< 8	171 (29.8)	187 (32.5)
≥ 8	386 (67.2)	373 (64.8)
Volume of disease[b], n (%)		
Low	220 (38.3)	203 (35.2)
High	354 (61.7)	373 (64.8)
Prior docetaxel therapy[b], n (%)		
None	471 (82.1)	474 (82.3)
1 to 5 cycles	14 (2.4)	11 (1.9)
6 cycles	89 (15.5)	91 (15.8)
Previous use of ADT, n (%)		
None	39 (6.8)	61 (10.6)

Baseline Characteristic	Xtandi (N = 574)	Placebo (N = 576)
≤ 3 months	414 (72.1)	394 (68.4)
> 3 months	121 (21.1)	120 (20.8)
Unknown[c]	0	1 (0.2)

All patients who were randomized in the study (ITT population).
The analysis data cut-off date was 14 Oct 2018.
ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; ICR: independent central review; ITT: intent-to-treat; PSA: prostate-specific antigen.

a. PSA levels of 0 were observed, which could have been due to prior treatment with docetaxel and/or use of ADT within 3 months of study start. One patient receiving placebo plus ADT had a baseline PSA level of > 19000 ng/mL, which impacted the calculation of mean baseline PSA for this group.
b. Volume of disease and prior docetaxel therapy were stratification factors at randomization. High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone.
c. The patient had ADT; however, the duration of ADT use was not known.

Non-Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy (PROSPER)

The PROSPER study enrolled 1401 patients with non-metastatic CRPC who continued on androgen deprivation therapy (ADT; defined as GnRH analogue or prior bilateral orchiectomy). Patients were randomized 2:1 to receive either Xtandi at a dose of 160 mg once daily (N = 933) or placebo (N = 468).

Patients discontinued treatment for radiographic disease progression confirmed by blinded independent central review (BICR), unacceptable toxicity, initiation of new treatment, or withdrawal. PSA results were blinded and were not used for treatment discontinuation.

Patients were required to have a PSA doubling time ≤ 10 months (considered to be at high risk of developing metastatic disease), PSA ≥ 2 ng/mL, and confirmation of non-metastatic disease by (BICR) using conventional scans.

Metastasis-free survival (MFS) was the primary endpoint defined as the time from randomization to loco-regional and/or distant radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first. Radiographic progression for bone disease was defined as the appearance of 1 or more metastatic lesions on the bone assessed by whole-body radionuclide bone scan, while assessment of soft tissue disease was performed by CT or MRI performed every 16 weeks (earlier if progression was clinically suspected). Radiographic progression for soft tissue disease was defined by RECIST 1.1.

Key secondary endpoints assessed in the study were time to PSA progression time to first use of new antineoplastic therapy and overall survival. PSA progression was defined according to PCWG2 guidelines; time to PSA progression was defined as the time from randomization to the date of first PSA value demonstrating progression, which was subsequently confirmed.

The demographic and baseline characteristics were balanced between the two treatment arms (Table 9). The median age at randomization was 74 years in the Xtandi arm and 73 years in the placebo arm.

Fifty-four percent (54%) of patients received prior treatment for prostate cancer with either surgery or radiation. Sixty-three percent (63%) of patients received prior treatment with an anti-androgen; 56% of patients received bicalutamide and 11% of patients received flutamide.

Table 9 – PROSPER Key Demographics and Baseline Disease Characteristics (ITT Population)

Baseline Characteristic	**Xtandi (N = 933)**	**Placebo (N = 468)**
Age (years)		
Mean (SD)	73.8 (7.83)	72.9 (7.63)
Min, Max	50, 95	53, 92
Race		
White	671 (71.9%)	320 (68.4%)
Other, multiple, or unknown	99 (10.6%)	50 (10.7%)
Asian	142 (15.2%)	88 (18.8%)
Black	21 (2.3%)	10 (2.1%)
Time from initial diagnosis to randomization, months		
Mean (SD)	99.1 (57.27)	94.1 (56.73)
Median (minimum, maximum)	90.4 (2.2, 381.8)	86.8 (2.2, 275.7)
Total Gleason Score at initial diagnosis, n (%)		
Low (2 to 4)	21 (2.3%)	12 (2.6%)
Medium (5 to 7)	491 (52.6%)	230 (49.1%)
High (8 to 10)	381 (40.8%)	207 (44.2%)
Unknown or missing	40 (4.3%)	19 (4.1%)
Baseline use of BTA		
No	828 (88.7%)	420 (89.7%)
Yes	105 (11.3%)	48 (10.3%)
1	103 (11.0%)	47 (10.0%)
2	2 (0.2%)	1 (0.2%)
PSA Doubling Time Category n (%)		
< 6 months	715 (76.6%)	361 (77.1%)
$\geq$ 6 months	217 (23.3%)	107 (22.9%)
Missing	1 (0.1%)	0
Baseline serum PSA (ng/mL)		
N	933	468
Mean (SD)	22.2 (46.14)	22.1 (41.08)
Median	11.1	10.2

Baseline Characteristic	Xtandi (N = 933)	Placebo (N = 468)
Min, max	0.8, 1071.1	0.2, 467.5
Baseline ECOG performance status		
0	747 (80.1%)	382 (81.6%)
1	185 (19.8%)	85 (18.2%)
> 1	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	1 (0.2%)

ITT: Intent to Treat; BTA: Bone targeting agents; PSA: Prostate Specific Antigen. Patients with soft tissue pelvic disease were eligible if lesions do not qualify as target lesions (e.g., lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is < 15 mm).

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

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 antineoplastic therapy during the first 12 weeks of therapy and was discouraged as a criterion to start a new systemic antineoplastic 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 10). 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 10 – 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%)
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%)

Baseline Characteristic	Xtandi (N = 872)	Placebo (N = 845)
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 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.

mCRPC Patients with Prior Docetaxel Treatment (AFFIRM)

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 11).

Table 11 – 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%)

	Xtandi (160 mg/day) N = 800	Placebo N = 399
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[a]		
< 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[b]	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

a. 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.
b. Bone and or soft tissue.

14.2 Study Results

Metastatic Castration-Sensitive Prostate Cancer (ARCHES)

Xtandi demonstrated a statistically significant 61% reduction in the risk of an rPFS event compared to placebo [HR = 0.39 (95% CI: 0.30, 0.50); p < 0.0001]. The median time to an rPFS event was not reached in the enzalutamide plus ADT arm and was 19.0 months (95% CI: 16.6, 22.2) in the placebo plus ADT arm (Table 12, Figure 1).

The rPFS results were further supported by clinically meaningful and statistically significant improvements in overall survival in addition to 4 other key secondary endpoints. At the pre-specified final analysis for overall survival, conducted when 356 deaths were observed, a statistically significant 34% reduction in the risk of death was demonstrated in the group randomised to receive enzalutamide compared with the group randomised to receive placebo [HR = 0.66, (95% CI: 0.53; 0.81), p < 0.0001]. The median time for overall survival was not reached in either treatment group (see Figure 3). Assessments of Patient Reported Outcomes data showed that patients enrolled in ARCHES had a high baseline level of Quality of Life, with the Xtandi plus ADT arm showing no statistically significant difference versus the placebo plus ADT arm over time.

Table 12 – Summary of efficacy results in the ARCHES study (intent-to-treat analysis)

	Xtandi (N = 574)	**Placebo (N = 576)**
Primary Endpoint		
Radiographic Progression-free Survival[a]		
Number of Events (%)	91 (15.9)	201 (34.9)
Median, months (95% CI)[b]	NR (NR, NR)	19.0 (16.6, 22.2)
Hazard Ratio (95% CI)[c]	0.39 (0.30, 0.50)	
P-value[c]	p < 0.0001	
Key Secondary Efficacy Endpoints		
Overall Survival[d]		
Number of Events (%)	154 (26.8)	202 (35.1)
Median, months (95% CI)[b]	NR (NR, NR)	NR (49.7, NR)
Hazard Ratio (95% CI)[c]	0.66 (0.53, 0.81)	
P-value[c]	p < 0.0001	
Time to PSA progression[a,e]		
Number of Events (%)	45 (7.8)	189 (32.8)
Median, months (95% CI)[b]	NR (NR, NR)	NR (16.6, NR)
Hazard Ratio (95% CI)[c]	0.19 (0.13, 0.26)	
P-value[c]	p < 0.0001	
Time to first use of new antineoplastic therapy[a]		
Number of Events (%)	46 (8.0)	133 (23.1)
Median, months (95% CI)[b]	30.2 (NR, NR)[f]	NR (21.1, NR)
Hazard Ratio (95% CI)[c]	0.28 (0.20, 0.40)	
P-value[c]	p < 0.0001	

