1. NAME OF THE MEDICINAL PRODUCT

Xtandi™ 40 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 40 mg of enzalutamide.

Excipients with known effect:
Each soft capsule contains 57.8 mg of sorbitol.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule.
White to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with "ENZ" in black ink on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Xtandi is indicated as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy (see Clinical efficacy and safety).

- Xtandi is indicated for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (see Clinical efficacy and safety).

- Xtandi is indicated for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see Clinical efficacy and safety).
- Xtandi in combination with androgen deprivation therapy is indicated for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not clinically indicated.

- Xtandi is indicated for the second line treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

4.2 Posology and method of administration

Posology
The recommended dose is 160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.

Medical castration with a luteinizing hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients with CRPC or mHSPC who are not surgically castrated.
Patients with high-risk BCR nmHSPC may be treated with Xtandi with or without a LHRH analogue. For patients who receive Xtandi with or without a LHRH analogue, treatment can be suspended if PSA is undetectable (< 0.2 ng/mL) after 36 weeks of therapy. Treatment should be reinitiated when PSA has increased to ≥ 2.0 ng/mL for patients who had prior radical prostatectomy or ≥ 5.0 ng/mL for patients who had prior primary radiation therapy. If PSA is detectable (≥ 0.2 ng/mL) after 36 weeks of therapy, treatment should continue (see section 5.1).

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 usual daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

Concomitant use with strong CYP2C8 inhibitors
The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (see section 4.5).

Elderly
No dose adjustment is necessary for elderly patients (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively) (see sections 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild or moderate renal impairment (see section 5.2). Caution is advised in patients with severe renal impairment or end-stage renal disease (see section 4.4).

Pediatric population
There is no relevant use of enzalutamide in the pediatric population in the indication of treatment of adult men with CRPC, mHSPC, or high-risk BCR nmHSPC.

Method of administration
Xtandi is for oral use. The soft capsules should be swallowed whole with a sufficient amount of water, and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see sections 4.6 and 6.3).

4.4 Special warnings and precautions for use

Risk of seizure
Use of enzalutamide has been associated with events of seizure (see section 4.8). Permanently discontinue Xtandi in patients who develop a seizure during treatment.

Posterior reversible encephalopathy syndrome
There have been rare 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, 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). Discontinuation of Xtandi in patients who develop PRES is recommended.

Concomitant use with other medicinal products
Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see examples in section 4.5). A review of concomitant medicinal products should

therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolizing enzymes or transporters (see section 4.5) should generally be avoided if their therapeutic effects is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If Xtandi is co-administered with an anticoagulant metabolized by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalized Ratio (INR) monitoring should be conducted (see section 4.5).

Renal impairment
Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.

Severe hepatic impairment
An increased half-life of enzalutamide has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged time to reach steady state concentrations is however anticipated, and the time to maximum pharmacological effect as well as time for onset and decline of enzyme induction (see section 4.5) may be increased.

Recent cardiovascular disease
The phase 3 studies excluded patients with 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. This should be taken into account if Xtandi is prescribed in these patients.

Use with chemotherapy
The safety and efficacy of concomitant use of Xtandi with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel; however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.

Excipients
Xtandi contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Dysphagia related to product formulation
There have been reports of patients experiencing difficulty swallowing Xtandi, including reports of choking. The swallowing difficulties and choking events were mostly reported with the capsule formulation, which could be related to a larger product size. Patients should be advised to swallow the capsules whole with a sufficient amount of water.

Hypersensitivity reactions
Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal edema have been observed with enzalutamide (see section 4.8).

Androgen deprivation therapy may prolong the QT interval
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval physicians should assess the benefit risk ratio including the potential for *Torsade de pointes* prior to initiating Xtandi.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect enzalutamide exposure

CYP2C8 inhibitors

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while C_{max} of enzalutamide decreased by 18%. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while C_{max} decreased by 19%. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (see section 4.2).

CYP3A4 inhibitors

CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while C_{max} was again unchanged. No dose adjustment is necessary when Xtandi is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers

Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampin (600 mg once daily) to healthy male subjects, the AUC of enzalutamide plus the active metabolite decreased by 37% while C_{max} remained unchanged. No dose adjustment is necessary when Xtandi is co-administered with inducers of CYP2C8 or CYP3A4.

Potential for enzalutamide to affect exposures to other medicinal products

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19 and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (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). UGT1A1 may have been induced as well. In a clinical study in patients with metastatic CRPC, Xtandi (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m^2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) = 0.882 (90% CI: 0.767, 1.02)] while C_{max} decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)].

Interaction with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)

- Anticancer agents (e.g. cabazitaxel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressives (e.g. tacrolimus)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days, see section 5.2), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

CYP1A2 and CYP2C8 substrates
Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while C_{max} decreased by 18%. The AUC and C_{max} of caffeine decreased by 11% and 4%, respectively. No dose adjustment is indicated when a CYP1A2 or CYP2C8 substrate is co-administered with Xtandi.

P-gp substrates
In vitro data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. The effect of enzalutamide of P-gp substrates has not been evaluated *in vivo*; however, under conditions of clinical use, enzalutamide may be an inducer of P-gp via activation of the nuclear pregnane receptor (PXR). Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with Xtandi and may require dose adjustment to maintain optimal plasma concentrations.

BCRP, MRP2, OAT3 and OCT1 substrates
Based on *in vitro* data, inhibition of BCRP and MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown.

Effect of food on enzalutamide exposures
Food has no clinically significant effect on the extent of exposure to enzalutamide. In clinical trials, Xtandi was administered without regard to food.

Medicinal products which prolong the QT interval
Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Xtandi with medicinal products known to prolong the QT interval or medicinal products able to induce *Torsade de pointes* such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant (see sections 4.3, 5.3 and 6.6).

Contraception in males and females
It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see sections 4.3, 5.3, and 6.3).

Breast-feeding
Enzalutamide is not for use in women. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk (see section 5.3).

Fertility
Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

Enzalutamide may have moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported (see section 4.8). Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to evaluate the effects of enzalutamide on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are asthenia/fatigue, hot flush, hypertension, fractures and fall. Other important adverse reactions include ischemic heart disease and seizure.

Seizure occurred in 0.6% of enzalutamide-treated patients, 0.1% of placebo-treated patients, and 0.3% in bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide-treated patients (see section 4.4).

Tabulated summary of adverse reactions
Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

MeDRA System organ class	Frequency
Blood and lymphatic system disorders	Uncommon: leucopenia, neutropenia Not known[1]: thrombocytopenia
Immune system disorders	Not known[1]: face edema, tongue edema, lip edema, pharyngeal edema
Metabolism and nutrition disorders	Not known[1]: decreased appetite
General disorders and administration site conditions	Very common: asthenia, fatigue
Psychiatric disorders	Common: anxiety Uncommon: visual hallucinations
Nervous system disorders	Common: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome, cognitive disorder Uncommon: seizure[2] Not known[1]: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease[3] Not known[1]: QT-prolongation (see sections 4.4 and 4.5)
Reproductive system and breast disorders	Common: gynaecomastia, nipple pain[6], breast tenderness[6]
Vascular disorders	Very common: hot flush, hypertension
Gastrointestinal disorders	Not known[1]: dysphagia[7], nausea, vomiting, diarrhea
Skin and subcutaneous tissue disorders	Common: dry skin, pruritus Not known[1]: severe skin reactions[5], rash
Musculoskeletal and connective tissue disorders	Very common: fractures[4] Not known[1]: myalgia, muscle spasms, muscular weakness, back pain
Injury, poisoning and procedural complications	Very common: fall

1. Spontaneous reports from post-marketing experience.
2. As evaluated by narrow SMQs of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death.
3. As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, and arteriosclerosis coronary artery.
4. Includes all preferred terms with the word 'fracture' in bones.
5. As evaluated by narrow SMQ of 'Severe Cutaneous Adverse Reactions'. Acute generalized exanthematous pustulosis, dermatitis bullous, dermatitis exfoliative generalized, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, exfoliative rash, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and toxic skin eruption have been reported in post-marketing cases.
6. Adverse reaction for enzalutamide as monotherapy.
7. There have been reports of dysphagia, including reports of choking. Both events have mostly been reported with the capsule formulation, which could be related to a larger product size (see section 4.4).

Description of selected adverse reactions

Seizure

In controlled clinical studies, 31 patients (0.6%) experienced a seizure out of 5110 patients treated with a daily dose of 160 mg enzalutamide, whereas four patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

In the 9785-CL-0403 (UPWARD) single-arm trial to assess incidence of seizure in patients with predisposing factors for seizure (where of 1.6% had a history of seizures), 8 of 366 (2.2%) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.

The mechanism by which enzalutamide may lower the seizure threshold is not known but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.

Ischemic Heart Disease
In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 3.5% of patients treated with enzalutamide plus ADT compared to 2% of patients treated with placebo plus ADT. Fourteen (0.4%) patients treated with enzalutamide plus ADT and 3 (0.1%) patients treated with placebo plus ADT had an ischemic heart disease event that led to death.

In the EMBARK study, ischemic heart disease occurred in 5.4% of patients treated with enzalutamide plus leuprolide and 9% of patients treated with enzalutamide as monotherapy. No patients treated with enzalutamide plus leuprolide and one (0.3%) patient treated with enzalutamide as monotherapy had an ischemic heart disease event that led to death.

Gynaecomastia
In the EMBARK study, gynaecomastia (all grades) was observed in 29 of 353 patients (8.2%) who were treated with enzalutamide plus leuprolide and 159 of 354 patients (44.9%) who were treated with enzalutamide as monotherapy. Grade 3 or higher gynaecomastia was not observed in any patients who were treated with enzalutamide plus leuprolide, and was observed in 3 patients (0.8%) who were treated with enzalutamide as monotherapy.

Nipple pain
In the EMBARK study, nipple pain (all grades) was observed in 11 of 353 patients (3.1%) who were treated with enzalutamide plus leuprolide and 54 of 354 patients (15.3%) who were treated with enzalutamide as monotherapy. Grade 3 or higher nipple pain was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Breast tenderness
In the EMBARK study, breast tenderness (all grades) was observed in 5 of 353 patients (1.4%) who were treated with enzalutamide plus leuprolide and 51 of 354 patients (14.4%) who were treated with enzalutamide as monotherapy. Grade 3 or higher breast tenderness was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

- Email to PV@id.astellas.com or
- Pusat Farmakovigilans/MESO Nasional
  Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,
  Psikotropika, Prekursor dan Zat Adiktif
  Badan Pengawas Obat dan Makanan
  Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
  Email: pv-center@pom.go.id
  Telephone: +62-21-4244691 Ext.1079
  Website: https://e-meso.pom.go.id/ADR

4.9 Overdose

There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures of following an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-androgen, hormone antagonists and related agents, ATC code: L02BB04.

Mechanism of action
Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signaling. Despite low or even undetectable levels of serum androgen, androgen receptor signaling continues to promote disease progression. Stimulation of tumor cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signaling inhibitor that blocks several steps in the androgen receptor signaling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumor regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

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

In another phase 3 clinical trial (PREVAIL) in chemo-naïve patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 78.0% versus 3.5% (difference = 74.5%, $p < 0.0001$).

In a phase 2 clinical trial (TERRAIN) in chemo-naïve patients, patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving bicalutamide, 82.1% versus 20.9% (difference = 61.2%, $p < 0.0001$).

In the MDV3100-09 clinical trial (STRIVE) of non-metastatic and metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher total confirmed PSA response rate (defined as a ≥ 50% reduction from baseline) compared with patients receiving bicalutamide, 81.3% versus 31.3% (difference = 50.0%, $p < 0.0001$).

In the MDV3100-14 clinical trial (PROSPER) of non-metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 76.3% versus 2.4% (difference = 73.9%, $p < 0.0001$).

Clinical efficacy and safety
Efficacy of enzalutamide was established in three randomized placebo-controlled multicenter phase 3 clinical studies [MDV3100-14 (PROSPER), CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive prostate cancer who had disease progression on androgen deprivation therapy (LHRH analogue or after bilateral orchiectomy). The PREVAIL study enrolled metastatic CRPC chemotherapy-naïve patients; whereas the AFFIRM study enrolled metastatic CRPC patients who had received prior docetaxel; and the PROSPER study enrolled patients with non-metastatic CRPC. Efficacy in patients with mHSPC was established in one randomized, placebo-controlled multicenter phase 3 clinical study [9785-CL-0335 (ARCHES)]. Another randomised, placebo controlled multicentre phase 3 clinical study [MDV3100 13 (EMBARK)] established efficacy in patients with high-risk BCR nmHSPC. All patients were treated with a LHRH analogue or had prior bilateral orchiectomy, unless otherwise indicated.

In the active treatment arm, Xtandi was administered orally at a dose of 160 mg daily. In the five clinical studies (EMBARK, ARCHES, PROSPER, AFFIRM and PREVAIL), patients received placebo in the control arm and patients were not required to take prednisone.

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in the five studies it was recommended that patients be maintained on their study treatments until suspension or discontinuation criteria were met as specified below for each study.

