

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 in combination with androgen deprivation therapy is indicated for the treatment of adult men with metastatic castration-resistant prostate cancer 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 castration-resistant prostate cancer 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 luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

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 \geq Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to \leq 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 metastatic castration-resistant prostate cancer.

Method of administration

Xtandi is for oral use. The soft capsules should be swallowed whole with 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) \geq 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.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema 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/m² 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, 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 cognitive disorder, and neutropenia.

Seizure occurred in 0.5% 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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 oedema, tongue oedema, lip oedema, pharyngeal oedema
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 Uncommon: cognitive disorder, 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
Vascular disorders	Very common: hot flush, hypertension
Gastrointestinal disorders	Not known ¹ : 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	Very common: fall

MeDRA System organ class	Frequency
complications	

- 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.

Description of selected adverse reactions

Seizure

In controlled clinical studies, 22 patients (0.5%) experienced a seizure out of 4168 patients treated with a daily dose of 160 mg enzalutamide, whereas three 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 3.7% of patients treated with enzalutamide plus ADT compared to 1.5 % patients treated with placebo plus ADT. Fifteen (0.4%) patients treated with enzalutamide and 2 (0.1%) patients treated with placebo had an ischemic heart disease event that led to death.

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 signalling 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 signalling 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 $\geq 50\%$ 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 $\geq 50\%$ reduction from baseline), compared with patients receiving bicalutamide, 82.1% versus 20.9% (difference = 61.2%, $p < 0.0001$).

Clinical efficacy and safety

Efficacy of enzalutamide was established in two randomized placebo-controlled multicentre phase 3 clinical studies [CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive metastatic prostate cancer who had failed 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. All patients continued on a LHRH analogue or had prior bilateral orchiectomy. In the active treatment arm, Xtandi was administered orally at a dose of 160 mg daily. In both clinical trials, patients received placebo in the control arm and patients were allowed, but not required, to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent).

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

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 ($\geq 50\%$ 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 2, Figure 1). 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 2: 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 1: Kaplan-Meier Curves of Overall Survival Based on 5-year Survival Analysis in the PREVAIL Study (Intent-to-Treat Analysis)