	Xtandi (N = 574)	Placebo (N = 576)
PSA Undetectable Rates[a]		
Patients with PSA detectable at baseline	511	506
Patients with PSA undetectable at baseline	63	70
Undetectable PSA during treatment period	348/511 (68.1)	89/506 (17.6)
95% CI for rate	(63.9, 72.1)	(14.4, 21.2)
Difference in rate (95% CI)[c]	50.5% (45.3, 55.7)	
P-value	p < 0.0001	
Objective Response Rate[a]		
Patients with PSA detectable at baseline	177	182
Number of Events (%)	147 (83.1)	116 (63.7)
95% CI for rate	(76.7, 88.3)	(56.3, 70.7)
Difference in rate (95% CI)[c]	19.3% (10.4, 28.2)	
P-value	p < 0.0001	
Time to deterioration in urinary symptoms[a,g]		
Events, n (%)	184 (32.06)	201 (34.90)
Kaplan-Meier median (95% CI)[b] (months)	NR (19.35, NR)	16.8 (14.06, NR)
Hazard Ratio (95% CI)[c]	0.88 (0.72, 1.08)	
P-value[c]	p = 0.2162	
Other Secondary Efficacy Endpoints		
Time to first SSE (Symptomatic Skeletal Event)[a,h]		
Patients with SSE events, n (%)	31 (5.40)	56 (9.72)
Median, months (95% CI)[b]	NR (NR, NR)	NR (NR, NR)
Hazard Ratio (95% CI)[c]	0.52 (0.33, 0.80)	
P-value (nominal)[c]	p = 0.0026	
Time to castration resistance[a,i]		
Events, n (%)	90 (15.68)	257 (44.62)
Kaplan-Meier median (95% CI)[b] (months)	NR (NR, NR)	13.9 (11.40, 17.18)
Hazard Ratio (95% CI)[c]	0.28 (0.22, 0.36)	
P-value (nominal)[c]	p < 0.0001	
Time to deterioration of quality of life[a,j]		
Events, n (%)	280 (48.78)	274 (47.57)

	Xtandi (N = 574)	Placebo (N = 576)
Kaplan-Meier median (95% CI)[b] (months)	11.3 (11.04, 13.83)	11.1 (8.48, 13.83)
Hazard Ratio (95% CI)[c]	0.96 (0.81, 1.14)	
P-value (nominal)[c]	p = 0.6548	
Time to pain progression[a,k]		
Events, n (%)	324 (56.45)	329 (57.12)
Kaplan-Meier median (95% CI)[b] (months)	8.3 (8.25, 10.91)	8.3 (5.65, 8.38)
Hazard Ratio (95% CI)[c]	0.92 (0.78, 1.07)	
P-value (nominal)[c]	0.2715	

NR = Not reached.

a. Based upon a pre-specified analysis with data cut-off date of 14 October 2018
b. Calculated using Brookmeyer and Crowley method.
c. Stratified by volume of disease (low vs high) and prior docetaxel use (yes or no).
d. Based upon a pre-specified final analysis with data cut-off date of 28 May 2021.
e. PSA progression was defined as a ≥ 25% increase and an absolute increase of ≥ 2 µg/L above nadir.
f. While an estimate of the median time was provided for the enzalutamide plus ADT arm (30.2 months), this estimate was not reliable as it resulted from an event observed in the only remaining patient at risk at approximately 30 months, leading to a vertical drop at the end of the Kaplan-Meier curve.
g. A deterioration in urinary symptoms was defined as an increase in the QLQ-PR25 modified urinary symptoms score by ≥ 50% of the standard deviation observed in the QLQ-PR25 modified urinary symptoms score at baseline. In patients with a deterioration in urinary symptoms, the time to deterioration in urinary symptoms was defined as the time interval between randomization and the first deterioration in urinary symptoms. In patients without a deterioration in urinary symptoms the time to deterioration in urinary symptoms was censored on the date that the last urinary symptoms QLQ-PR25 score was calculable.
h. An SSE was defined as radiation or surgery to bone, clinically apparent pathological bone fracture or spinal cord compression whichever occurred first. Time to the first SSE was the time from randomization to the occurrence of the first SSE. In patients with no SSE, time to SSE was censored on the last visit date or the date of randomization, whichever occurred last.
i. A castration resistance event was defined as an occurrence of radiographic disease progression by ICR, PSA progression or an SSE with castration levels of testosterone (< 50 ng/mL), whichever occurred first. In patients with a castration resistance event, the time to castration resistance was the time from randomization to the first castration resistance event. In patients with no documented castration resistance event, the time to castration resistance was censored on the latest date from the following: the last radiologic assessment, the last PSA sample taken prior to the start of any new prostate cancer therapy and prior to 2 or more consecutive missed PSA assessments or the last visit date performed.
j. Deterioration of QoL was defined as a decrease from baseline of a least 10 points in the FACT-P total score. In patients with a deterioration in QoL, the time to deterioration in QoL was the time interval from the date of randomization to the first date a decline from baseline of 10 points or more in the FACT-P total score was recorded. In patients without FACT-P progression, the time to deterioration of QoL was censored on the date that the last FACT-P total score was calculable.
k. Pain progression was defined as an increase of ≥ 30% from baseline in the average BPI-SF item scores. In patients with pain progression, time to pain progression was defined as the time from randomization to the first pain progression event. In patients with no pain progression event, time to pain progression was censored on the last visit date where BPI-SF data were collected.

Figure 1: Kaplan-Meier Curve of rPFS in ARCHES study (Intent-to-Treat Analysis)

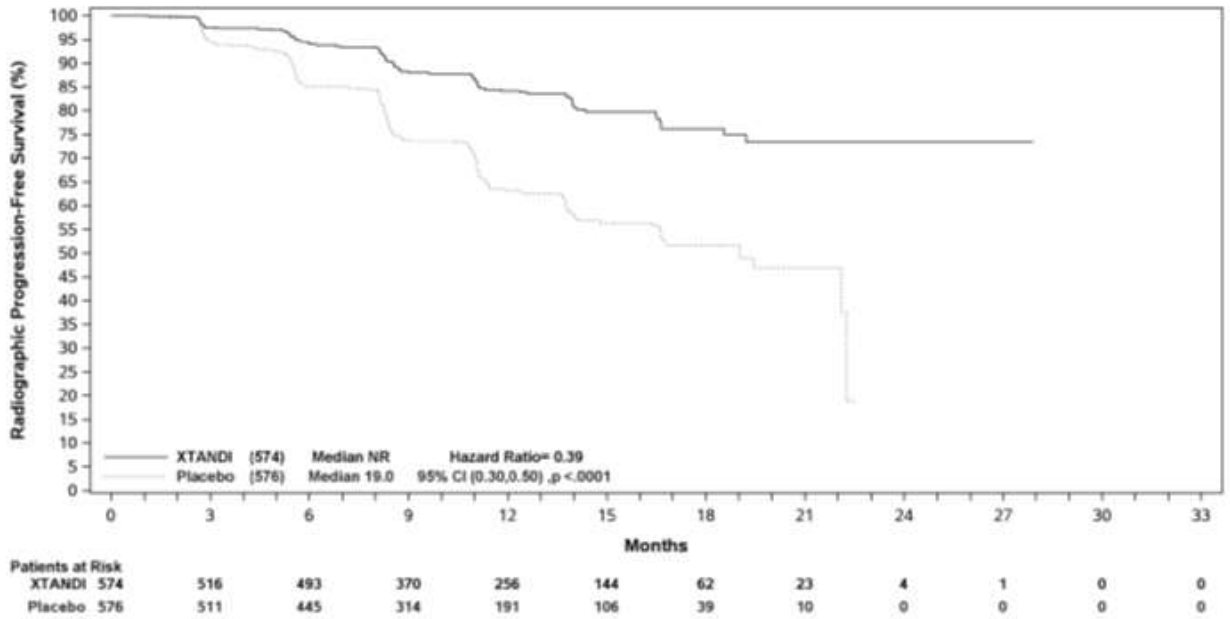


Figure 2: Forest Plot of rPFS by Prespecified Subgroup in ARCHES (Intent-to-Treat Analysis)