MDV3100-13 (EMBARK) Study (patients with high-risk BCR non-metastatic HSPC)

The EMBARK study enrolled 1068 patients with high-risk BCR nmHSPC who were randomised 1:1:1 to receive treatment with enzalutamide orally at a dose of 160 mg once daily concurrently with ADT (N = 355), enzalutamide orally at a dose of 160 mg once daily as open-label monotherapy (N = 355), or placebo orally once daily concurrently with ADT (N = 358) (ADT defined as leuprolide). All patients had prior definitive therapy with radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. Patients were required to have confirmation of non-metastatic disease by blinded independent central review (BICR), and high-risk biochemical recurrence (defined by a PSA doubling time ≤ 9 months). Patients were also required to have PSA values ≥ 1 ng/mL if they had prior radical prostatectomy (with or without radiotherapy) as the primary treatment for prostate cancer, or PSA values at least 2 ng/mL above the nadir if they had prior radiotherapy only. Patients who had a prior prostatectomy and were suitable candidates for salvage radiotherapy as determined by the investigator were excluded from the study.

Patients were stratified by screening PSA (≤ 10 ng/mL vs. > 10 ng/mL), PSA doubling time (≤ 3 months versus > 3 months to ≤ 9 months), and prior hormonal therapy (prior hormonal therapy vs. no prior hormonal therapy). For patients whose PSA values were undetectable (< 0.2 ng/mL) at week 36, treatment was suspended at week 37 and then reinitiated when PSA values increased to ≥ 2.0 ng/mL for patients with prior prostatectomy or ≥ 5.0 ng/mL for patients without prior prostatectomy. For patients whose PSA values were detectable at week 36 (≥ 0.2 ng/mL), treatment continued without suspension until permanent treatment discontinuation criteria were met. Treatment was permanently discontinued when development of radiographic progression was confirmed by central review after the initial local read.

The demographic and baseline characteristics were well balanced between the three treatment groups. The overall median age at randomisation was 69 years (range: 49.0 – 93.0). Most patients in the total population were Caucasian (83.2%), 7.3% were Asian, and 4.4% were Black. The median PSA doubling time was 4.9 months. Seventy-four percent of patients had prior definitive therapy with radical prostatectomy, 75% of patients had prior therapy with radiotherapy (including brachytherapy), and 49% of patients had prior therapy with both. Thirty-two percent of patients had a Gleason score of ≥ 8. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 92% of patients and 1 for 8% of patients at study entry.

Metastasis-free survival (MFS) in patients randomised to receive enzalutamide plus ADT compared to patients randomised to receive placebo plus ADT was the primary endpoint. Metastasis-free survival was defined as the time from randomisation to radiographic progression or death on study, whichever occurred first.

Multiplicity tested secondary endpoints that were assessed were time to PSA progression, time to first use of antineoplastic therapy, and overall survival. Another multiplicity tested secondary endpoint was MFS in patients randomised to receive enzalutamide as monotherapy compared to patients randomised to receive placebo plus ADT.

Enzalutamide plus ADT and as monotherapy demonstrated a statistically significant improvement in MFS as compared to placebo plus ADT. Key efficacy results are presented in Table 2.

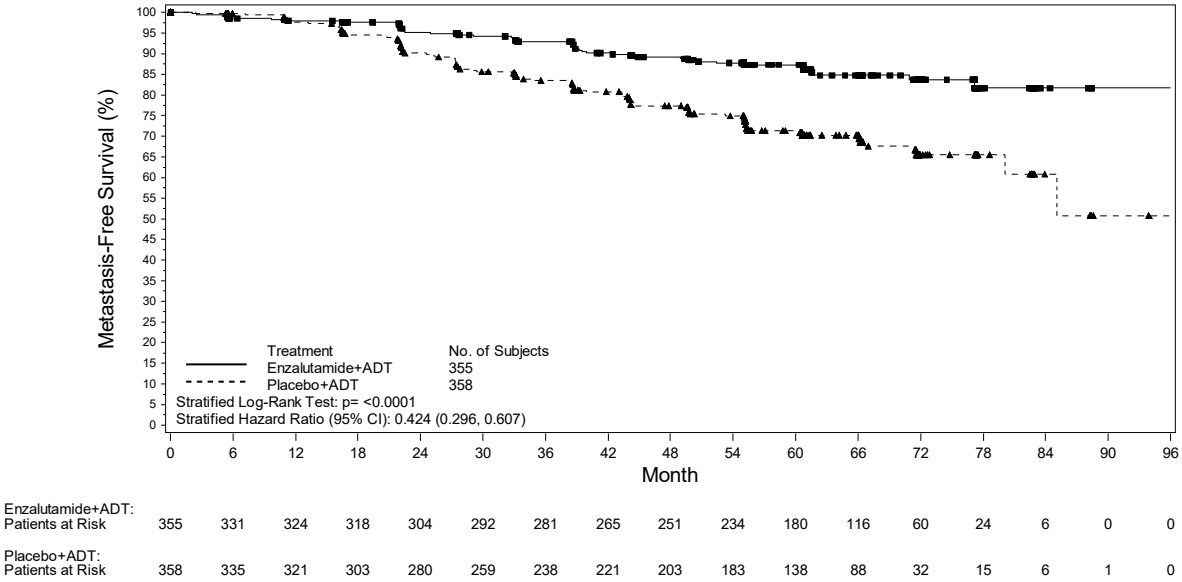
Table 2: Summary of efficacy in patients treated with either enzalutamide plus ADT, placebo plus ADT, or enzalutamide as monotherapy, in the EMBARK study (intent-to-treat analysis)

	Enzalutamide plus ADT (N = 355)	Placebo plus ADT (N = 358)	Enzalutamide as Monotherapy (N = 355)
Metastasis-free Survival[1]			
Number of events (%)[2]	45 (12.7)	92 (25.7)	63 (17.7)
Median, months (95% CI)[3]	NR (NR, NR)	NR (85.1, NR)	NR (NR, NR)
Hazard ratio relative to Placebo plus ADT (95% CI)[4]	0.42 (0.30, 0.61)	--	0.63 (0.46, 0.87)
P-value for comparison to Placebo plus ADT[5]	$p < 0.0001$	--	$p = 0.0049$
Time to PSA Progression[6]			
Number of events (%)[2]	8 (2.3)	93 (26.0)	37 (10.4)
Median, months (95% CI)[3]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Hazard ratio relative to Placebo plus ADT (95% CI)[4]	0.07 (0.03, 0.14)	--	0.33 (0.23, 0.49)
P-value for comparison to Placebo plus ADT[5]	$p < 0.0001$	--	$p < 0.0001$
Time to Start of New Antineoplastic Therapy			
Number of events (%)[7]	58 (16.3)	140 (39.1)	84 (23.7)
Median, months (95% CI)[3]	NR (NR, NR)	76.2 (71.3, NR)	NR (NR, NR)
Hazard ratio relative to Placebo plus ADT (95% CI)[4]	0.36 (0.26, 0.49)	--	0.54 (0.41, 0.71)
P-value for comparison to Placebo plus ADT[5]	$p < 0.0001$	--	$p < 0.0001$
Overall Survival[8]			
Number of events (%)	33 (9.3)	55 (15.4)	42 (11.8)
Median, months (95% CI)[3]	NR (NR, NR)	NR (NR, NR)	NR (NR, NR)
Hazard ratio relative to Placebo plus ADT (95% CI)[4]	0.59 (0.38, 0.91)	--	0.78 (0.52, 1.17)
P-value for comparison to Placebo plus ADT[5]	$p = 0.0153$[9]	--	$p = 0.2304$[9]

NR = Not reached.

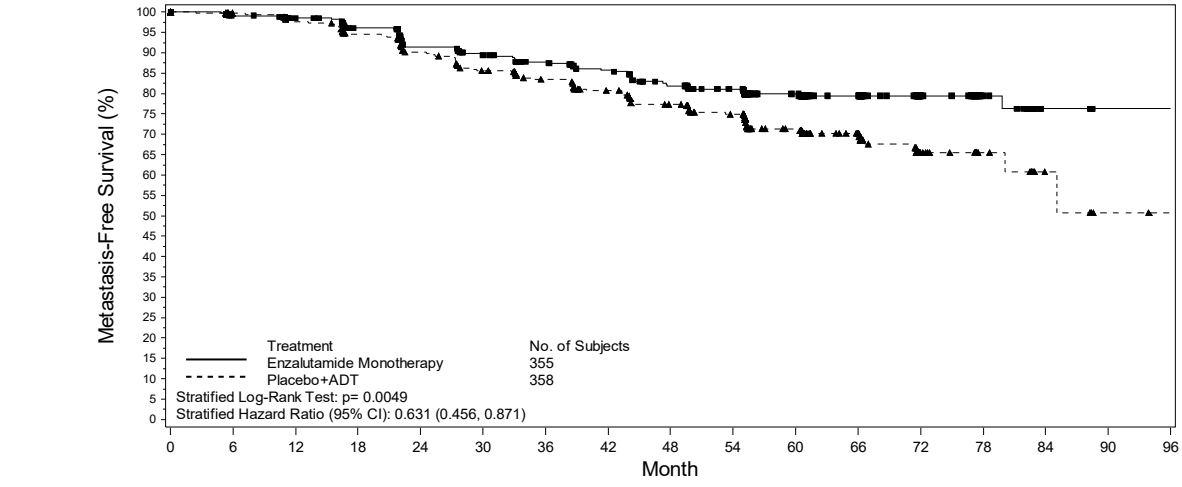
1. Median follow-up time of 61 months.
2. Based on the earliest contributing event (radiographic progression or death).
3. Based on Kaplan-Meier estimates.
4. Hazard Ratio is based on a Cox regression model stratified by screening PSA, PSA doubling time, and prior hormonal therapy.
5. Two-sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy.
6. Based on the PSA Progression compliant with Prostate Cancer Clinical Trials Working Group 2 criteria.
7. Based on the first postbaseline use of antineoplastic therapy for prostate cancer.
8. Based upon a pre-specified interim analysis with data cutoff date of 31 Jan 2023 and a median follow-up time of 65 months.
9. The result did not meet the pre-specified two-sided significance level of $p \leq 0.0001$.

Figure 1: Kaplan-Meier curves of MFS in the Enzalutamide plus ADT vs. Placebo plus ADT treatment arms of the EMBARK study (intent-to-treat analysis)



Enzalutamide+ADT: Patients at Risk	355	331	324	318	304	292	281	265	251	234	180	116	60	24	6	0	0
Placebo+ADT: Patients at Risk	358	335	321	303	280	259	238	221	203	183	138	88	32	15	6	1	0

Figure 2: Kaplan-Meier curves of MFS in the Enzalutamide as Monotherapy vs. Placebo plus ADT treatment arms of the EMBARK study (intent-to-treat analysis)



Enzalutamide Monotherapy: Patients at Risk	355	342	328	309	287	273	260	247	228	209	171	108	52	26	5	0	0
Placebo+ADT: Patients at Risk	358	335	321	303	280	259	238	221	203	183	138	88	32	15	6	1	0

Following the administration of ADT as enzalutamide plus ADT or placebo plus ADT, testosterone levels rapidly decreased to castrate levels and remained low until treatment interruption at 37 weeks. Following the interruption, testosterone levels gradually rose to near-baseline levels. Upon re-initiation of treatment, they fell again to castrate levels. In the enzalutamide as monotherapy arm, testosterone levels increased after treatment initiation and returned towards baseline levels upon treatment interruption. They increased once again after treatment with enzalutamide was re-initiated.

9785-CL-0335 (ARCHES) Study (patients with metastatic HSPC)

The ARCHES study enrolled 1150 patients with mHSPC randomized 1:1 to receive treatment with enzalutamide plus ADT or placebo plus ADT (ADT defined as LHRH analogue or bilateral orchiectomy). Patients received enzalutamide at 160 mg once daily (N = 574) or placebo (N = 576).

Patients with metastatic prostate cancer documented by positive bone scan (for bone disease) or metastatic lesions on CT or MRI scan (for soft tissue) were eligible. Patients whose disease spread was limited to regional pelvic lymph nodes were not eligible. Patients were allowed to receive up to 6 cycles

of docetaxel therapy with final treatment administration completed within 2 months of day 1 and no evidence of disease progression during or after the completion of docetaxel therapy. Excluded were patients with known or suspected brain metastasis or active leptomeningeal disease or with a history of seizure or any contribution that may dispose to seizure.

The demographic and baseline characteristics were well balanced between the two treatment groups. The median age at randomization was 70 years in both treatment groups. Most patients in the total population were Caucasian (80.5%), 13.5% were Asian and 1.4% were Black. 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. Patients were stratified by low versus high volume of disease and prior docetaxel therapy for prostate cancer. Thirty-seven percent of patients had a low volume of disease and 63% of patients had a high volume of disease. Eighty-two percent of patients had not received prior docetaxel therapy, 2% received 1-5 cycles and 16% received 6 prior cycles. Treatment with concurrent docetaxel was not allowed.