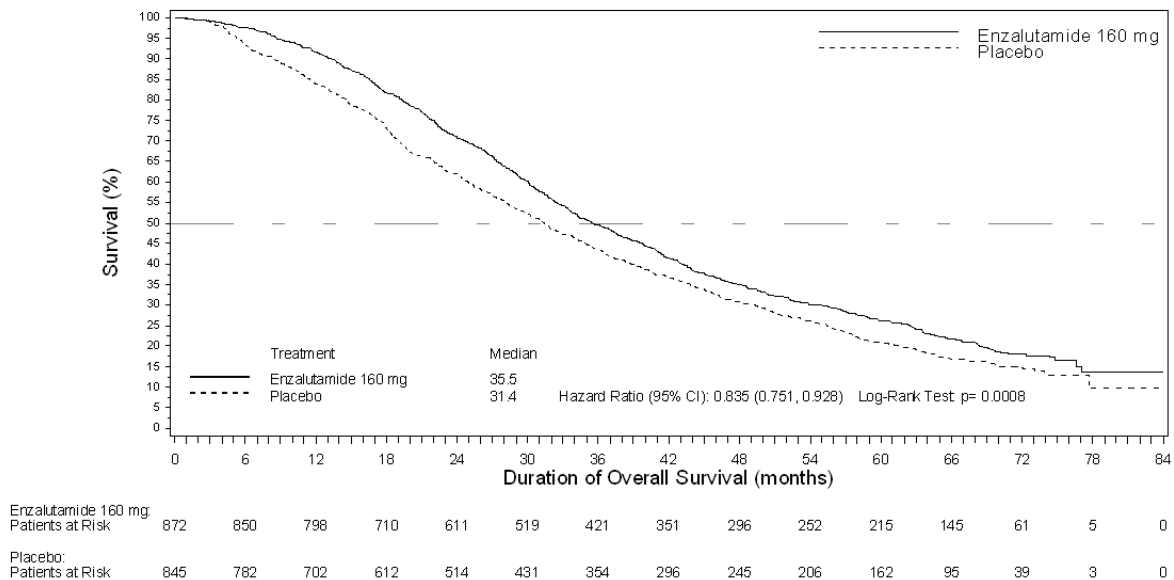
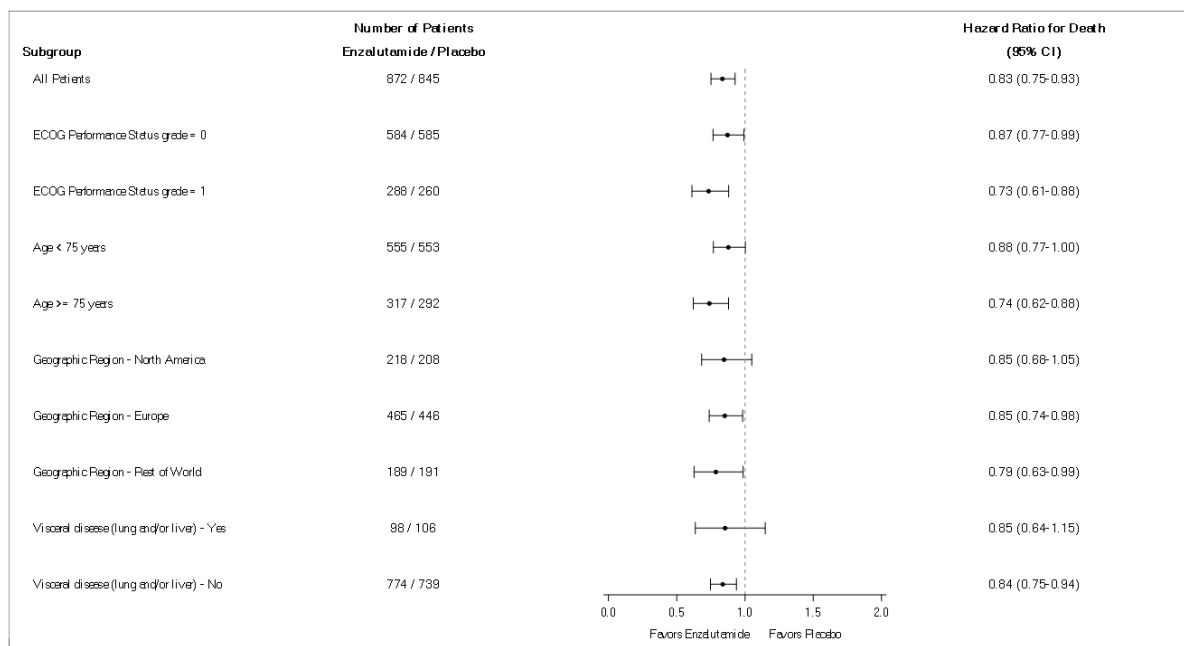
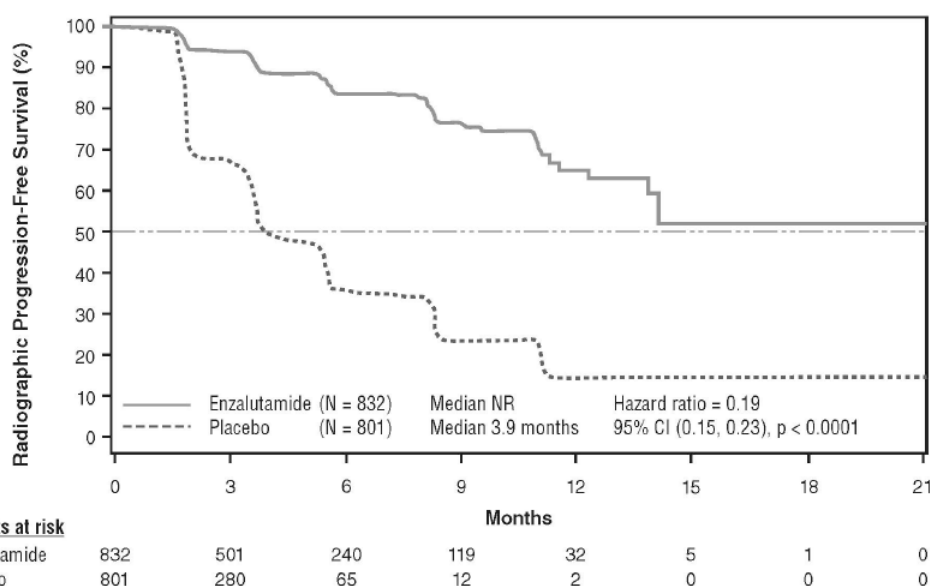