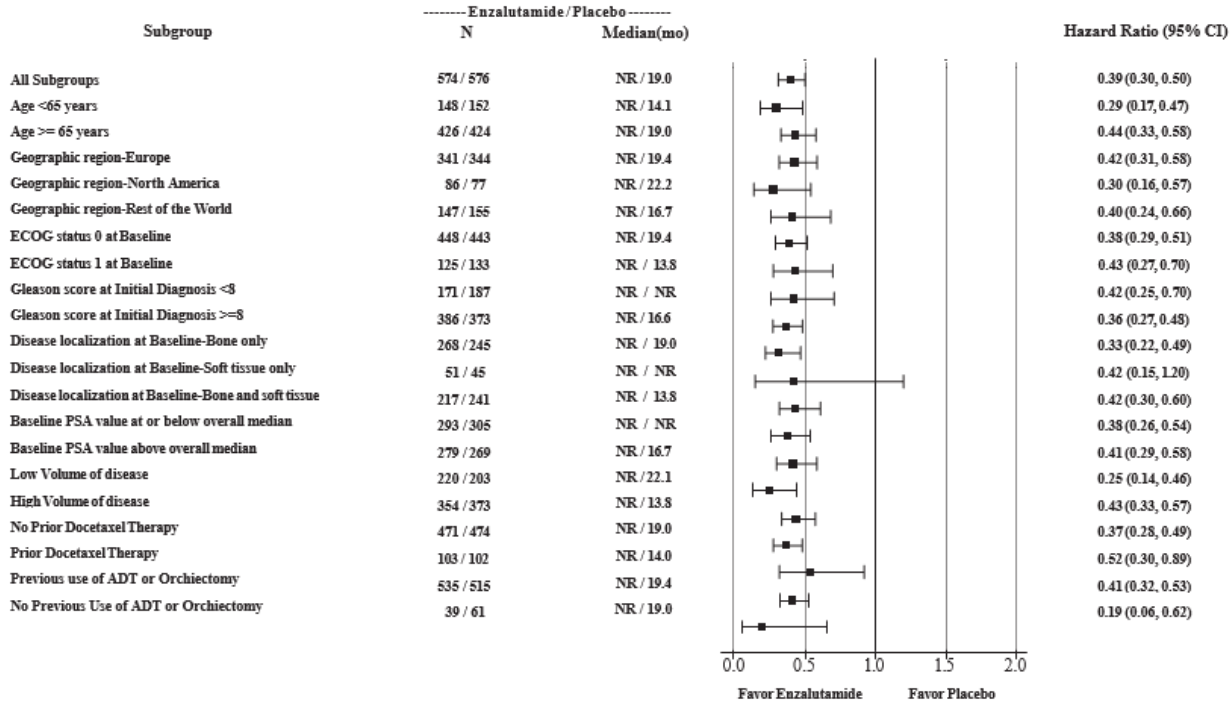
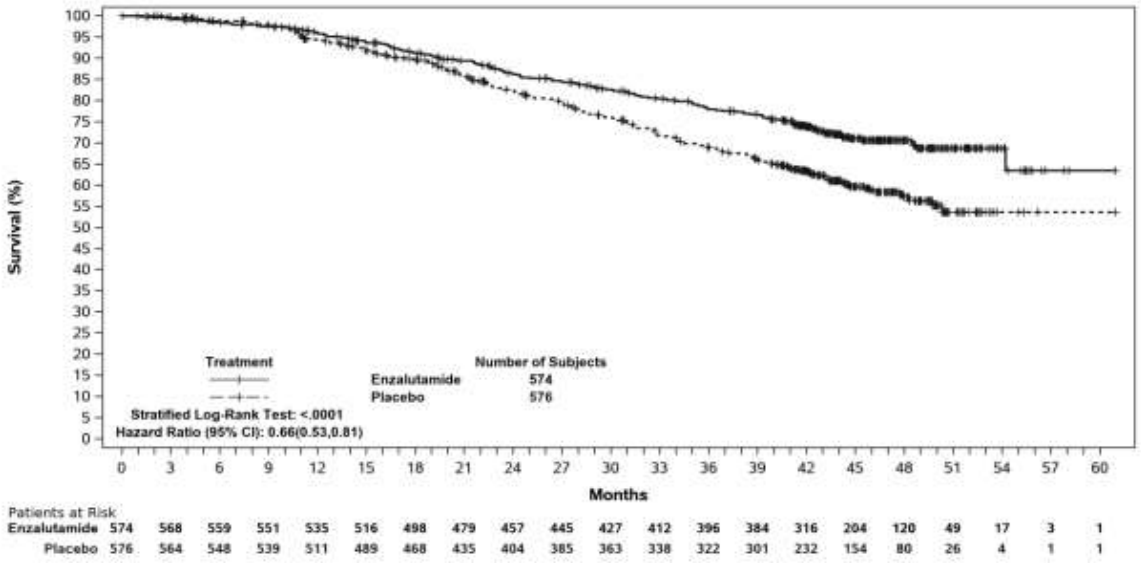


Figure 3: Kaplan-Meier Curves of Final Overall Survival in the ARCHES Study (Intent-to-Treat Analysis)



Non-Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy (PROSPER)

Xtandi demonstrated a statistically significant 71% reduction in relative risk of radiographic progression or death as compared to placebo [HR = 0.29 (95% CI: 0.24, 0.35), p < 0.0001]. Median MFS was 36.6 months (95% CI: 33.1, NR) in the Xtandi arm versus 14.7 months (95% CI: 14.2, 15.0) in the placebo arm (Table 13, Figure 4). Consistent MFS results were observed across all pre-specified patient subgroups (Figure 5).

In addition to the primary efficacy endpoint, statistically significant improvements were shown for secondary endpoints overall survival, time to PSA progression, and time to first use of new antineoplastic therapy (Table 13).

At a prespecified interim analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomized to receive Xtandi compared with patients randomized to receive placebo with a 26.6% reduction in risk of death [hazard ratio (HR) = 0.734, (95% CI: 0.608; 0.885) p = 0.0011] (Figure 6).

The median follow-up time was 48.6 months in the enzalutamide group and 47.2 months in the placebo group.

Table 13 – Summary of efficacy results in the PROSPER study (intent-to-treat analysis)

	Xtandi (N = 933)	**Placebo (N = 468)**
Primary Endpoint		
Metastasis-free survival		
Number of Events (%)	219 (23.5)	228 (48.7)

	Xtandi (N = 933)	Placebo (N = 468)
Median, months (95% CI)[a]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard Ratio (95% CI)[b]	0.29 (0.24, 0.35)	
P-value[c]	p < 0.0001	
Key Secondary Efficacy Endpoints		
Overall Survival[d]		
Number of Events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[a]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard Ratio (95% CI)[b]	0.734 (0.608, 0.885)	
P-value[c]	P = 0.0011	
Time to PSA progression		
Number of Events (%)	208 (22.3)	324 (69.2)
Median, months (95% CI)[a]	37.2 (33.1, NR)	3.9 (3.8, 4.0)
Hazard Ratio (95% CI)[b]	0.07 (0.05, 0.08)	
P-value[c]	p < 0.0001	
Time to first use of new antineoplastic therapy		
Number of Events (%)	142 (15.2)	226 (48.3)
Median, months (95% CI)[a]	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard Ratio (95% CI)[b]	0.21 (0.17, 0.26)	
P-value[c]	p < 0.0001	

NR = Not reached.

a. Based on Kaplan-Meier estimates.
b. HR is based on a Cox regression model (with treatment as the only covariate) stratified by PSA doubling time and prior or concurrent use of a bone-targeting agent. The HR is relative to placebo with < 1 favouring enzalutamide.
c. P-value is based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no).
d. Based upon a prespecified interim analysis with data cut-off date of 15 Oct 2019.

Figure 4: Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)