Radiographic progression-free survival (rPFS), based on independent central review, was the primary endpoint defined as the time from randomization to the first objective evidence of radiographic disease progression or death (due to any cause from time of randomization up until 24 weeks from study drug discontinuation), whichever occurred first.

Enzalutamide 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]. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. The median time to an rPFS event was not reached in the enzalutamide arm and was 19.0 months (95% CI: 16.6, 22.2) in the placebo arm.

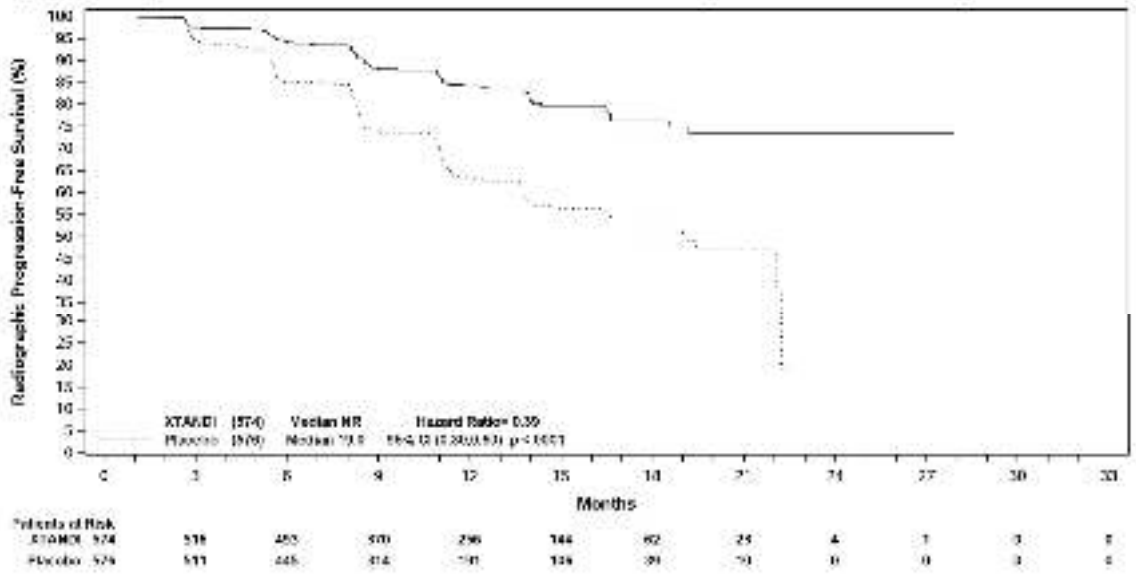
Table 3: Summary of efficacy in patients treated with either enzalutamide or placebo in the ARCHES study (intent-to-treat analysis)

	Enzalutamide plus ADT (N = 574)	**Placebo plus ADT (N = 576)**
Radiographic Progression-free Survival		
Number of events (%)	91 (15.9)	201 (34.9)
Median, months (95% CI)[1]	NR	19.0 (16.6, 22.2)
Hazard ratio (95% CI)[2]	0.39 (0.30, 0.50)	
P-value[2]	p < 0.0001	

NR = Not reached.

1. Calculated using Brookmeyer and Crowley method.
2. Stratified by volume of disease (low vs high) and prior docetaxel use (yes or no).

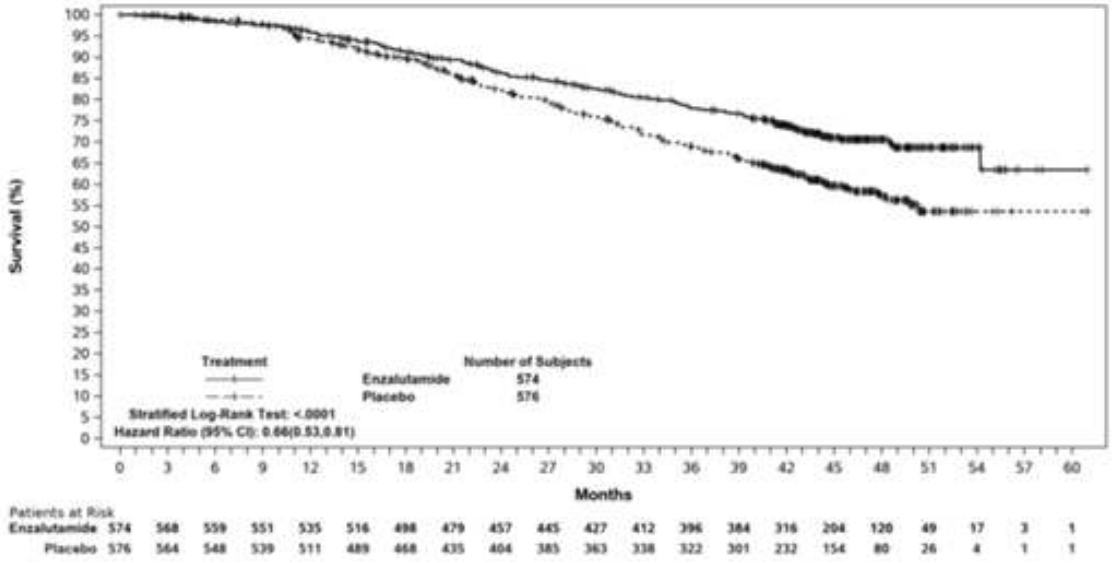
Figure 3: Kaplan-Meier curve of rPFS in ARCHES study (intent-to-treat analysis)



Key secondary efficacy endpoints assessed in the study included time to PSA progression, time to start of new antineoplastic therapy, PSA undetectable rate (decline to < 0.2 µg/L), and objective response rate (RECIST 1.1 based on independent review). Statistically significant improvements in patients treated with enzalutamide compared to placebo were demonstrated for all these secondary endpoints.

Another key secondary efficacy endpoint assessed in the study was overall survival. At the prespecified 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 randomized to receive enzalutamide compared with the group randomized 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. The estimated median follow-up time for all patients was 44.6 months (see Figure 4).

Figure 4: Kaplan-Meier Curves of overall survival in the ARCHES study (intent-to-treat analysis)



MDV3100-14 (PROSPER) study (patients with non-metastatic CRPC)

The PROSPER study enrolled 1401 patients with asymptomatic, high-risk non-metastatic CRPC who continued on androgen deprivation therapy (ADT; defined as LHRH analogue or prior bilateral

orchiectomy). 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).

Patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medicinal products associated with lowering the seizure threshold were allowed. Patients were excluded with a previous history of seizure, a condition that might predispose them to seizure, or certain prior treatments for prostate cancer (i.e., chemotherapy, ketoconazole, abiraterone acetate, aminoglutethimide and/or enzalutamide).

Patients were randomized 2:1 to receive either enzalutamide at a dose of 160 mg once daily (N = 933) or placebo (N = 468). Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) (< 6 months or ≥ 6 months) and the use of bone-targeting agents (yes or no).

The demographic and baseline characteristics were well-balanced between the two treatment arms. The median age at randomization was 74 years in the enzalutamide arm and 73 years in the placebo arm. Most patients (approximately 71%) in the study were Caucasian, 16% were Asian and 2% were Black. Eighty-one percent (81%) of patients had an ECOG performance status score of 0 and 19% patients had an ECOG performance status of 1.

Metastasis-free survival (MFS) was the primary endpoint defined as the time from randomization to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first. Key secondary endpoints assessed in the study were time to PSA progression, time to first use of new antineoplastic therapy (TTA), overall survival (OS). Additional secondary endpoints included time to first use of cytotoxic chemotherapy and chemotherapy-free survival. See results below (Table 4).

Enzalutamide demonstrated a statistically significant 71% reduction in the relative risk of radiographic progression or death 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) on the enzalutamide arm versus 14.7 months (95% CI: 14.2, 15.0) on the placebo arm. Consistent MFS results were also observed in all pre-specified patient sub-groups including PSADT (< 6 months or ≥ 6 months), demographic region (North America, Europe, rest of world), age (< 75 or ≥ 75), use of a prior bone-targeting agent (yes or no) (see Figure 5).

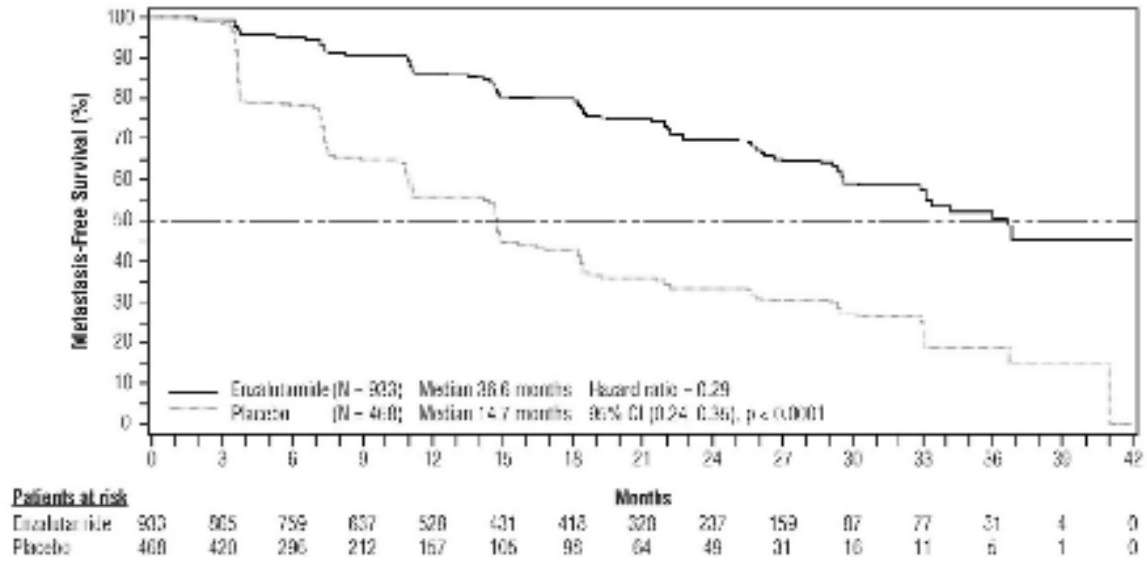
Table 4: Summary of efficacy results in the PROSPER study (intent-to-treat analysis)

	Enzalutamide (N = 933)	Placebo (N = 468)
Primary Endpoint		
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[3]	p < 0.0001	
Key Secondary Efficacy Endpoints		
Overall Survival[4]		
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]	0.734 (0.608, 0.885)	
P-value[3]	p = 0.0011	
Time to PSA progression		
Number of Events (%)	208 (22.3)	324 (69.2)
Median, months (95% CI)[1]	37.2 (33.1, NR)	3.9 (3.8, 4.0)
Hazard Ratio (95% CI)[2]	0.07 (0.05, 0.08)	
P-value[3]	p < 0.0001	
Time to first use of new antineoplastic therapy		
Number of Events (%)	142 (15.2)	226 (48.3)
Median, months (95% CI)[1]	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard Ratio (95% CI)[2]	0.21 (0.17, 0.26)	
P-value[3]	p < 0.0001	

NR = Not reached.

1. Based on Kaplan-Meier estimates.
2. 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 favoring enzalutamide.
3. 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).
4. Based upon a prespecified interim analysis with data cut off date of 15 Oct 2019.

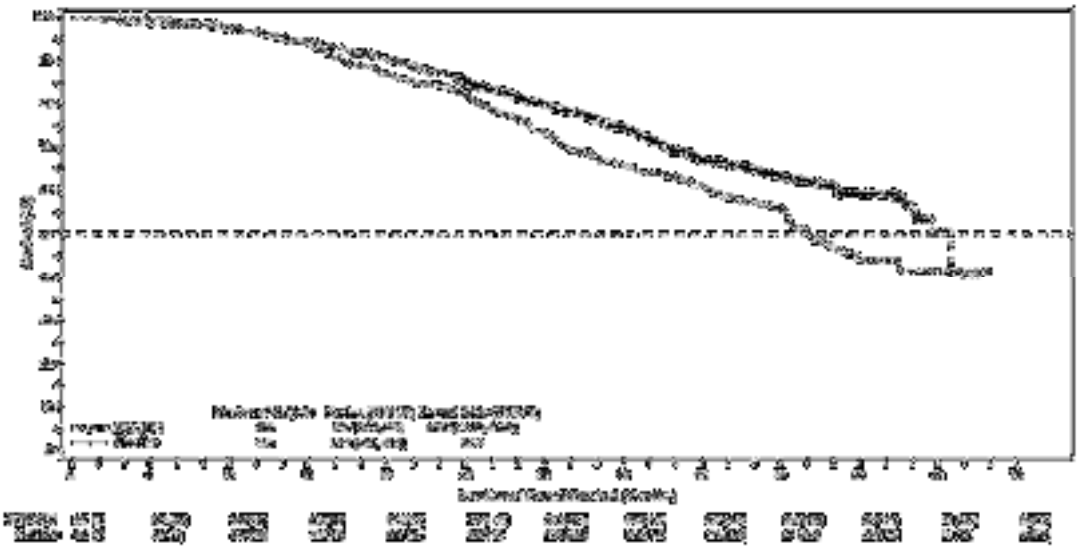
Figure 5: Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)



At the final analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomized to receive enzalutamide 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] (see Figure 6). The median follow-

up time was 48.6 and 47.2 months for the enzalutamide and placebo groups, respectively. Thirty-three percent of enzalutamide-treated and 65% of placebo-treated patients received at least one subsequent antineoplastic therapy that may prolong overall survival.