Figure 2: 5-year Overall Survival Analysis by Subgroup: Hazard Ratio and 95% Confidence Interval in the PREVAIL Study (Intent-to-Treat Analysis)



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 3). 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 3: 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 3 and Figures 4 and 5).

Table 3: 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 4: Kaplan-Meier Curves of Overall Survival in the AFFIRM Study (Intent-to-Treat Analysis)

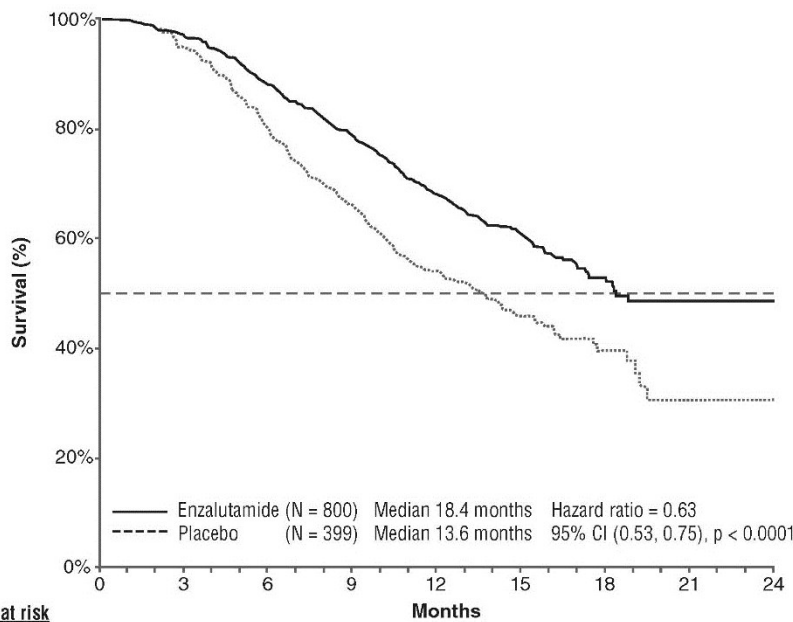


Figure 5: Overall Survival by Subgroup in the AFFIRM Study – Hazard Ratio and 95% Confidence Interval

Subgroup	Number of Patients Enzalutamide/Placebo	Hazard Ratio for Death (95% CI)	Overall Survival Median (mo) Enzalutamide/Placebo
All Patients	800/399	0.63 (0.53–0.75)	18.4/13.6
Age			
<65	232/130	0.63 (0.46–0.87)	—/12.4
≥65	568/269	0.63 (0.51–0.78)	18.4/13.9
Baseline ECOG Performance Status Score			
0–1	730/367	0.62 (0.52–0.75)	—/14.2
2	70/32	0.65 (0.39–1.07)	10.5/7.2
Baseline Mean Pain Score on BPI-SF (Question #3)			
<4	574/284	0.59 (0.47–0.74)	—/18.2
≥4	228/115	0.71 (0.54–0.94)	12.4/9.1
Number of Prior Chemotherapy Regimens			
1	579/296	0.59 (0.48–0.73)	—/14.2
≥2	221/103	0.74 (0.54–1.03)	15.9/12.3
Type of Progression at Study Entry			
PSA Progression Only	326/164	0.62 (0.46–0.83)	—/19.5
Radiographic Progression ± PSA Progression	470/234	0.64 (0.52–0.80)	17.3/13.0
Baseline PSA Value			
≤median (111.2 µg/L)	412/188	0.67 (0.50–0.89)	—/19.2
>median (111.2 µg/L)	388/211	0.62 (0.50–0.78)	15.3/10.3
Baseline LDH Value			
≤median (211 U/L)	411/192	0.63 (0.46–0.88)	—/19.2
>median (211 U/L)	389/205	0.61 (0.50–0.76)	12.4/8.5
Total Gleason Score at Diagnosis			
≤7	360/175	0.67 (0.51–0.88)	18.4/14.8
≥8	366/193	0.60 (0.47–0.76)	18.2/11.3
Visceral Lung and/or Liver Disease at Screening			
Yes	196/82	0.78 (0.56–1.09)	13.4/9.5
No	604/317	0.56 (0.46–0.69)	—/14.2