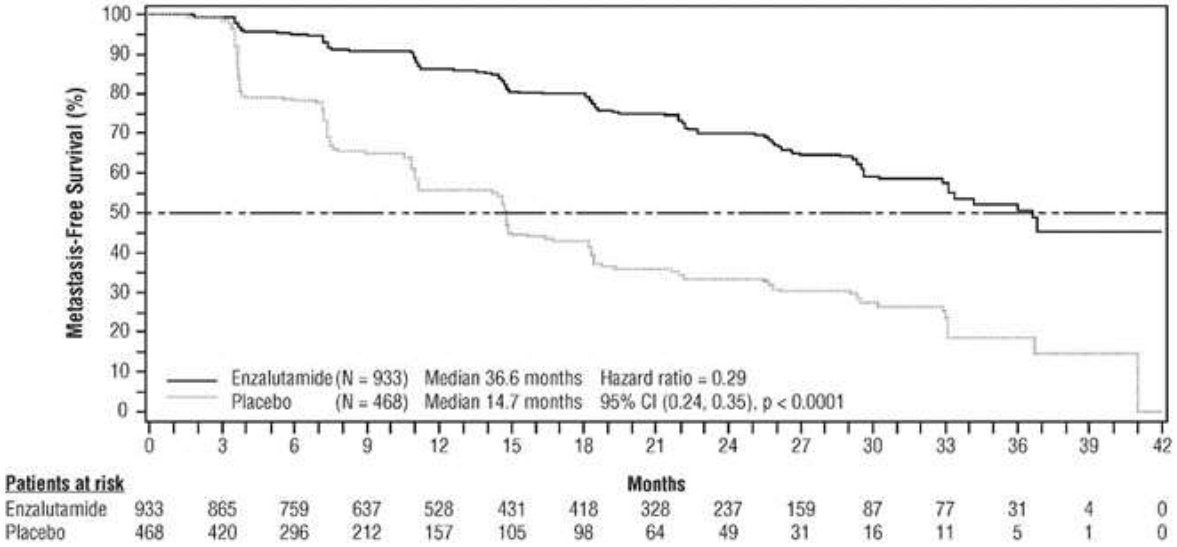
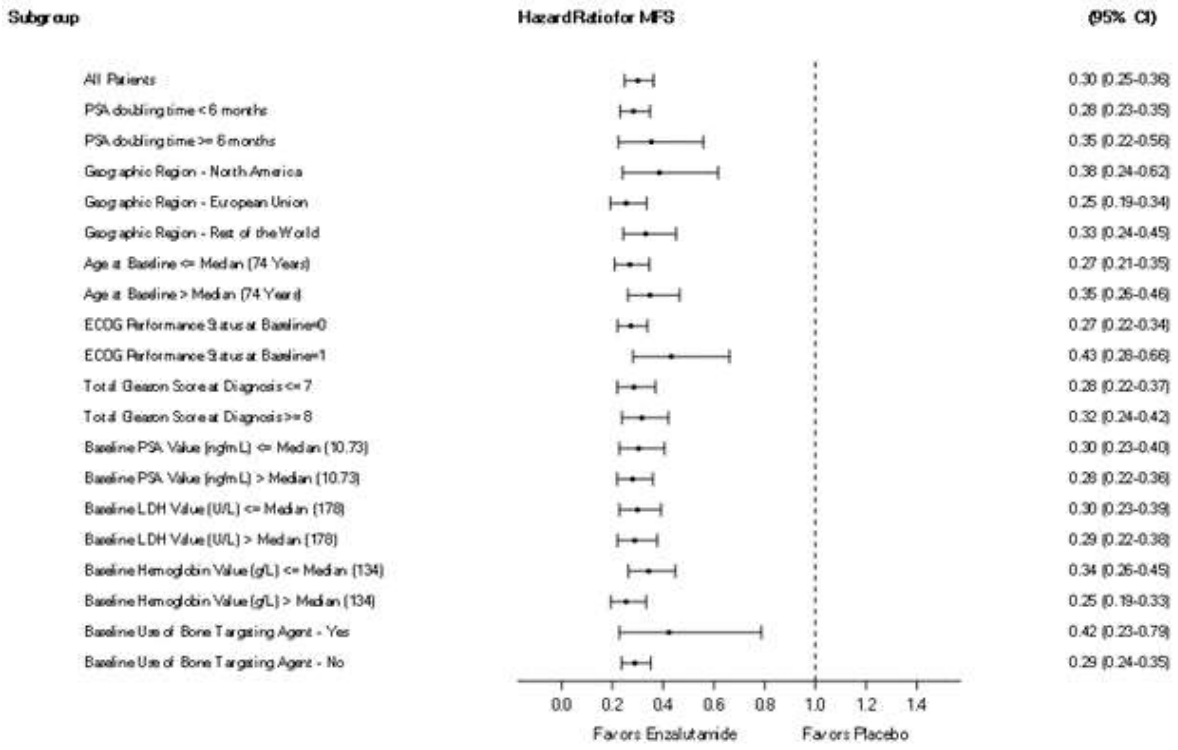


Figure 5: Forest Plot of MFS in Study MDV3100-14 - Subgroup Analysis (ITT Population)



All patients randomly assigned to study treatment and based on randomized treatment assignment regardless of whether or not treatment was administered (ITT Population).

Hazard ratios for all patients and for all other subgroups were based on an unstratified Cox regression model with treatment as the only covariate.

ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; LDH: lactate dehydrogenase; MFS: metastasis-free survival; PSA: prostate-specific antigen.

Figure 6: Kaplan-Meier Curves of overall survival in the PROSPER study (intent-to-treat analysis)

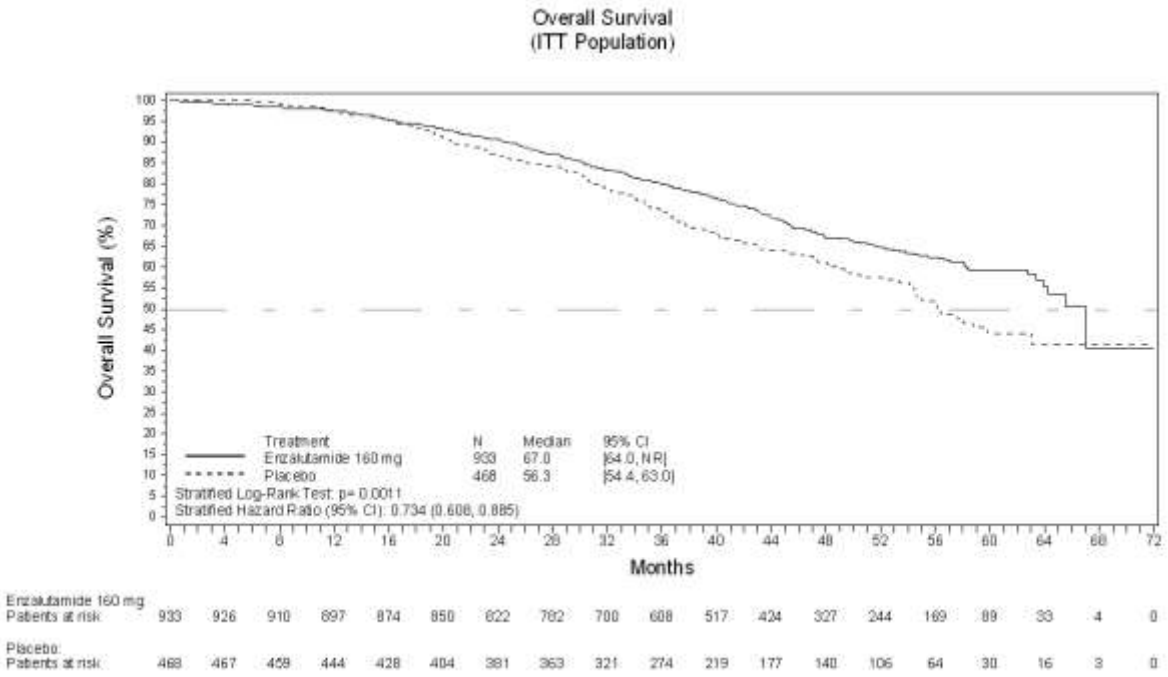
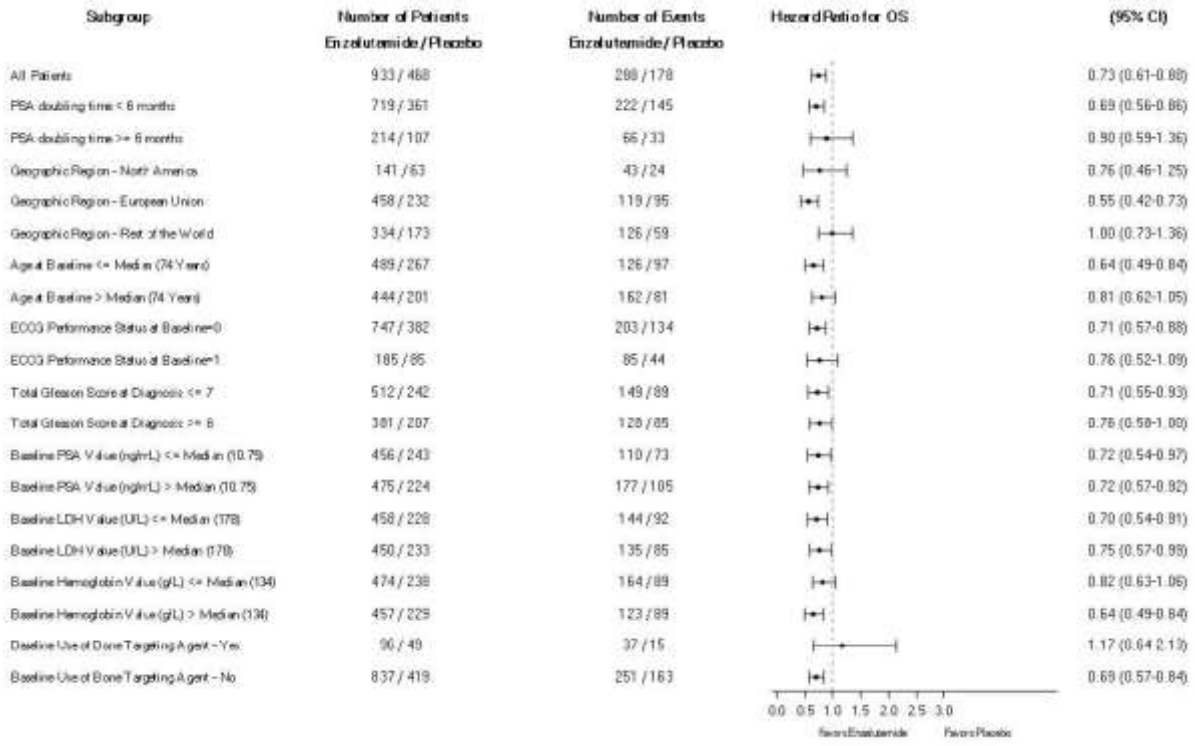


Figure 7: Forest Plot of overall survival in the PROSPER study (intent-to-treat analysis)



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

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 (Table 14). 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.