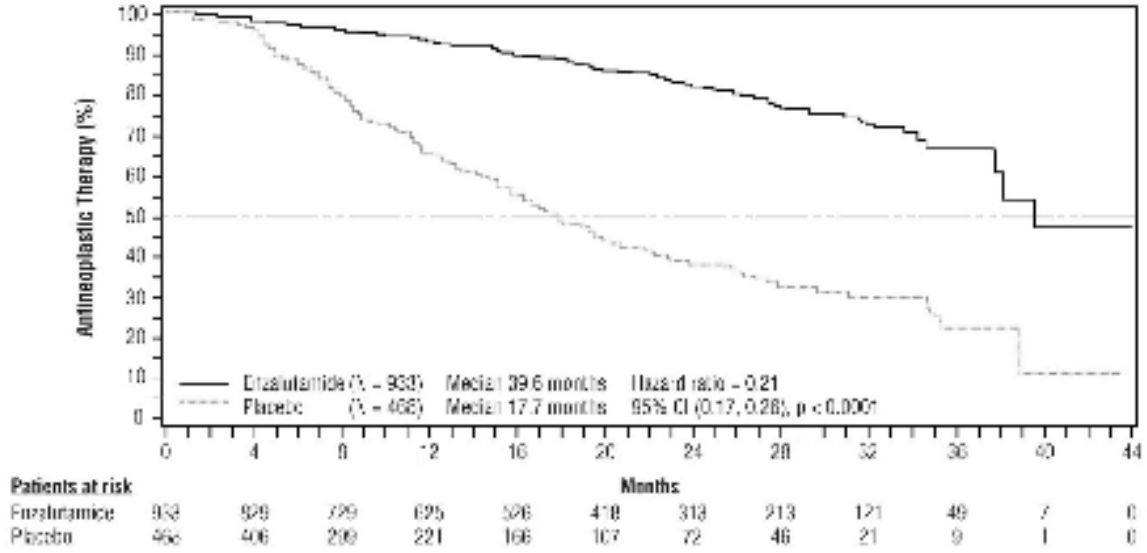
Figure 6: Kaplan-Meier Curves of overall survival in the PROSPER study (intent-to-treat analysis)



Enzalutamide demonstrated a statistically significant 93% reduction in the relative risk of PSA progression compared to placebo [HR = 0.07 (95% CI: 0.05, 0.08), p < 0.0001]. Median time to PSA progression was 37.2 months (95% CI: 33.1, NR) on the enzalutamide arm versus 3.9 months (95% CI: 3.8, 4.0) on the placebo arm.

Enzalutamide demonstrated a statistically significant delay in the time to first use of new antineoplastic therapy compared to placebo [HR = 0.21 (95% CI: 0.17, 0.26), p < 0.0001]. Median time to first use of new antineoplastic therapy was 39.6 months (95% CI: 37.7, NR) on the enzalutamide arm versus 17.7 months (95% CI: 16.2, 19.7) on the placebo arm (see Figure 7).

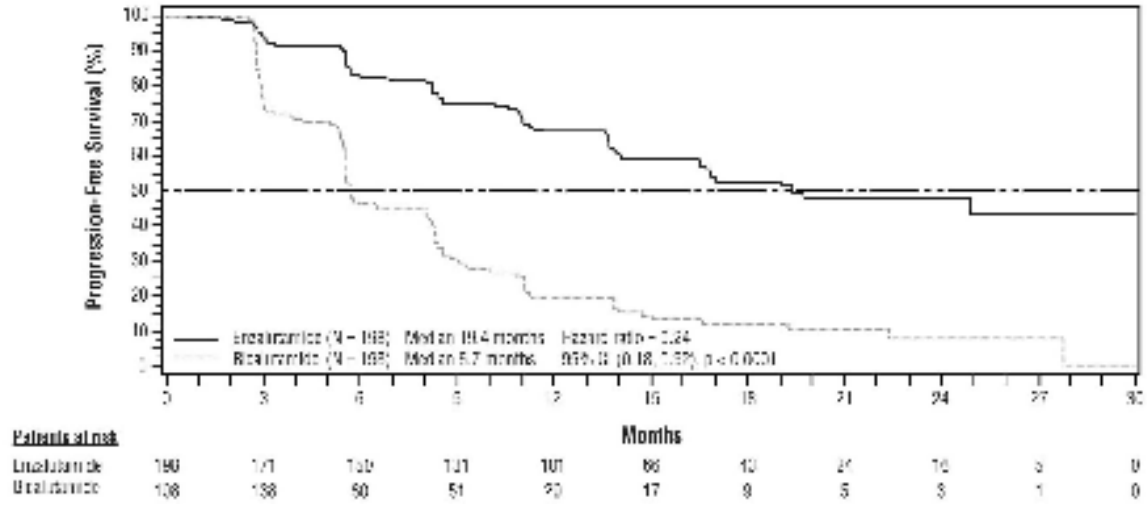
Figure 7: Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)



MDV3100-09 (STRIVE) study (chemotherapy-naïve patients with non-metastatic/metastatic CRPC)

The STRIVE study enrolled 396 non-metastatic or metastatic CRPC patients who had serologic or radiographic disease progression despite primary androgen deprivation therapy who were randomized to receive either enzalutamide at a dose of 160 mg once daily (N = 198) or bicalutamide at a dose of 50 mg once daily (N = 198). PFS was the primary endpoint defined as the time from randomization to the earliest objective evidence of radiographic progression, PSA progression, or death on study. Median PFS was 19.4 months (95% CI: 16.5, not reached) in the enzalutamide group versus 5.7 months (95% CI: 5.6, 8.1) in the bicalutamide group [HR = 0.24 (95% CI: 0.18, 0.32), p < 0.0001]. Consistent benefit of enzalutamide over bicalutamide on PFS was observed in all pre-specified patient subgroups. For the non-metastatic subgroup (N = 139) a total of 19 out of 70 (27.1%) patients treated with enzalutamide and 49 out of 69 (71.0%) patients treated with bicalutamide had PFS events (68 total events). The hazard ratio was 0.24 (95% CI: 0.14, 0.42) and the median time to a PFS event was not reached in the enzalutamide group versus 8.6 months in the bicalutamide group (see Figure 8).

Figure 8: Kaplan-Meier Curves of progression-free survival in the STRIVE study (intent-to-treat analysis)



MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients with metastatic CRPC)

A total of 1717 asymptomatic or mildly symptomatic chemotherapy-naïve patients were randomized 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medicinal products 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.

Patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range 42 - 93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% other or unknown races. Sixty-eight percent (68%) of patients had an ECOG performance status score of 0 and 32% patients had an ECOG performance status of 1. 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 on a scale of 0 to 10). Approximately 45% of patients had measurable soft tissue disease at study entry, and 12% of patients had visceral (lung and/or liver) metastases.

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 time to initiation of cytotoxic

chemotherapy, best overall soft tissue response, time to first skeletal-related event, PSA response (≥ 50% decrease from baseline), time to PSA progression, and time to FACT-P total score degradation. 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.

At the pre-specified interim analysis for overall survival when 540 deaths were observed, treatment with enzalutamide demonstrated a statistically significant improvement in overall survival compared to treatment with placebo with a 29.4% reduction in risk of death [HR = 0.71 (95% CI: 0.60, 0.84), p < 0.0001]. An updated survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the interim analysis (Table 5, Figure 9). At the updated analysis 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic CRPC that may prolong overall survival.

A final analysis of 5-year PREVAIL data showed a statistically significant increase in overall survival was 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 5: Overall Survival of Patients Treated with Either Enzalutamide or Placebo in the PREVAIL Study (Intent-to-Treat Analysis)

	Enzalutamide (N = 872)	**Placebo (N = 845)**
Pre-specified interim analysis		
Number of deaths (%)	241 (27.6%)	299 (35.4%)
Median survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.71 (0.60, 0.84)	
Updated survival analysis		
Number of deaths (%)	368 (42.2%)	416 (49.2%)
Median survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
P-value[1]	p = 0.0002	
Hazard ratio (95% CI)[2]	0.77 (0.67, 0.88)	
5-year survival analysis		
Number of deaths (%)	689 (79)	693 (82)
Median survival, months (95% CI)	35.5 (33.5, 38.0)	31.4 (28.9, 33.8)
P-value[1]	p = 0.0008	
Hazard ratio (95% CI)[2]	0.835 (0.75, 0.93)	

NR = Not reached.

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 enzalutamide.

Figure 9: Kaplan-Meier Curves of Overall Survival Based on 5-year Survival Analysis in the PREVAIL Study (Intent-to-Treat Analysis)

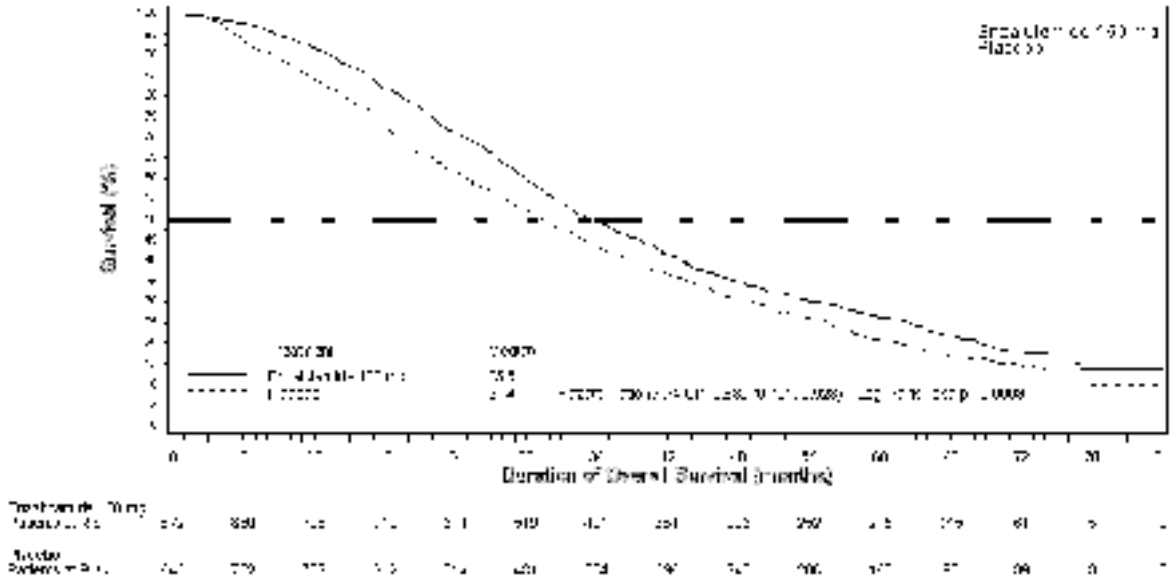
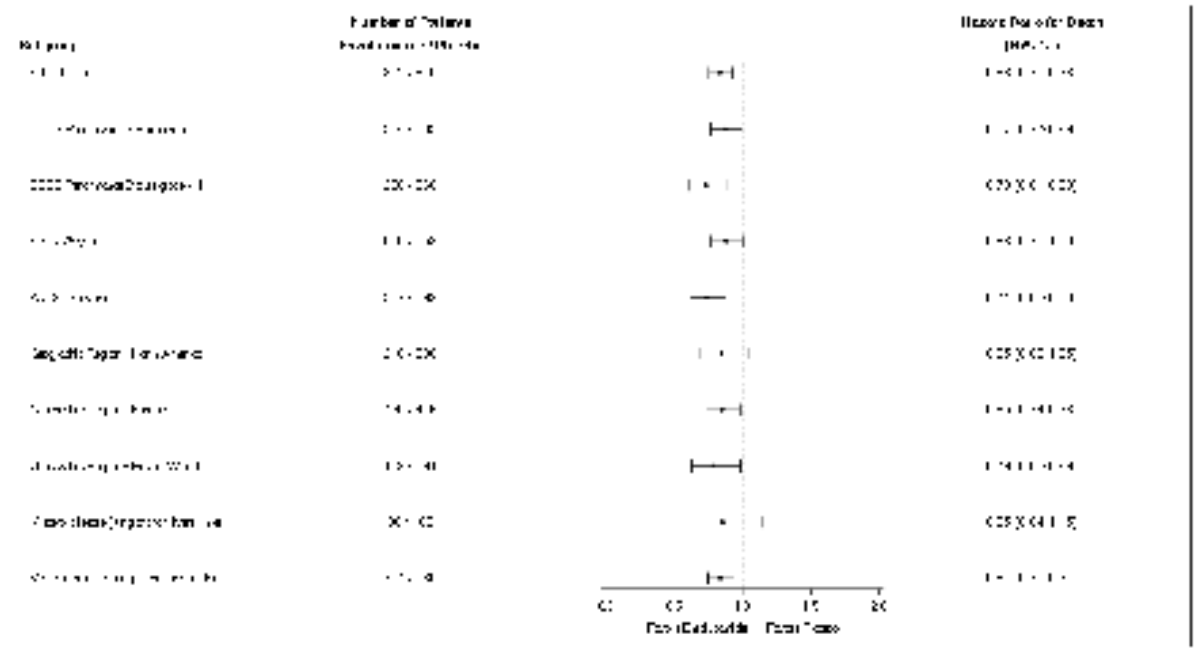
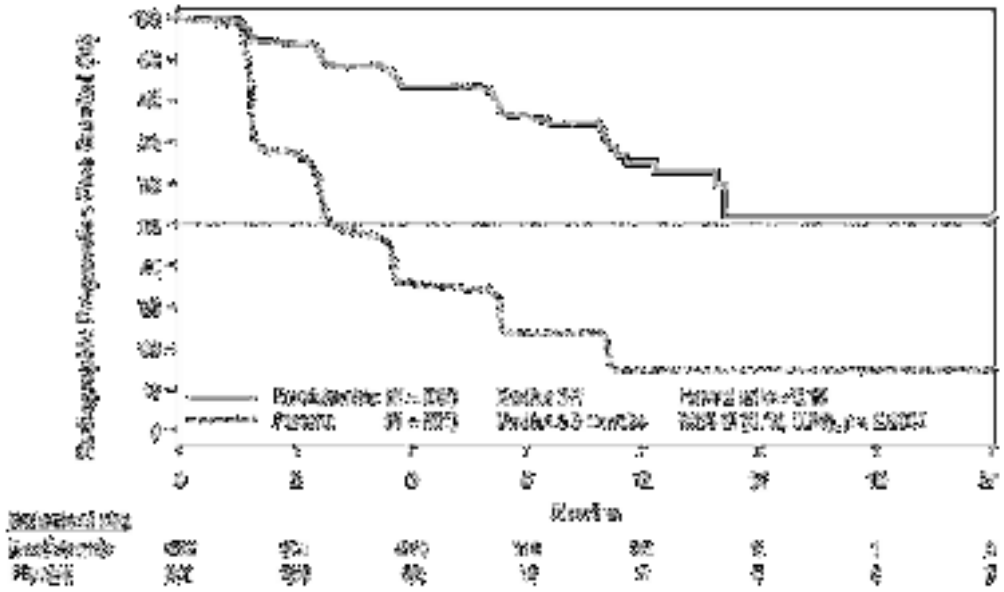