0.0 0.5 1.0 1.5 2.0
 Favors Enzalutamide Favors Placebo

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 4168 patients in the controlled clinical trials who received enzalutamide, 3265 patients (78%) were 65 years and over and 1469 patients (35%) 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 macroglycerides as emulsifier/surfactant. In preclinical studies, the absorption of enzalutamide was increased when dissolved in caprylocaproyl macroglycerides.

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 $\mu\text{g/mL}$ (23% coefficient of variation [CV]) and 12.7 $\mu\text{g/mL}$ (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 ¹⁴C-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 (> 77%) 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 resolved 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 ¹⁴C-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 ¹⁴C-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 ($AUC_{24h} \sim 317 \mu\text{g}\cdot\text{h/mL}$), which resulted in plasma exposure levels similar to the clinical exposure ($AUC_{24h} \sim 322 \mu\text{g}\cdot\text{h/mL}$) 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. 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

Informasi untuk pasien

Xtandi™ 40 mg kapsul lunak Enzalutamide

Bacalah leaflet ini dengan seksama sebelum anda mengkonsumsi 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 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
2. Apa yang perlu diketahui sebelum menggunakan Xtandi
3. Bagaimana cara menggunakan Xtandi
4. Kemungkinan efek samping yang dapat terjadi
5. Bagaimana menyimpan Xtandi
6. Isi kemasan dan informasi lainnya

1. Apa itu Xtandi dan digunakan untuk apa

Xtandi mengandung zat aktif enzalutamide. Xtandi digunakan untuk mengobati pria dewasa dengan kanker prostat yang sudah tidak respon dengan *androgen deprivation therapy* yang telah menyebar kebagian tubuh lainnya.

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 5 dalam 1.000 pasien yang menggunakan Xtandi, dan kurang dari 1 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’).

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 schizoprenia (misal diazepam, midazolam, haloperidol)
- Mengobati gangguan tidur (misal zolpidem)
- Mengobati gangguan jantung atau menurunkan tekanan darah (misal bisoprolol, digoxin, diltiazem, felodipine, nifedipine, 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
- 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, beritahu 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 5 dalam 1.000 orang yang menggunakan Xtandi dan kurang dari 1 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*), gejala dari sindrom *restless leg* (dorongan yang tak terkendali untuk memindahkan bagian tubuh, terutama kaki), penurunan konsentrasi, mudah lupa, perubahan pada indera perasa.

Tidak umum (dapat mempengaruhi sampai dengan 1 dari 100 orang)

Halusinasi, kesulitan berpikir jernih, penurunan sel darah putih

Tidak diketahui (frekuensi tidak dapat diestimasi dari data yang tersedia)

Nyeri otot, kram otot, lemah otot, nyeri punggung, perubahan pada ECG (perpanjangan QT), 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..

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.

Produsen dan pemegang izin edar

Diproduksi oleh:

Catalent Pharma Solutions LLC
2725 Scherer Drive, St. Petersburg,
FL 33716

Dikemas oleh Anderson Brecon Inc., Rockford,, USA dirilis oleh Astellas US Technologies Inc, USA

Pemegang izin edar:

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

Dipasarkan oleh:

PT. Astellas Pharma Indonesia
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.co.id