An analysis of 5-year data (September 30, 2017) showed a statistically significant increase in overall survival maintained in patients treated with enzalutamide compared to placebo [HR = 0.835, (95% CI: 0.75, 0.93); p-value = 0.0008] despite 28% of patients on placebo crossing over to enzalutamide. The 5-year OS rate was 26% for the enzalutamide arm compared to 21% for the placebo arm (Table 14, Figure 8).

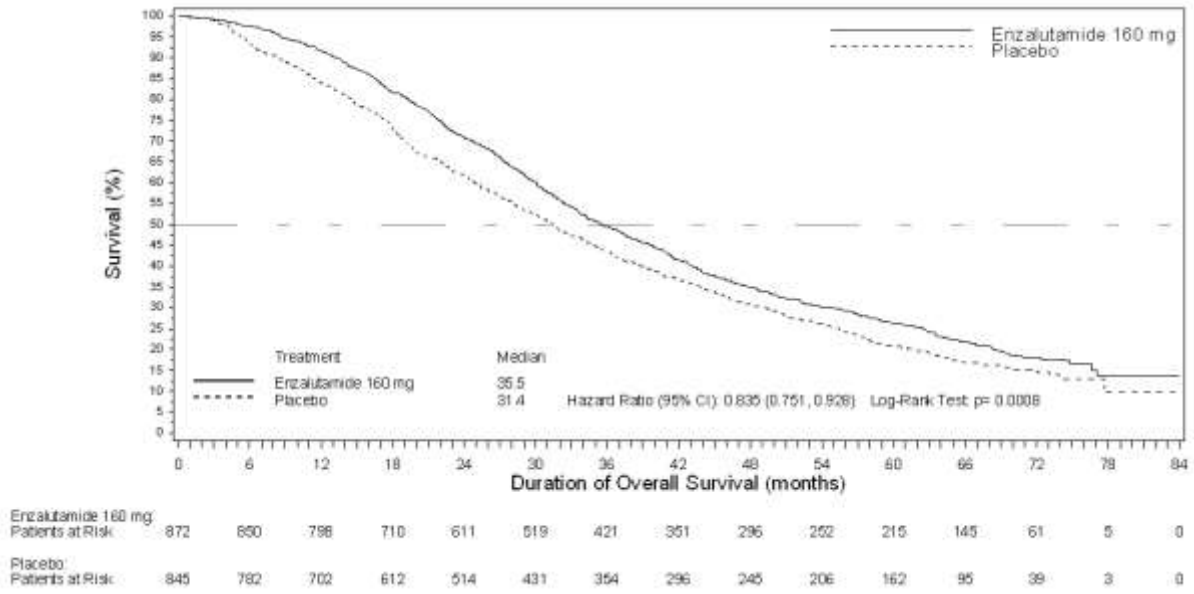
Table 14 – PREVAIL Duration of Overall Survival – Co-primary Analysis (ITT Population)

Parameter	Xtandi (N = 872)	Placebo (N = 845)
Pre-Specified Interim Analysis[a]		
Deaths	241 (27.6%)	299 (35.4%)
Median survival, months (95% CI)	32.4 (30.1, NYR)	30.2 (28.0, NYR)
P-value[b]	< 0.0001	
Hazard ratio (95% CI)[c]	0.706 (0.596, 0.837)	
5-year Survival Analysis[a]		
Deaths	689 (79)	693 (82)
Median survival, months (95% CI)	35.5 (33.5, 38.0)	31.4 (28.9, 33.8)
P-value[b]	P = 0.0008	
Hazard ratio (95% CI)[c]	0.835 (0.75, 0.93)	

a. Cut-off dates: September 16, 2013 (interim analysis) and September 30, 2017 (5-year analysis).
b. P-value is derived from unstratified log-rank test.
c. The hazard ratio is based on an unstratified Cox regression model (with treatment as the only covariate) and is relative to placebo with < 1 favouring Xtandi. ITT, intent-to-treat; NYR, not yet reached.

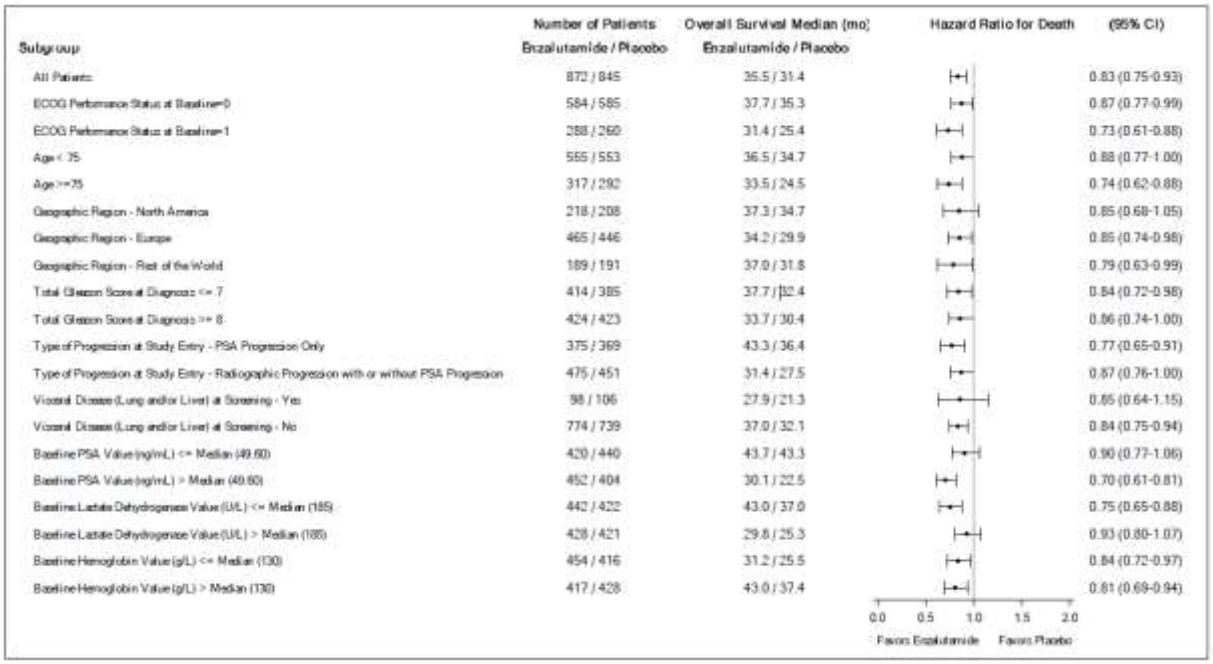
The treatment effect was apparent after the first three months of treatment and maintained through the follow-up period (Figure 8). Subgroup survival analysis showed a consistent survival benefit for treatment with Xtandi (Figure 9).

Figure 8: Kaplan-Meier Overall Survival Curves of Patients Treated with Either Xtandi or Placebo in the PREVAIL Study (Intent-to-Treat Analysis*)



* 5-year survival analysis (September 30, 2017)

Figure 9: Overall Survival Analysis by Subgroup: Hazard Ratio and 95% Confidence Interval in the PREVAIL Study (Intent-to-Treat Analysis*)



* 5-year survival analysis (September 30, 2017)

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 10, Table 15). Consistent rPFS benefit was observed across all pre-specified patient subgroups (Figure 11). 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.

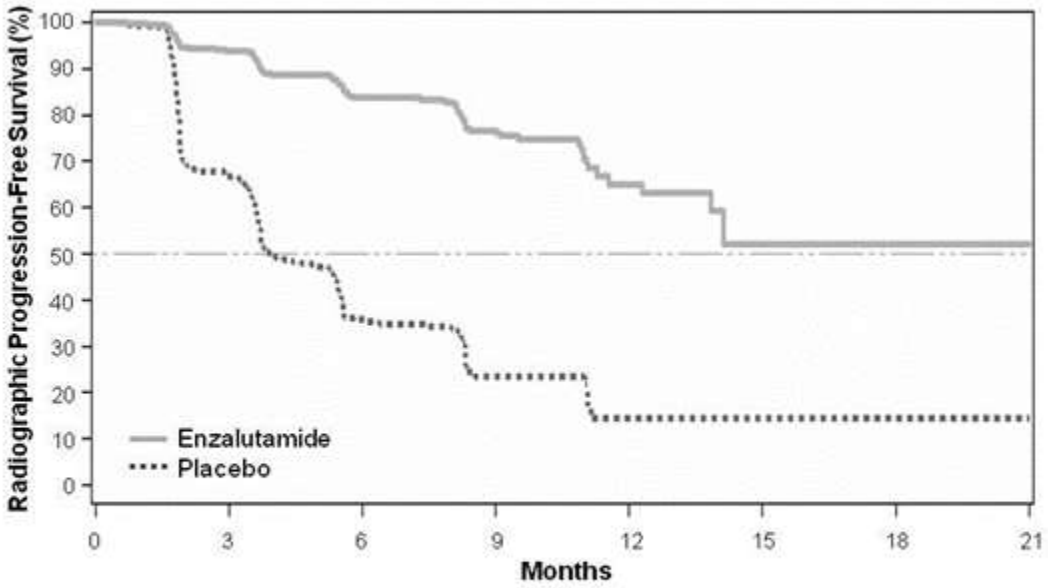
Table 15 – PREVAIL, Duration of Radiographic Progression-Free Survival – Co-primary Analysis Based on Independent Central Review (ITT Population)

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).