Figure 10: 5-year Overall Survival Analysis by Subgroup: Hazard Ratio and 95% Confidence Interval in the PREVAIL Study (Intent-to-Treat Analysis)



At the pre-specified rPFS analysis, a statistically significant improvement was demonstrated between the treatment groups with an 81.4% reduction in risk of radiographic progression or death [HR = 0.19 (95% CI: 0.15, 0.23), p < 0.0001]. One hundred and eighteen (14%) enzalutamide-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 enzalutamide-treated group and was 3.9 months (95% CI: 3.7, 5.4) in the placebo-treated group (Figure 11). Consistent rPFS benefit was observed across all pre-specified patient subgroups (e.g., age, baseline ECOG performance, baseline PSA and LDH, Gleason score at diagnosis, and visceral disease at screening). A pre-specified follow-up rPFS analysis based on the investigator assessment of radiographic progression demonstrated a statistically significant improvement between the treatment groups with a 69.3% reduction in risk of radiographic progression or death [HR = 0.31 (95% CI: 0.27, 0.35), p < 0.0001]. The median rPFS was 19.7 months in the enzalutamide group and 5.4 months in the placebo group.

Figure 11: Kaplan-Meier Curves of Radiographic Progression-Free Survival in the PREVAIL Study (Intent-to-Treat Analysis)



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

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

The median time to initiation of cytotoxic chemotherapy was 28.0 months for patients receiving enzalutamide and 10.8 months for patients receiving placebo [HR=0.35 (95% CI: 0.30, 0.40), p<0.0001].

The proportion of enzalutamide-treated patients with measurable disease at baseline who had an objective soft tissue response was 58.8% (95% CI: 53.8, 63.7) compared with 5.0% (95% CI: 3.0, 7.7) of patients receiving placebo. The absolute difference in objective soft tissue response between enzalutamide and placebo arms was [53.9% (95% CI: 48.5, 59.1), p<0.0001]. Complete responses were reported in 19.7% of enzalutamide-treated patients compared with 1.0% of placebo-treated patients, and partial responses were reported in 39.1% of enzalutamide-treated patients versus 3.9% of placebo-treated patients.

Enzalutamide significantly decreased the risk of the first skeletal related event by 28% [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. The analysis included 587 skeletal related events, of which 389 events (66.3%) were radiation to bone, 79 events (13.5%) were spinal cord compression, 70 events (11.9%) were pathologic bone fracture, 45 events (7.6%) were change in antineoplastic therapy to treat bone pain, and 22 events (3.7%) were surgery to bone.
Patients receiving enzalutamide demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 78.0% versus 3.5% (difference = 74.5%, p < 0.0001).

The median time to PSA progression per PCWG2 criteria was 11.2 months for patients treated with enzalutamide and 2.8 months for patients who received placebo [HR=0.17, (95% CI: 0.15, 0.20), p<0.0001].

Treatment with enzalutamide decreased the risk of FACT-P degradation by 37.5% compared with placebo (p<0.0001). The median time to degradation in FACT-P was 11.3 months in the enzalutamide group and 5.6 months in the placebo group.

9785-CL-0222 (TERRAIN) study (chemotherapy-naïve patients with metastatic CRPC)

The TERRAIN study enrolled 375 chemo- and antiandrogen-therapy naïve patients with metastatic CRPC who were randomized to receive either enzalutamide at a dose of 160 mg once daily (N = 184) or bicalutamide at a dose of 50 mg once daily (N = 191). Median PFS was 15.7 months for patients on enzalutamide versus 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), $p < 0.0001$]. Progression-free survival was defined as objective evidence of radiographic disease progression by independent central review, skeletal-related events, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Consistent PFS benefit was observed across all pre-specified patient subgroups.

CRPC2 (AFFIRM) study (patients with metastatic CRPC who previously received chemotherapy)

The efficacy and safety of enzalutamide in patients with metastatic castration-resistant prostate cancer who had received docetaxel and were using a LHRH analogue or had undergone orchiectomy were assessed in a randomized, placebo-controlled, multicenter phase 3 clinical trial. A total of 1199 patients were randomized 2:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed but not required to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients randomized to either arm were to continue treatment until disease progression (defined as confirmed radiographic progression or the occurrence of a skeletal-related event) and initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline disease characteristic were balanced between the treatment arms. The median age was 69 years (range 41 - 92) and the racial distribution was 93% Caucasian, 4% Black, 1% Asian, and 2% Other. The ECOG performance score was 0 - 1 in 91.5% of patients and 2 in 8.5% of patients; 28% had a mean Brief Pain Inventory score of ≥ 4 (mean of patient's reported worst pain over the previous 24 hours calculated for seven days prior to randomization). Most (91%) patients had metastases in bone and 23% had visceral lung and/or liver involvement. At study entry, 41% of randomized patients had PSA progression only, whereas 59% of patients had radiographic progression. Fifty-one percent (51%) of patients were on bisphosphonates at baseline.

The AFFIRM study excluded patients with medical conditions that may predispose them to seizures (see section 4.8) and medicinal products known to decrease the seizure threshold, as well as clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).

The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with enzalutamide compared to placebo (Table 6 and Figures 12 and 13).

Table 6: Overall Survival of Patients Treated with Either Enzalutamide or Placebo in the AFFIRM Study (Intent-to-Treat Analysis)

	Enzalutamide (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[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 ECOG performance status score (0-1 vs. 2) and mean pain score (< 4 vs. ≥ 4).
2. Hazard ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favors enzalutamide.

Figure 12: Kaplan-Meier Curves of Overall Survival in the AFFIRM Study (Intent-to-Treat Analysis)

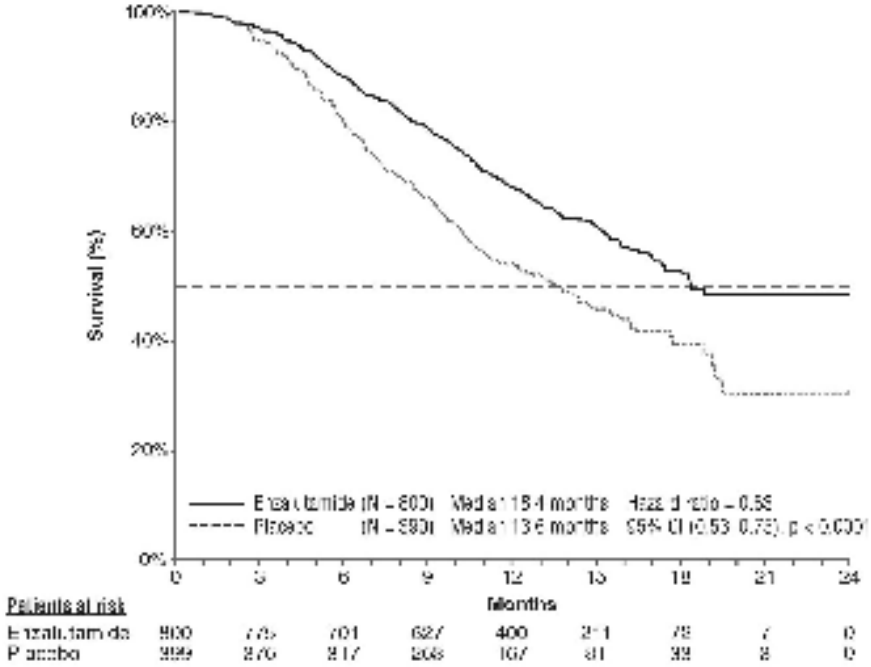
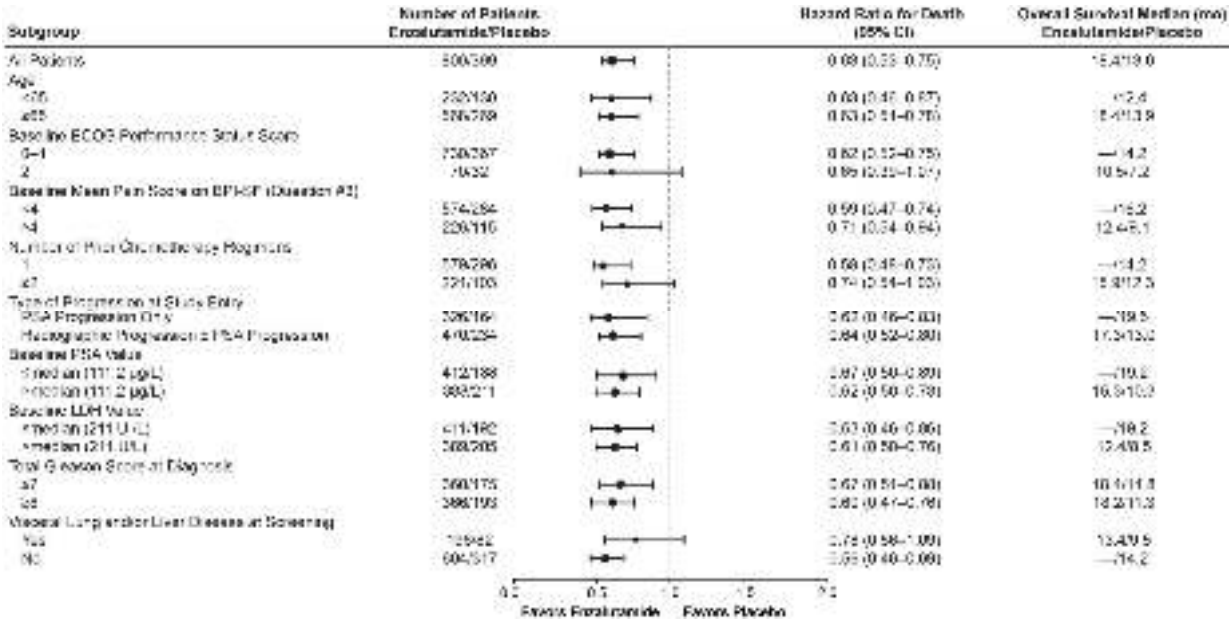


Figure 13: Overall Survival by Subgroup in the AFFIRM Study – Hazard Ratio and 95% Confidence Interval



ECOG: Eastern Cooperative Oncology Group; BPI-SF: Brief Pain Inventory-Short Form;
PSA: Prostate Specific Antigen

In addition to the observed improvement in overall survival, key secondary endpoints (PSA progression, radiographic progression-free survival, and time to first skeletal-related event) favored enzalutamide and were statistically significant after adjusting for multiple testing.