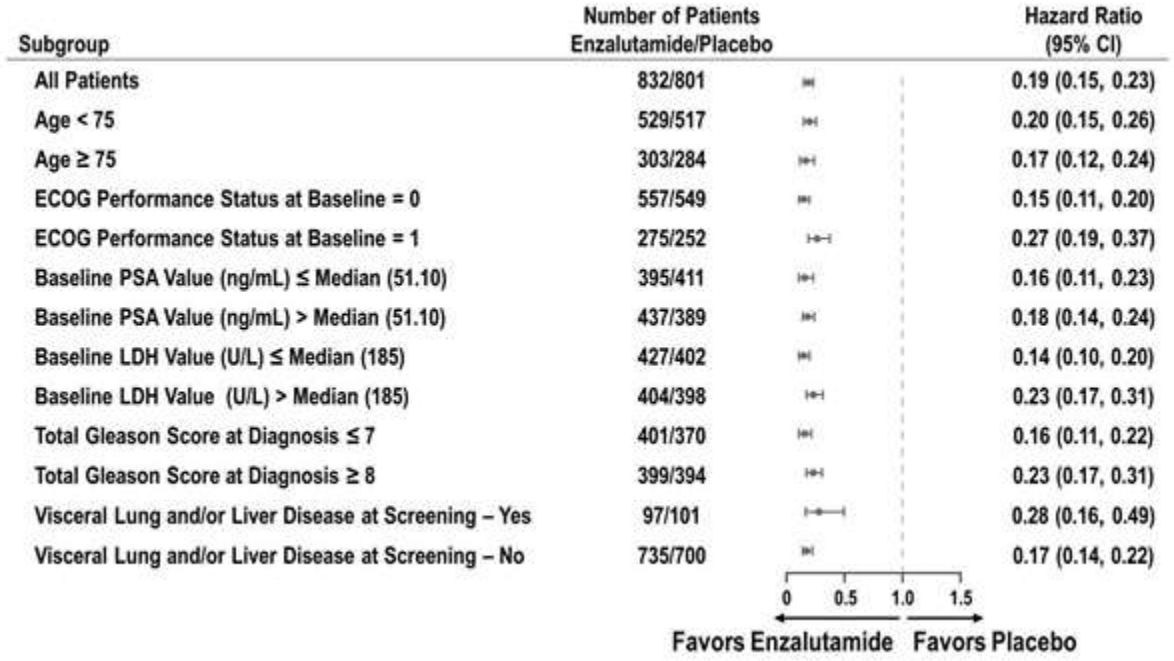
b. Patients who were not known to have had an rPFS event at the time of analysis data cut-off are censored at date of last assessment showing no objective evidence of radiographic progression prior to scan modality change, new antineoplastic treatment, initiation of radiation therapy for prostate cancer, skeletal-related event, treatment discontinuation, and 2 or more consecutive missed tumour 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 favouring Xtandi. ITT, intent-to-treat; NYR, not yet reached; rPFS, radiographic progression-free survival.

Figure 10: 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 11: 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 16.

Table 16 – 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

Endpoint	Xtandi	Placebo	Hazard Ratio [95% CI]	P-Value
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)

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 17). 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 12). The median duration of follow-up was 14.4 months.

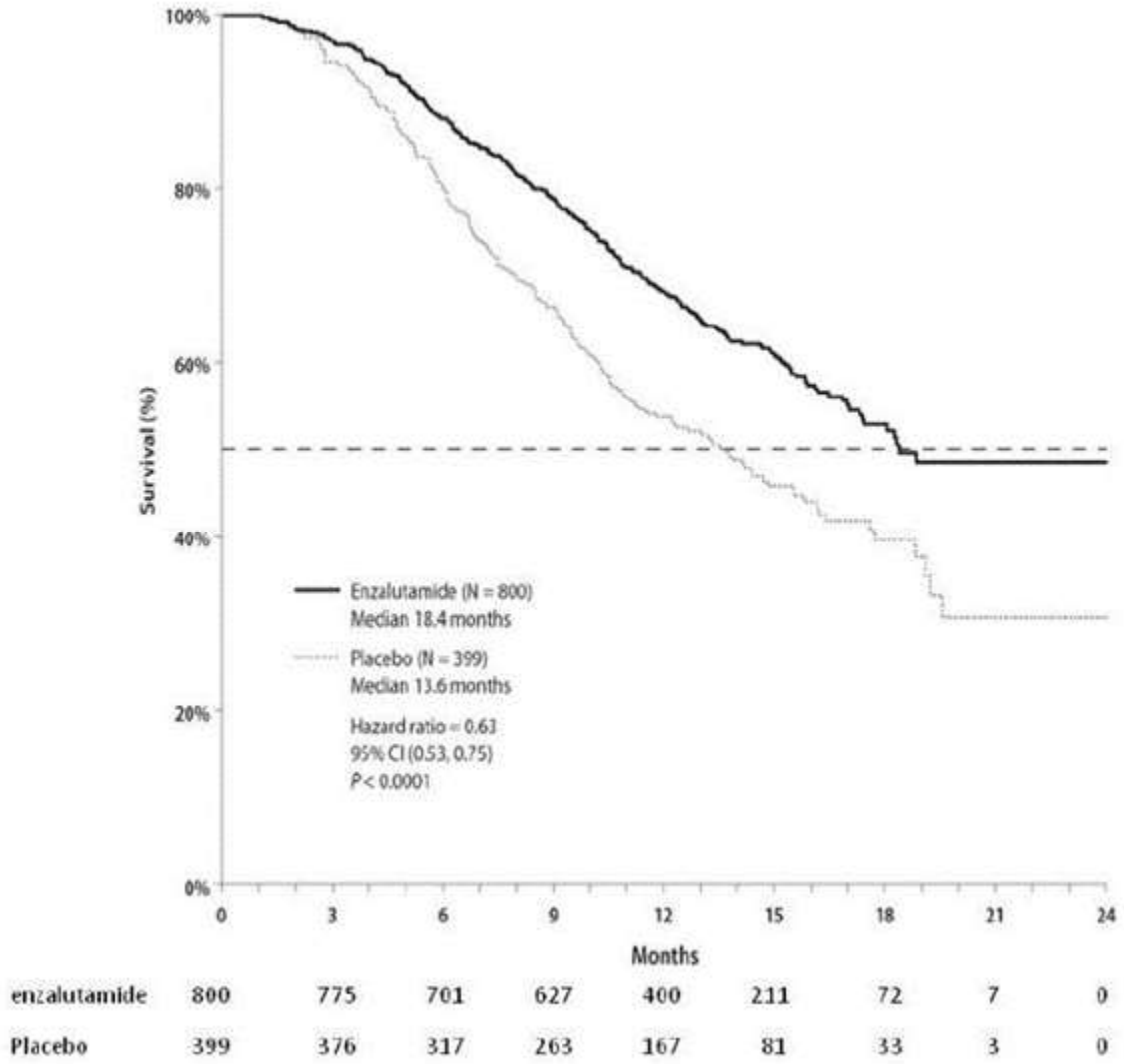
Table 17 – Overall Survival of Patients Treated with Either Xtandi or Placebo in the AFFIRM Study (Intent-to-Treat Analysis)

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[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.631 (0.529, 0.752)	

a. 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).

b. Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours Xtandi. NR: not reached.

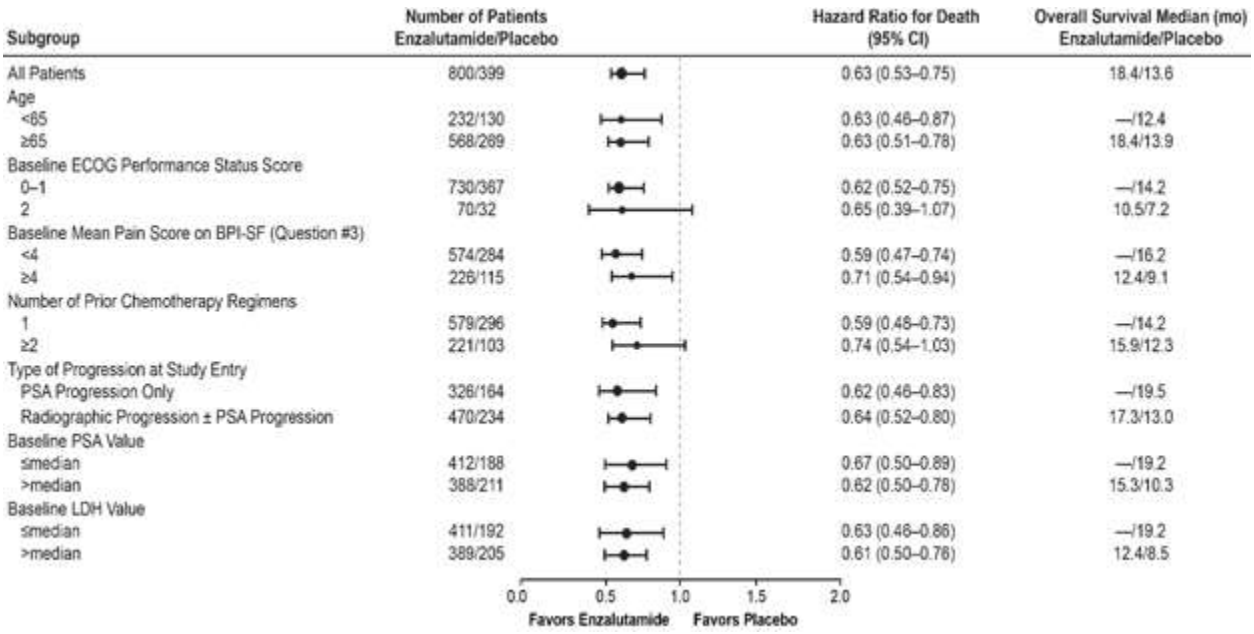
Figure 12: Kaplan-Meier Overall Survival Curves of Patients Treated with Either Xtandi or Placebo in the AFFIRM Study (Intent-to-Treat Analysis)



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

Subgroup survival analysis demonstrated a consistent favourable survival benefit for treatment with Xtandi (Figure 13).

Figure 13: 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 18).

Table 18 – 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			NA	
≥ 50% Decrease	54.0%	1.5%		< 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.

14.3 Comparative Bioavailability Studies

Not Applicable

15 MICROBIOLOGY

Not Applicable

16 NON-CLINICAL TOXICOLOGY

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 19 – 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

	Studies	Observation
	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.

Studies in lactating rats have shown that enzalutamide and/or its metabolites are secreted in rat milk. After oral administration of radiolabeled ^{14}C-enzalutamide to lactating rats at a dose of 30 mg/kg, the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results also have shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

Studies in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to fetuses. After oral administration of radiolabeled ^{14}C-enzalutamide to rats on day 14 of pregnancy at a dose of 30 mg/kg, the maximum radioactivity in the fetus was reached 4 hours after administration and was lower than that in the maternal plasma with a tissue/plasma ratio of 0.27. The radioactivity in the fetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

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 20 – 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[a]	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.

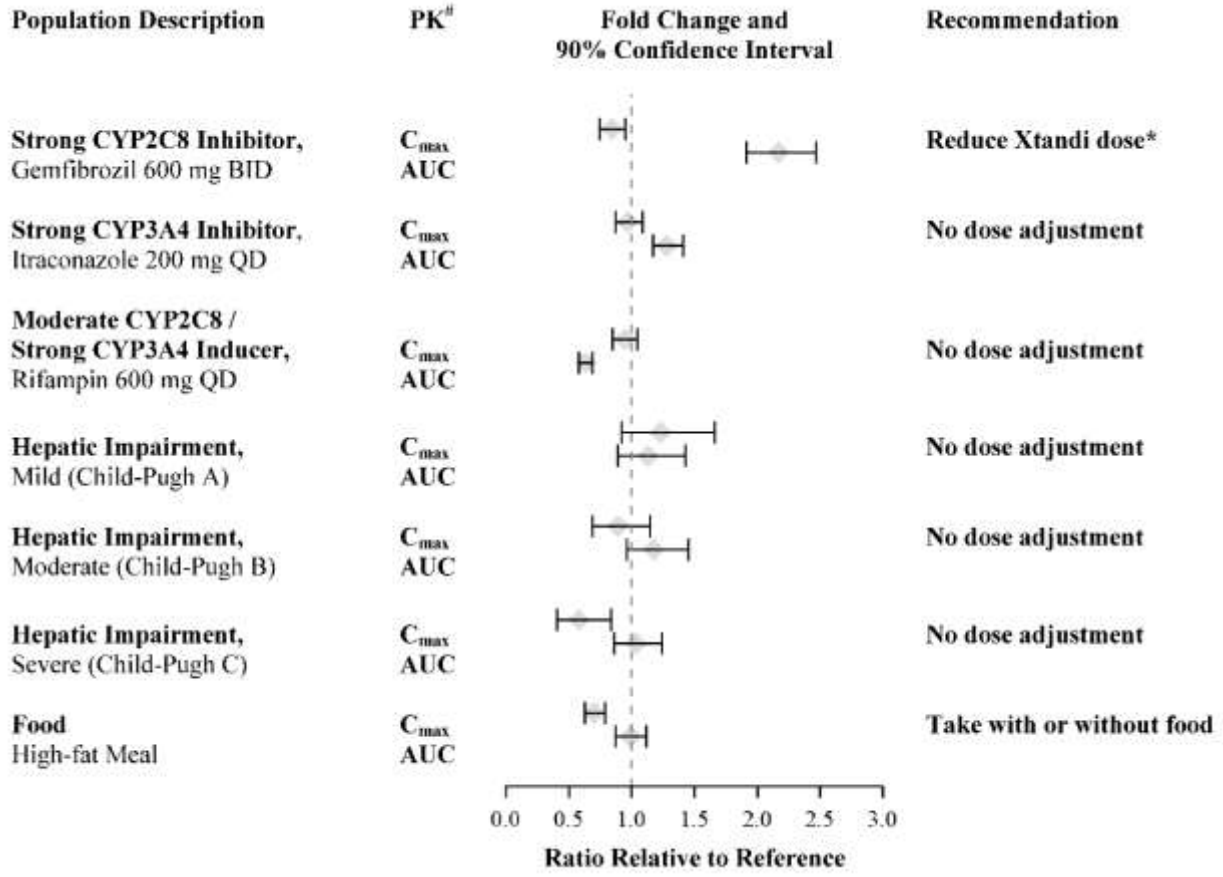
Type of Study	Results and Conclusion
Inhibition of CYP enzymes in human liver microsomes	Enzalutamide, M1, and/or M2 are inhibitors of CYP2C8 and CYP2C19 with lesser inhibitory effects on CYP2B6 and CYP2C9. Enzalutamide showed time-dependent inhibition of CYP1A2 with a pattern suggesting that a metabolite 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.

a. 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.

Human Pharmacology – *In Vivo*

See **DRUG INTERACTIONS** and **CLINICAL PHARMACOLOGY** sections.
The results of studies evaluating the Effect of Intrinsic/Extrinsic Factors on the PK of enzalutamide are shown in Figure 14.

Figure 14: Effect of Intrinsic/Extrinsic Factors on the PK of Enzalutamide



PK parameters (C_{max} and $AUC_{0\text{-}inf}$) are for enzalutamide plus M2, except in the food-effect trial, where they are for enzalutamide alone.

* See Dosage and Administration.
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).

In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day (AUC_{24h} ~317 µg.h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC_{24h} 322 µg.h/mL) in metastatic CRPC patients receiving 160 mg daily.

Daily oral dosing of rats for two years with enzalutamide at 10, 30 and 100 mg/kg/day increased the incidence of neoplastic findings that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumours in the testes in males; benign granulosa cell tumour in the ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes. In addition, urothelial papilloma and carcinoma of the urinary bladder in male rats were observed at the 100 mg/kg/day dose. Benign Leydig cell tumours are expected based on the pharmacological properties of this antiandrogen drug and not considered relevant to humans. The observed urothelium papilloma and carcinoma of the urinary bladder may be due to continuous irritation caused by urinary bladder crystals/calculi which is more pronounced in rats because of anatomical differences and positioning of the rat urinary bladder (horizontal in rat versus upright in human). However, no obvious mechanistic rationale to explain specifically this malignancy can be established. Taking into account that exposure levels based on AUC for enzalutamide plus its active metabolite M1 and M2 (AUC_{24}: enzalutamide ~457 µg•h/mL, M1 ~321 µg•h/mL, M2 ~35 µg•h/mL), achieved in this study in male rats at week 26 at 100 mg/kg/day, were less than or similar to those in prostate cancer patients at the recommended dose of 160 mg/day (AUC_{24}: enzalutamide ~322 µg•h/mL, M1 ~193 µg•h/mL, M2 ~278 µg•h/mL), urinary bladder carcinogenicity potential of enzalutamide in humans cannot be excluded.