Radiographic progression-free survival as assessed by the investigator using RECIST v1.1 for soft tissue and appearance of 2 or more bone lesions in bone scan was 8.3 months for patients treated with enzalutamide and 2.9 months for patients who received placebo [HR = 0.40 (95% CI: 0.35, 0.47), $p < 0.0001$]. The analysis involved 216 deaths without documented progression and 645 documented progression events, of which 303 (47%) were due to soft tissue progression, 268 (42%) were due to bone lesion progression and 74 (11%) were due to both soft tissue and bone lesions.

Confirmed PSA decline of 50% or 90% were 54.0% and 24.8%, respectively, for patients treated with enzalutamide and 1.5% and 0.9%, respectively, for patients who received placebo (p<0.0001). The median time to PSA progression was 8.3 months for patients treated with enzalutamide and 3.0 months for patients who received placebo [HR = 0.25 (95% CI: 0.20, 0.30), p < 0.0001].

The median time to first skeletal-related event was 16.7 months for patients treated with enzalutamide and 13.3 months for patients who received placebo [HR = 0.69 (95% CI: 0.57, 0.84), p < 0.0001]. A 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. The analysis involved 448 skeletal-related events, of which 277 events (62%) were radiation to bone, 95 events (21%) were spinal cord compression, 47 events (10%) were pathologic bone fracture, 36 events (8%) were change in antineoplastic therapy to treat bone pain, and 7 events (2%) were surgery to bone.

Elderly
Of the 5110 patients in the controlled clinical studies who received enzalutamide, 3988 patients (78%) were 65 years and over and 1703 patients (33%) were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

5.2 Pharmacokinetic properties

Enzalutamide is poorly water soluble. In this product, the solubility of enzalutamide is increased by caprylocaproyl macrogolglycerides as emulsifier/surfactant. In preclinical studies, the absorption of enzalutamide was increased when dissolved in caprylocaproyl macrogolglycerides.

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption
Maximum plasma concentration (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. Based on a mass balance study in humans, 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. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16.6 µg/mL: (23% coefficient of variation [CV]) and 12.7 µg/mL (30% CV), respectively.

Food has no clinically significant effect on the extent of absorption. 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 its active metabolite can cross the blood brain barrier.

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

Biotransformation
Enzalutamide is extensively metabolized. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolized by CYP2C8 and to a lesser extent by CYP3A4/5 (see section 4.5), both of which play a role in the formation of the active metabolite. *In vitro*, N-desmethyl enzalutamide is metabolized to the carboxylic acid metabolite by carboxylesterase 1, which also plays a minor role in the metabolism of

enzalutamide to the carboxylic acid metabolite. N-desmethyl enzalutamide was not metabolized by CYPs *in vitro*.

Under conditions of clinical use, enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically relevant effect on CYP2C8 (see section 4.5).

Elimination
The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of ^{14}C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

In vitro data indicate that enzalutamide is not a substrate for OATP1B1, OATP1B3, or OCT1; and N-desmethyl enzalutamide is not a substrate for P-gp or BCRP.

In vitro data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OATP1B1, OATP1B3, OCT2, or OAT1.

Linearity
No major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The steady-state C_{min} values of enzalutamide and the active metabolite in individual patients remained constant during more than one year of chronic therapy, demonstrating time-linear pharmacokinetics once steady-state is achieved.

Renal impairment
No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. 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). Enzalutamide 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.

Hepatic impairment
Hepatic impairment did not have a pronounced effect on the total exposure to enzalutamide or its active metabolite. The half-life of enzalutamide was however doubled in patients with severe hepatic impairment compared with healthy controls (10.4 days compared to 4.7 days), possibly related to an increased tissue distribution.

The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N = 6) or moderate (N = 8) or severe (N = 8) hepatic impairment (Child-Pugh Class A, B, or C respectively) and in 22 matched control subjects with normal hepatic function. Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, and the AUC and C_{max} of enzalutamide in subjects with severe impairment increased by 5% and decreased by 41%, respectively, compared to healthy control subjects. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased by 14% and 19%, respectively, the AUC and C_{max} in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, and the AUC and C_{max} in subjects with severe hepatic impairment increased by 34% and decreased by 27%, respectively, compared to healthy control subjects.

Race
Most patients in the controlled clinical studies (> 75%) were Caucasian. Based on pharmacokinetic data from studies in Japanese and Chinese patients with prostate cancer, there were no clinically relevant

differences in exposure among the populations. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

Elderly
No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the elderly population pharmacokinetic analysis.

5.3 Preclinical safety data

Enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Fertility studies were not conducted with enzalutamide, but in studies in rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), atrophy, aspermia/hypospermia, and hypertrophy/hyperplasia in the reproductive system were noted, consistent with the pharmacological activity of enzalutamide. In studies in mice (4 weeks), rats (4 and 26 weeks) and dogs (4, 13 and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Leydig cell hypertrophy and/or hyperplasia were observed in mice (4 weeks) and dogs (39 weeks). Additional changes to reproductive tissues included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicle in rats and testicular hypospermia and seminiferous tubule degeneration in dogs. Gender differences were noted in rat mammary glands (male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reserved or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver, in either species.

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 (~ 1.9 times the maximum dose indicated in humans), the maximum radioactivity in the fetus was reached 4 hours after administration and was lower than that in the maternal plasma with tissue/plasma ratio of 0.27. The radioactivity in the fetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

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 (~ 1.9 times the maximum dose indicated in humans), 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.

Enzalutamide was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests. 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 mCRPC patients receiving 160 mg, daily.

Daily dosing of rats for two years with enzalutamide produced an increased incidence of neoplastic findings. These included benign thymoma, fibroadenoma in the mammary glands, benign Leydig cell tumours in the testes and urothelium papilloma and carcinoma of urinary bladder in males; benign granulosa cell tumour in the ovaries in females and adenoma in the pars distalis of the pituitary in both sexes. The human relevance of thymoma, pituitary adenoma and mammary fibroadenoma as well as urothelium papilloma and carcinoma of urinary bladder cannot be ruled out.

Enzalutamide was not phototoxic *in vitro*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Caprylocaproyl macrogol-8 glycerides
Butylhydroxyanisole (E320)
Butylhydroxytoluene (E321)

Capsule shell
Gelatin
Sorbitol sorbitan solution
Glycerol
Titanium dioxide (E171)
Purified water

Printing ink
Iron oxide black (E172)
Polyvinyl acetate phthalate

6.2 Shelf life

36 months.

Store below 30°C.

6.3 Special precautions for use and handling

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, Xtandi 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. See section 5.3 Pre-clinical safety data.

Swallow capsules whole with a sufficient amount of water. The soft capsules should not be chewed, dissolved or opened.

Keep out of the reach of children.

Packaging:
Box, 28 sachets @ 1 blister @ 4 soft capsules

"HARUS DENGAN RESEP DOKTER"

Reg. No.: DKI1717400102A1

MANUFACTURED BY: Catalent Pharma Solutions, LLC, Florida, USA, Packed by AndersonBrecon, Rockford, USA, released by Astellas US Technologies Inc, USA

REPACKED BY: Zuellig Pharma Specialty Solutions Group Pte, Ltd., Changi North Way, Singapore

MARKETING AUTHORIZATION HOLDER: PT. Meprofarm Pharmaceutical Industries, Bandung, Indonesia

MARKETED BY: PT. Astellas Pharma Indonesia, Jakarta, Indonesia

Information for patients

Xtandi™ 40 mg soft capsules

Enzalutamide

Please read this leaflet carefully before taking this medicine. There is important information inside.
- Keep this leaflet in a safe place. You may need to read it again.
- If you have any further questions, please ask your doctor.
- This medicine is prescribed for you. Do not give it to others. This medicine might be harmful to them, even though they have the same symptoms.
- If you experience any side effects, contact your doctor immediately. This includes any side effects that are not listed in this leaflet.

What's in this leaflet:

1. What is Xtandi and what it is used for

Xtandi contains enzalutamide as its active substance. Xtandi is used:
- As monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy.
- To treat adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.
- To treat adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- In combination with androgen deprivation therapy to treat adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not clinically indicated.
- For the second line treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

How Xtandi works
Xtandi is a drug that works by inhibiting androgen hormone activities (such as testosterone). By inhibiting androgens, enzalutamide slows the growth and spread of prostate cancer cells.

2. What to know before taking Xtandi

Do not take Xtandi:
- If you are allergic (hypersensitive) to enzalutamide or other substances contained in this drug (listed in section 6).
- If you are pregnant or may become pregnant (see “Pregnancy, breastfeeding, and fertility”).

Warnings and Cautions
Seizures
Seizures have been reported by 6 people out of 1,000 patients when using Xtandi, and fewer than 3 people out of 1,000 patients when using placebo (see also “Other drugs and Xtandi” in this section and section 4 “Possible side effects”).

Before using Xtandi, ask your physician or pharmacist:
- If you have seizure history or high risk of experiencing seizure.
- If you have kidney or liver problem.
- If you have abnormalities in the heart, including irregular heartbeat.
- If you have high blood pressure. Xtandi can increase your blood pressure. Your physician will measure your blood pressure before the treatment and periodically during treatment with Xtandi.
- If you have sudden unconsciousness.
- If you have history of fall or fractures.
- If you have electrolyte imbalance (such as low levels of magnesium and potassium in blood) or condition that can affect electrolyte imbalance (e.g. vomiting, diarrhea, dehydration, or eating disorder).
- If you have intolerance to fructose, a rare heredity. This is because Xtandi contains sorbitol.
- If you currently taking or have recently taken all medicinal product (including traditional medicine).
- If you use other drugs that can cause seizures or drugs that can increase the possibility of seizures (see "Other drugs and Xtandi" below).

If you experience seizures during therapy:
Stop using Xtandi and do not take it. Contact your doctor as soon as possible.

Posterior Reversible Encephalopathy Syndrome (PRES)
Reports of the occurrence of PRES are very rare (a rare condition that is reversible in the brain) in patients that using Xtandi. If you experience seizures, worsening headaches, confusion, blindness, or other vision issues, contact your doctor immediately (see also section 4 "Possible side effects").

Difficulty swallowing related to product formulation
There have been reports of patients experiencing difficulty swallowing this medicine, including reports of choking. The swallowing difficulties or choking events were more commonly observed in patients receiving capsules, which could be related to a larger product size. Swallow the capsules whole with a sufficient amount of water.

If you have difficulties swallowing large capsules or a history of dysphagia, you can have difficulties swallowing Xtandi capsules, or a risk of choking.

Talk to your doctor before taking Xtandi:
- If you take drugs to inhibit blood clotting (e.g. warfarin, acenocoumarol, clopidogrel).
- If you have liver disease.
- If you have kidney disease.
- If you use chemotherapy, like docetaxel.

Notify your doctor if you have:
Heart or blood vessel conditions, including arrhythmia, or are using drugs to improve such conditions. Arrhythmia risk may increase when using Xtandi. If you are allergic to enzalutamide, this may result in a rash or swelling of the face, tongue, lip or throat. If you are allergic to enzalutamide or any of the other ingredients of this medicine, do not take Xtandi.

If you experience any of the above or if you are not sure, talk to your doctor before taking this medicine.

Children and adolescents
This drug is not intended to be used by children and adolescents.

Other drugs and Xtandi
Tell your doctor if you are taking or were recently taking other drugs. You need to know which medications you are taking. Make a list of drugs that you are using, to be shown to your doctor when you are given new drugs. You should not start or stop taking any medication before talking to your doctor whom provides Xtandi.

Tell your doctor if you are taking any of the medications below. When used in conjunction with Xtandi, these drugs may increase the risk of seizures:
- Certain medications used to treat asthma and other respiratory diseases (e.g. aminophylline, theophylline)
- Drugs that are used to treat certain psychic diseases such as depression and schizophrenia (e.g. clozapine, olanzapine, risperidone, ziprasidone, bupropion, lithium, chlorpromazine, mesoridazine, thioridazine, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Certain medications used to treat pain (e.g. pethidine)

Tell your doctor if you are taking any of the medications below. These medications may affect Xtandi, or Xtandi may affect these drugs:

This includes certain medications that are used for:
- Decreasing the cholesterol level (e.g. gemfibrozil, atorvastatin, simvastatin)
- Treating pain (e.g. fentanyl, tramadol)
- Treating cancer (e.g. cabazitaxel)
- Treating epilepsy (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Treating certain psychic diseases such as severe anxiety or schizophrenia (e.g. diazepam, midazolam, haloperidol)
- Treating sleep disorders (e.g. zolpidem)
- Treating heart problems or low blood pressure (e.g. bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil)
- Treating serious diseases associated with inflammation (e.g. dexamethasone, prednisolone)
- Treating HIV infection (e.g. indinavir, ritonavir)
- Treating bacterial infections (e.g. clarithromycin, doxycycline, rifampicin)
- Treating thyroid disorders (e.g. levothyroxine)
- Treating gout (e.g. colchicine)
- Preventing heart disorder or stroke (dabigatran etexilate)
- Treat stomach disorder (e.g. omeprazole)
- Prevent organ rejection (e.g. tacrolimus)

Xtandi may interfere with some medications used to treat heart rhythm issues (e.g. quinidine, procainamide, amiodarone, and sotalol) or it may increase the risk of heart rhythm issues when used with some other medications (e.g. methadone (used to relieve pain and part of detoxification for drug addictions), moxifloxacin (antibiotics), antipsychotics (used for serious mental illness)).

Tell your doctor if you are taking the medications listed above. Xtandi dosage or other medications used may need to be adjusted.

Pregnancy, breastfeeding, and fertility
- **Xtandi should not be used for women**.
- This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. It must not be taken by women who are pregnant, may become pregnant, or who are breastfeeding.
- This drug is likely to affect male fertility.
- If you have sex with a fertile woman, use condoms and other contraceptive methods during and for 3 months after the therapy with this drug. If you have sex with a pregnant woman, use condoms to protect the unborn baby.

Driving and operating machines
Xtandi may have moderate effects in affecting your ability to drive vehicles or operating equipment or machinery, as the side effect of Xtandi includes seizures. If you feel that you have a high risk of seizures (see section 2), consult with your doctor.

Xtandi contains sorbitol
This drug contains sorbitol (a type of sugar). If you have been notified by your doctor for sugar intolerance, tell your doctor before taking this drug.

3. How to take Xtandi

Always take this medicine in accordance with the doctor recommendations. Talk to your doctor if you are not sure.

A typical dose of 160 mg (four capsules) is consumed once per day.

Taking Xtandi
- Swallow and consume the whole capsules orally with a sufficient amount of water.
- Do not chew, dilute, or open the capsules.
- Xtandi can be taken with or without food.
- Xtandi should not be handled by persons other than the patient or his caregivers. Women who are or may become pregnant should not handle damaged or opened Xtandi capsules without wearing protection like gloves.

If you take Xtandi more than you should
If you take more than prescribed, stop taking Xtandi and contact your doctor. You may experience an increased risk of seizures or other side effects.

Your doctor may also prescribe other medicine while you are taking Xtandi.

If you forget to take Xtandi
- If you forget to take Xtandi when you normally take it, take it immediately with the normal dose as soon as you remember.
- If you forget to take Xtandi all day, take the usual dose the day after.
- If you forget to take Xtandi more than a day, tell your doctor as soon as possible.
- **Do not double the dose** to cover for a forgotten dose.

If you stop taking Xtandi
Do not stop taking this medicine unless your doctor recommends it.

If you have any further questions regarding the use of this medication, ask your doctor.

4. Possible side effects that may occur

As with any other drugs, this drug may cause side effects, although not everyone experienced such side effects.

Seizures
Seizures have been reported by 6 people out of 1,000 patients when using Xtandi and fewer than 3 people out of 1,000 patients when using placebo.
Seizures are more likely to occur if you take this medication more than the recommended dose, if you use certain other medications, or if you have a high risk of seizures (see section 2).

If you experience seizures, see your doctor as soon as possible. Do not use Xtandi.

Posterior Reversible Encephalopathy Syndrome (PRES)
Reports of the occurrence of PRES are very rare (may occur to 1 out of 1,000 patients), a rare condition that is reversible in the brain, in patients that using Xtandi. If you experience seizures, worsening headaches, confusion, blindness, or other vision issues, contact your doctor immediately.

Other possible side effects include:

Very common (may affect more than 1 out of 10 people):
Fatigue, fall, fracture, burning sensation, increased blood pressure

General (may affect up to 1 out of 10 people):
Headache, anxiety, dry skin, itching, difficulty to remember something, blockage of the arteries in the heart (ischemic heart disease), male breast enlargement (gynecomastia), nipple pain, breast tenderness, symptoms of restless leg syndrome (uncontrolled urge to move body parts, especially the legs), decreased concentration, forgetfulness, change in sense of taste, difficulty thinking clearly

Uncommon (may affect up to 1 out of 100 people):
Hallucinations, decreased white blood cells

Not known (frequency cannot be estimated from available data):
Muscle aches, muscle cramps, muscle weakness, back pain, changes in ECG (extension of QT), difficulty swallowing this medicine including choking, abdominal pain including sickness (nausea), severe skin rash, skin peeling, blistering, mouth sores, redness, feeling sick (vomiting), face edema, tongue edema, lip edema, pharyngeal edema, blood platelet reduction (may increase the risk of bleeding or bruising), diarrhea, decreased appetite

Reporting of suspected adverse reactions
If you experience any side effects or discomfort during or after using the medication, talk to your doctor or other healthcare professional. You can also report side effects to PT. Astellas Pharma Indonesia at PV@id.astellas.com. Please note that reporting to PT. Astellas Pharma Indonesia is only for gathering data and not a substitute for consulting your doctor or healthcare professional. By reporting side effects, you can help provide more information on the safety of this medicine. Always talk to your doctor or healthcare professional for medical advice.

5. How to store Xtandi

Keep this medicine away from the sight and reach of children.

Do not use this drug after the expiry date listed on the boxes and blisters. Expiration date refers to the last day of the month.

Store below 30°C.

Do not take this medicine if there are signs of leaks, damage, or tampering.

Do not dispose of this medicine into drains or household waste. Ask your pharmacist of ways to dispose of drugs that you do not use anymore. This can help in maintaining the environment.

6. Package contents and other information

What is contained in Xtandi
- Enzalutamide is the active substance. Each capsule contains 40 mg of enzalutamide.
- Other additives are caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320), and butylhydroxytoluene (E321).
- Ingredients for capsule shell are gelatin, sorbitol sorbitan solution (see section 2), glycerol, titanium dioxide (E171), and pure water.
- Ingredients for ink are iron oxide black (E172) and polyvinyl acetate phthalate.

Appearance of Xtandi and contents of the packaging
- Xtandi is provided in white to pale white capsules, soft oval capsules (approximately 20 mm to 9 mm) with “ENZ” marked on one side of the capsule.
- Each box contains 112 capsules in 28 sachets, each containing 4 capsules.

“HARUS DENGAN RESEP DOKTER”

Reg. No.: DKI1717400102A1

Manufacture and distribution license holders

Manufactured by
Catalent Pharma Solutions LLC
275 Scherer Drive, St. Petersburg,
FL 33716
USA

Packaged by
AndersonBrecon, Rockford, USA, released by Astellas US Technologies Inc, USA

Distribution license holder
PT. Meprofarm Pharmaceutical Industries
Jl. Soekarno-Hatta No. 789
Bandung 40294
Indonesia

Marketed by
PT. Astellas Pharma Indonesia
Plaza Oleos Lt.5, Jl. TB Simatupang No 53A
Jakarta 12520, Indonesia

For more information about this drug, please contact:
PT. Astellas Pharma Indonesia
Website: www.astellas.com/id

Informasi untuk pasien

Xtandi™ 40 mg kapsul lunak
Enzalutamide

Bacalah leaflet ini dengan seksama sebelum anda mengonsumsi obat ini karena berisi informasi yang penting untuk anda.
- Simpanlah leaflet ini. Anda mungkin perlu untuk membacanya lagi.
- Jika anda memiliki pertanyaan lebih lanjut, silahkan bertanya kepada dokter Anda.
- Obat ini diresepkan untuk Anda. Jangan memberikannya kepada orang lain. ~~Hal tersebut~~ Obat ini mungkin dapat membahayakan mereka, walaupun tanda gejala dan penyakit mereka sama dengan Anda.
- Jika anda mengalami efek samping, segera hubungi dokter Anda. Termasuk efek samping yang tidak tercantum dalam leaflet ini.

Apa saja yang terdapat dalam leaflet ini:

1. Apa itu Xtandi dan digunakan untuk apa
Xtandi mengandung zat aktif enzalutamide. Xtandi digunakan:
- Sebagai monoterapi atau dikombinasikan dengan androgen deprivation therapy untuk mengobati pria dewasa dengan risiko tinggi *biochemical recurrent* (BCR) *non-metastatic hormone sensitive prostate cancer* (nmHSPC) yang tidak dapat menerima radioterapi.

- Untuk mengobati pria dewasa dengan *metastatic hormone sensitive prostate cancer* (mHSPC) dalam kombinasi dengan *androgen deprivation therapy*.
- Untuk mengobati pria dewasa dengan *high-risk non-metastatic castration-resistant prostate cancer* (CRPC).
- Dikombinasikan dengan *androgen deprivation therapy* untuk mengobati pria dewasa dengan *metastatic* CRPC yang tanpa gejala atau dengan gejala ringan setelah kegagalan pengobatan dengan *androgen deprivation therapy* dan belum pernah mendapatkan kemoterapi.
- Untuk pengobatan lini kedua pada pria dewasa dengan *metastatic* CRPC yang mengalami pemburukan pada saat atau setelah terapi dengan docetaxel.

Bagaimana Xtandi bekerja
Xtandi merupakan obat yang bekerja dengan menghambat aktivitas hormon androgen (seperti testosteron). Dengan menghambat androgen, enzalutamide menghentikan pertumbuhan dan penyebaran sel kanker prostat.

2. Apa yang perlu diketahui sebelum menggunakan Xtandi

Jangan menggunakan Xtandi:
- Jika anda alergi (hipersensitif) terhadap enzalutamide atau zat lain yang terkandung dalam obat ini (tercantum pada bagian 6)
- Jika Anda hamil atau mungkin dapat hamil (lihat “kehamilan, menyusui, dan kesuburan”)

Peringatan dan perhatian

Kejang

Kejadian kejang telah dilaporkan pada 6 dalam 1.000 pasien yang menggunakan Xtandi, dan kurang dari 3 dalam 1.000 orang yang menggunakan plasebo (lihat juga "Obat lain dan Xtandi" pada bagian ini dan bagian 4 "Kemungkinan efek samping yang terjadi").

Sebelum anda menggunakan Xtandi, tanyakan kepada dokter atau apoteker anda:

- Jika anda memiliki riwayat kejang atau risiko tinggi mengalami kejang
- Jika anda memiliki masalah pada ginjal dan hati
- Jika anda memiliki kelainan pada jantung, termasuk detak jantung yang tidak beraturan
- Jika anda memiliki tekanan darah tinggi. Xtandi dapat meningkatkan tekanan darah anda. Dokter anda akan mengukur tekanan darah anda sebelum memulai pengobatan dan secara periodik selama pengobatan dengan Xtandi
- Jika anda memiliki riwayat pingsan secara tiba-tiba
- Jika anda memiliki riwayat jatuh atau patah tulang
- Jika anda memiliki ketidakseimbangan elektrolit (misalnya tingkat magnesium atau kalium rendah dalam darah) atau kondisi yang dapat mempengaruhi ketidakseimbangan elektrolit (misalnya muntah, diare, dehidrasi, atau kelainan dalam makan)
- Jika anda memiliki intoleransi terhadap fruktosa, masalah keturunan yang jarang terjadi. Hal ini karena Xtandi mengandung sorbitol
- Jika Anda sedang mengonsumsi atau baru saja mengonsumsi semua produk obat (termasuk produk kesehatan alami).
- Jika anda menggunakan obat yang dapat menyebabkan kejang atau obat yang dapat meningkatkan terjadinya kejang (lihat "Obat lain dan Xtandi" dibawah)

Jika anda mengalami kejang selama terapi:

Hentikan penggunaan Xtandi dan jangan minum lagi. Hubungi dokter anda segera mungkin.

Posterior Reversible Encephalopathy Syndrome (PRES)

Laporan terjadinya PRES jarang, sebuah kondisi langka yang bersifat reversibel pada otak, pada pasien yang menggunakan Xtandi. Jika anda mengalami kejang, sakit kepala yang semakin memburuk, kebingungan, kebutaan atau masalah penglihatan lain, segera hubungi dokter anda. (Lihat juga bagian 4 'Kemungkinan efek samping yang terjadi').

Kesulitan menelan yang terkait dengan ukuran produk

Telah dilaporkan tentang pasien yang mengalami kesulitan menelan obat ini, termasuk laporan tersedak. Kesulitan menelan atau kejadian tersedak lebih umum diamati pada pasien yang menerima kapsul, yang mungkin terkait dengan ukuran produk yang lebih besar. Telan kapsul utuh dengan jumlah air yang cukup.

Jika Anda mengalami kesulitan menelan kapsul besar atau memiliki riwayat disfagia, Anda mungkin dapat mengalami kesulitan menelan kapsul Xtandi, atau berisiko tersedak.

Bicarakan dengan dokter anda sebelum menggunakan Xtandi

- Jika anda menggunakan obat untuk menghambat pembekuan darah (misal. warfarin, acenocoumarol, clopidogrel)
- Jika anda memiliki penyakit hati
- Jika anda memiliki penyakit ginjal
- Jika anda menggunakan kemoterapi, seperti docetaxel

Beritahukan kepada dokter anda jika anda memiliki:

Kondisi jantung atau pembuluh darah, termasuk masalah irama jantung (aritmia), atau sedang menggunakan obat untuk kondisi tersebut. Risiko masalah irama jantung dapat meningkat bila

menggunakan Xtandi. Jika anda alergi terhadap enzalutamide, hal ini dapat menghasilkan ruam, atau pembengkakan pada muka, lidah, bibir, atau tenggorokan. Jika tanda alergi terhadap enzalutamide atau bahan lain dalam obat ini, jangan gunakan Xtandi.