17 SUPPORTING PRODUCT MONOGRAPHS

Not Applicable

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]Xtandi®
enzalutamide capsules

Read this carefully before you start taking **Xtandi** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Xtandi**.

Serious Warnings and Precautions
Only take Xtandi under the care of a doctor experienced with the treatment of prostate cancer. Xtandi can cause serious side effects which may include: • Seizures • Posterior Reversible Encephalopathy Syndrome (reversible swelling in the back of the brain).

What is Xtandi used for?

Xtandi is used to treat prostate cancer that **has** spread to other parts of the body in men who:

- are receiving but no longer responding to the medicine or surgery to lower testosterone. They may have also received a cancer treatment with a drug called docetaxel.
- still respond to a medicine or surgery that lowers testosterone.

Xtandi is used to treat men with prostate cancer that **has not** spread to other parts of the body but no longer responds to medicine or surgery that lowers testosterone. Xtandi has not been studied in patients with low risk of the cancer spreading to other parts of the body. Talk to your healthcare professional if you have questions about this.

How does Xtandi work?

Xtandi blocks the activity of hormones called androgens (like testosterone). This can slow the growth of prostate cancer.

What are the ingredients in Xtandi?

Medicinal ingredients: enzalutamide
Non-medicinal ingredients: butylhydroxyanisole (E320), butylhydroxytoluene (E321), caprylocaproyl macrogolglycerides
Capsule shell: gelatin, glycerol, purified water, sorbitol sorbitan solution, titanium dioxide (E171)
Printing ink: ammonia solution concentrated, ethanol, ethyl acetate, iron oxide black (E172), isopropyl alcohol, macrogol 400, polyvinyl acetate phthalate, propylene glycol, purified water.

Xtandi comes in the following dosage forms:

Capsules: 40 mg

Do not use Xtandi if:

- you are allergic to enzalutamide or to any other ingredients in Xtandi.
- you are or may become pregnant.
- you are breast-feeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Xtandi. Talk about any health conditions or problems you may have, including if you:

- have history of seizures or are at a high risk of seizures. This is because Xtandi may increase your risk of seizures. Some situations in which you may have a higher risk of seizures include if you:
    - had earlier episodes of seizures
    - drink very large amounts of alcohol either regularly or from time to time
    - have had a serious head injury
    - have had a stroke or mini stroke
    - have had a brain tumour or spreading of cancer to the brain
    - are taking a medicine that can cause seizures or increase your chance of having seizures (see section **The following may interact with Xtandi** below for information about these medicines)
- have liver problems.
- have kidney problems.
- have or had any heart disorder, including irregular heartbeat, an abnormal electrical signal called “prolongation of the QT interval”.
- have high blood pressure. Xtandi can increase your blood pressure. Your doctor will measure your blood pressure before starting treatment with Xtandi and periodically during treatment.
- have a history of fainting spells.
- have a risk for falls or broken bones.
- 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).
- have fructose intolerance, which is a rare hereditary problem. This is because Xtandi contains sorbitol.

Other warnings you should know about:

Birth control
During treatment with Xtandi, use effective birth control each time you have sex with women who are pregnant, possibly pregnant, or who could become pregnant. Continue using birth control for at least three months after treatment.

Driving and using machines
Xtandi may affect your ability to drive and use machines. Before engaging in activities that require special attention, wait until you know how Xtandi affects you.

Women, children and adolescents
Xtandi is NOT for use in women and patients younger than 18 years of age.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Xtandi:

- Antibiotics used to treat bacterial infections (e.g. clarithromycin, doxycycline)
- Medicines used to treat certain psychiatric disorders such as severe anxiety or schizophrenia (e.g. diazepam, haloperidol, midazolam)
- Medicines used to treat gout (colchicine)
- Medicines used to lower cholesterol (e.g. atorvastatin, simvastatin)
- Medicines used to treat heart conditions and lower blood pressure (e.g. bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil)
- Medicines used to treat serious disease related to inflammation (e.g. dexamethasone, prednisone)
- Medicines used to prevent the rejection of organ transplants (e.g. cyclosporine, tacrolimus)
- Medicines used to treat HIV infection (e.g. indinavir, ritonavir)
- Medicines used to treat epilepsy (e.g. carbamazepine, clonazepam phenobarbital, phenytoin, primidone, valproic acid)
- Medicines used to prevent blood clots (e.g. acenocoumarol, dabigatran etexilate, warfarin, clopidogrel)
- Medicines used to treat cancer (e.g. cabazitaxel, irinotecan, sunitinib)
- Medicines used to treat pain (e.g. fentanyl, tramadol)
- Medicines used to treat thyroid conditions (e.g. levothyroxine)
- Medicines used to treat stomach disorders (e.g. omeprazole)

Also, the following list includes some, but not all medicines that may interact with Xtandi to increase your risk of having 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 opioids used to treat pain (e.g. meperidine)

You should check with your healthcare professional before taking any other medicines with Xtandi. The dose of any other medicines that you are taking may need to be changed.

How to take Xtandi:

- Always take this medicine exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take each dose at the same time each day.
- Swallow the capsules whole with water.
- Do not chew, dissolve or open the capsules.
- Take with or without food.

Do NOT start or stop Xtandi before you talk to your healthcare professional.

Instructions for handling Xtandi

- Xtandi should not be handled by persons other than the patient or their caregivers.
- Women who are or may become pregnant should NOT handle damaged or opened Xtandi capsules

without protection (e.g. gloves). Xtandi might harm your unborn baby.

Usual dose:

The usual dose is 160 mg (4 capsules) taken once a day.

Overdose:

If you think you, or a person you are caring for, have taken too much Xtandi, contact a healthcare professional, 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.

What are possible side effects from using Xtandi?

These are not all the possible side effects you may have when taking Xtandi. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Feeling tired (fatigue)
- Back pain
- Hot flush
- Constipation
- Joint Pain
- Decreased appetite
- Diarrhea
- Dizziness/vertigo
- Headache
- Feeling anxious
- Forgetfulness
- Having trouble remembering and solving problems
- Reduced concentration
- Weight loss
- Disturbance in attention
- Dry skin, itching
- Nose bleed
- Shingles
- Flu-like symptoms

- Drowsiness
- Uncontrollable urge to move a part of the body, usually the leg (restless leg syndrome)
- Hallucinations
- Low white blood cell count (shown in blood tests)
- Bruising
- Breast swelling in males
- Vomiting
- Nausea
- Rash
- Change in sense of taste

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

Xtandi can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results.

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 and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Bone Fractures (broken bones)		✓	
Falls		✓	
Heart Problems (including heart attack, angina, coronary artery disease or heart failure): pressure or pain in your chest or arms that may spread to your neck jaw or back, shortness of breath, changes in heartrate, dizziness or lightheadedness, nausea		✓	✓
Hypertension (high blood pressure)		✓	
Herpes Zoster Virus (shingles): a painful skin rash of fluid-filled blisters which can appear on the body or face, blisters appear along a strip of skin, itching		✓	
UNCOMMON			
Seizure: muscle twitching, changes in emotions, loss of consciousness with uncontrollable shaking		✓	✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Sepsis and septic shock (Infection of the blood): fever or dizziness, chills, high or very low body temperature, little or no urine, low blood pressure, palpitations, rapid breathing, rapid heartbeat			✓
Gastrointestinal Bleeding (bleeding in digestive tract)		✓	✓
REPORTED FROM POST-MARKETING			
Allergic reaction: rash, hives, swelling of the face, tongue, lip or throat, difficulty swallowing or breathing		✓	✓
Posterior Reversible Encephalopathy Syndrome (PRES) (reversible swelling in the back of the brain): high blood pressure, headache, loss of speech or vision, confusion, seizure		✓	✓
Severe Skin Reactions		✓	✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 15°C to 30°C. Keep out of the reach and sight of children.

If you want more information about Xtandi:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.astellas.ca, or by calling 1-888-338-1824.

This leaflet was prepared by Astellas Pharma Canada, Inc.

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Marketing Status in United States

Drug Databases (https://www.fda.gov/Drugs/InformationOnDrugs/)

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Home (index.cfm?resetfields=1) | Back to Search Results

Product Details for NDA 203415

XTANDI (ENZALUTAMIDE)
40MG
Marketing Status: Prescription

Active Ingredient: ENZALUTAMIDE
Proprietary Name: XTANDI
Dosage Form; Route of Administration: CAPSULE; ORAL
Strength: 40MG
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N203415
Product Number: 001
Approval Date: Aug 31, 2012
Applicant Holder Full Name: ASTELLAS PHARMA US INC
Marketing Status: Prescription
Patent and Exclusivity Information (patent_info.cfm?Product_No=001&Appl_No=203415&Appl_type=N)