Jika salah satu kejadian diatas terjadi pada Anda atau anda merasa kurang yakin, bicarakan dengan dokter anda sebelum menggunakan obat ini.

Anak – anak dan remaja
Obat ini tidak digunakan untuk anak – anak dan remaja.

Obat lain dan Xtandi
Beritahukan kepada dokter Anda jika Anda sedang, baru saja menggunakan atau mungkin menggunakan obat lain. Anda harus mengetahui obat – obatan yang anda gunakan. Buat daftar dari obat yang Anda gunakan agar dapat ditunjukkan kepada dokter ketika Anda diberikan obat baru. Anda jangan mulai atau menghentikan penggunaan obat apapun sebelum bicara dengan dokter yang memberikan Xtandi.

Beritahukan dokter Anda jika Anda menggunakan salah satu dari obat – obat dibawah. Ketika digunakan bersamaan dengan Xtandi, obat – obatan ini dapat meningkatkan risiko terjadinya kejang:
- Obat tertentu yang digunakan untuk mengobati asma dan penyakit pernafasan lainnya (misal aminophylline, theophylline)
- Obat – obat yang digunakan untuk mengobati penyakit psikis tertentu seperti depresi dan schizophrenia (misal clozapine, olanzapine, risperidone, ziprasidone, bupropion, lithium, chlorpromazine, mesoridazine, thioridazine, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
- Obat tertentu yang digunakan untuk mengobati nyeri (misal pethidine)

Beritahukan dokter Anda jika anda menggunakan salah satu dari obat – obat dibawah. Obat – obatan ini dapat mempengaruhi efek Xtandi, atau Xtandi dapat mempengaruhi efek dari obat – obatan ini:

Ini termasuk obat – obatan tertentu yang digunakan untuk:
- Menurunkan kolesterol (misal gemfibrozil, atorvastatin, simvastatin)
- Mengobati nyeri (misal fentanyl, tramadol)
- Mengobati kanker (misal cabazitaxel)
- Mengobati epilepsi (misal carbamazepin, clonazepam, phenytoin, primidone, valproic acid)
- Mengobati penyakit psikis tertentu seperti kegelisahan yang parah atau schizophrenia (misal diazepam, midazolam, haloperidol)
- Mengobati gangguan tidur (misal zolpidem)
- Mengobati gangguan jantung atau menurunkan tekanan darah (misal bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil)
- Mengobati penyakit serius yang berhubungan dengan radang (misal dexamethasone, prednisolone)
- Mengobati infeksi HIV (misal indinavir, ritonavir)
- Mengobati infeksi bakteri (misal clarithromycin, doxycycline, rifampicin)
- Mengobati gangguan tiroid (misal levothyroxine)
- Mengobati gout (misal colchicine)
- Mencegah gangguan jantung atau stroke (misal dabigatran etexilate)
- Mengobati penyakit lambung (misal omeprazole)
- Mencegah penolakan organ (misal tacrolimus)

Xtandi mungkin dapat mengganggu beberapa obat yang digunakan untuk mengobati masalah irama jantung (misalnya quinidin, procainamid, amiodaron dan sotalol) atau mungkin dapat meningkatkan risiko masalah irama jantung ketika digunakan dengan beberapa obat lain (misalnya metadon

(digunakan untuk menghilangkan rasa sakit dan bagian dari detoksifikasi kecanduan narkoba), moksifloksasin (antibiotik), antipsikotik yang digunakan untuk penyakit mental yang serius).

Beritahu dokter Anda jika anda menggunakan obat – obat yang tercantum diatas. Dosis Xtandi atau obat lain yang digunakan mungkin perlu untuk diganti.

Kehamilan, menyusui dan kesuburan
- **Xtandi tidak digunakan untuk wanita**.
- Obat ini berbahaya untuk bayi yang belum lahir atau berpotensi keguguran jika digunakan oleh wanita hamil. Jangan digunakan oleh wanita yang hamil atau menyusui.
- Obat ini kemungkinan berpengaruh pada kesuburan pria.
- Jika Anda berhubungan seksual dengan wanita yang dapat hamil, gunakan kondom dan alat kontrasepsi lain, selama dan untuk 3 bulan setelah terapi dengan obat ini. Jika Anda melakukan hubungan seksual dengan wanita yang sedang hamil, gunakan kondom untuk melindungi bayi yang belum lahir.

Mengemudi dan menggunakan mesin
Xtandi mungkin mempunyai efek sedang dalam mempengaruhi kemampuan Anda mengemudi kendaraan atau menggunakan peralatan atau mesin sebagai efek samping dari Xtandi termasuk kejang. Jika Anda merasa mempunyai risiko tinggi mengalami kejang (lihat Bagian 2), konsultasikan dengan dokter anda.

Xtandi mengandung sorbitol
Obat ini mengandung sorbitol (sejenis gula). Jika Anda telah diberitahukan oleh dokter jika Anda mempunyai intoleransi terhadap beberapa gula, beritahu dokter anda sebelum menggunakan obat ini.

3. Bagaimana cara menggunakan Xtandi

Selalu gunakan obat ini seperti yang dokter anjurkan. Bicarakan dengan dokter Anda jika anda tidak yakin.

Dosis umumnya 160 mg (empat kapsul), digunakan pada saat yang sama satu kali sehari.

Menggunakan Xtandi
- Telan seluruh kapsul menggunakan air yang cukup
- Jangan dikunyah, dilarutkan atau membuka kapsul sebelum ditelan
- Xtandi dapat digunakan dengan atau tanpa makanan
- Xtandi tidak boleh ditangani oleh orang lain selain pasien dan pengasuhnya. Wanita yang sedang hamil atau mungkin hamil tidak boleh menangani kapsul Xtandi yang rusak atau terbuka tanpa menggunakan alat perlindungan diri seperti sarung tangan.

Jika Anda menggunakan Xtandi lebih banyak dari yang seharusnya
Jika anda menggunakan lebih banyak dari yang diresepkan, hentikan penggunaan Xtandi dan hubungi dokter Anda. Anda mungkin mengalami peningkatan risiko terjadinya kejang atau efek samping lainnya.

Dokter Anda mungkin meresepkan obat lain ketika Anda mendapatkan Xtandi.

Jika anda lupa menggunakan Xtandi
- Jika Anda lupa menggunakan Xtandi saat biasanya anda menggunakan, gunakan segera mungkin dengan dosis biasa saat Anda ingat
- Jika Anda lupa menggunakan Xtandi seharian, gunakan dosis biasanya keesokan harinya
- Jika Anda lupa menggunakan Xtandi lebih dari sehari, beritahukan dokter Anda sesegera mungkin
- **Jangan melipatgandakan dosis** untuk menutupi dosis yang terlupa

Jika Anda berhenti menggunakan Xtandi
Jangan berhenti menggunakan obat ini kecuali atas anjuran dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter Anda.

4. Kemungkinan efek samping yang dapat terjadi

Seperti halnya obat lain, obat ini pun dapat menyebabkan efek samping, walaupun tidak semua orang mengalaminya.

Kejang
Kejadian kejang telah dilaporkan pada 6 dalam 1.000 orang yang menggunakan Xtandi dan kurang dari 3 dalam 1.000 orang yang menggunakan plasebo.
Kejang lebih dapat terjadi jika anda menggunakan obat ini lebih dari dosis yang dianjurkan, jika anda menggunakan obat – obat lain tertentu, atau jika Anda mempunyai risiko yang tinggi mengalami kejang (lihat Bagian 2).

Jika anda mengalami kejang, temui dokter Anda sesegera mungkin. Jangan menggunakan Xtandi lagi.

Posterior Reversible Encephalopathy Syndrome **(PRES)**
Laporan terjadinya PRES jarang (dapat terjadi pada hingga 1 dalam 1.000 orang), sebuah kondisi langka yang bersifat reversibel pada otak, pada pasien yang menggunakan Xtandi. Jika Anda mengalami kejang, sakit kepala yang semakin memburuk, kebingungan, kebutaan atau masalah penglihatan lain, segera hubungi dokter Anda.

Kemungkinan efek samping lain termasuk:
Sangat umum (dapat mempengaruhi lebih dari 1 dalam 10 orang)
Kelelahan, jatuh, patah tulang, rasa panas, tekanan darah meningkat

Umum (dapat mempengaruhi sampai dengan 1 dari 10 orang)
Sakit kepala, perasaan gelisah, kulit kering, gatal, kesulitan mengingat, penyumbatan pembuluh darah di jantung (penyakit jantung iskemik), pembesaran payudara pada pria (*gynaecomastia*), nyeri pada puting, nyeri payudara, gejala dari sindrom *restless leg* (dorongan yang tak terkendali untuk memindahkan bagian tubuh, terutama kaki), penurunan konsentrasi, mudah lupa, perubahan pada indera perasa, kesulitan berpikir jernih.

Tidak umum (dapat mempengaruhi sampai dengan 1 dari 100 orang)
Halusinasi, penurunan sel darah putih

Tidak diketahui (frekuensi tidak dapat diestimasikan dari data yang tersedia)
Nyeri otot, kram otot, lemah otot, nyeri punggung, perubahan pada ECG (perpanjangan QT) , kesulitan menelan produk ini termasuk tersedak, sakit perut termasuk perasaan sakit (mual), ruam kulit yang parah, pengelupasan kulit, melepuh, luka pada mulut, kemerahan, merasa sakit (muntah), pembengkakan pada muka, bibir, lidah dan/atau tenggorokan, pengurangan trombosit darah (dapat meningkatkan risiko pendarahan atau memar), diare, nafsu makan berkurang.

Pelaporan efek samping
Jika Anda Anda mengalami efek samping atau ketidaknyamanan selama atau setelah menggunakan obat ini, bicarakan dengan dokter atau tenaga kesehatan profesional Anda. Anda juga dapat langsung melaporkan efek samping ke PT. Astellas Pharma Indonesia melalui pv@id.astellas.com. Harap diketahui bahwa pelaporan ke PT. Astellas Pharma Indonesia hanya untuk mengumpulkan data dan tidak sebagai pengganti konsultasi pada dokter atau tenaga kesehatan profesional Anda. Dengan melaporkan efek samping, Anda dapat membantu menyediakan informasi keamanan untuk obat ini. Selalu bicarakan pada dokter atau tenaga kesehatan profesional Anda untuk saran medis.

5. Bagaimana menyimpan Xtandi

Simpan obat ini jauh dari pandangan dan jangkauan anak – anak.

Jangan gunakan obat ini setelah tanggal kadaluarsa yang tercantum pada dus dan blister. Tanggal kadaluarsa mengacu pada hari terakhir pada bulan tersebut.

Simpan dibawah suhu 30°C.

Jangan gunakan obat ini jika bocor, rusak, atau menunjukkan tanda – tanda dirusak.

Jangan buang obat ini di saluran air atau pada sampah rumah tangga. Tanyakan kepada apoteker Anda bagaimana cara membuang obat yang sudah tidak anda gunakan. Hal ini dapat membantu dalam menjaga lingkungan.

6. Isi kemasan dan informasi lainnya

Apa yang terkandung dalam Xtandi

- Zat aktifnya adalah enzalutamide. Tiap kapsul mengandung 40 mg enzalutamide.
- Zat tambahan lain adalah caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320), dan butylhydroxytoluene (E321).
- Bahan penyusun cangkang kapsul adalah gelatin, sorbitol sorbitan solution (lihat Bagian 2), glycerol, titanium dioxide (E171), dan air murni.
- Bahan penyusun tinta adalah iron oxide black (E172) dan polyvinyl acetate phthalate.

Seperti apa tampilan Xtandi dan isi kemasannya

- Kapsul Xtandi berwarna putih sampai putih pucat, kapsul lunak berbentuk lonjong (kira – kira berukuran 20 mm sampai 9 mm) dengan tulisan “ENZ” pada satu sisi kapsul.
- Tiap dus berisi 112 kapsul dalam 28 sachet masing – masing berisi 4 kapsul.

“HARUS DENGAN RESEP DOKTER”

Reg. No.: DKI1717400102A1

Produsen dan pemegang izin edar

Diproduksi oleh:
Catalent Pharma Solutions LLC
2725 Scherer Drive, St. Petersburg,
FL 33716
USA

Dikemas oleh AndersonBrecon Inc., Rockford, USA dirilis oleh Astellas US Technologies Inc, USA

Pemegang izin edar:
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Dipasarkan oleh:
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Plaza Oleos Lt.5, Jl. TB Simatupang No. 53A
Jakarta 12520, Indonesia

Untuk informasi lebih lanjut mengenai obat ini, harap menghubungi:
PT. Astellas Pharma Indonesia
Website: www.astellas.com/id