# AUSTRALIAN PRODUCT INFORMATION
# XTANDI® (ENZALUTAMIDE) SOFT CAPSULES

## 1 NAME OF THE MEDICINE

Enzalutamide

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each soft capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl macrogolglycerides.

Excipient(s) with known effect
Each soft capsule contains 57.8 mg of sorbitol.

For the full list of excipients, see Section 6.1 List of excipients.

## 3 PHARMACEUTICAL FORM

Capsule, soft

Supplied as white to off-white oblong soft gelatin capsules imprinted with “ENZ” in black ink on one side.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

XTANDI is indicated for:

- the treatment of patients with metastatic hormone-sensitive prostate cancer.
- the treatment of patients with non-metastatic castration-resistant prostate cancer (see PROSPER, section 5.1 Clinical trials).
- the treatment of patients with metastatic castration resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated.
- the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dose of XTANDI is 160 mg (four 40 mg capsules) as a single oral daily dose. XTANDI can be taken with or without food. XTANDI should be taken at the same time each day.

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 the daily dose.

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

Method of administration

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

XTANDI should not be handled by persons other than the patient or their caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, XTANDI may harm a developing foetus. Women who are or may become pregnant should not handle damaged or opened enzalutamide capsules without protection, e.g., gloves (Refer to Section 4.6 – FERTILITY, PREGNANCY AND LACTATION).

Keep out of the reach of children.

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, reduce the dose of XTANDI to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients with Hepatic Impairment:

No dose adjustment is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively).

Patients with Renal Impairment:

No dose adjustment is necessary for patients with mild or moderate renal impairment (Refer to Section 5.2 – PHARMACOKINETIC PROPERTIES – Pharmacokinetic Characteristics in Special Populations). Caution is advised in patients with severe renal impairment or end-stage renal disease (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in renal impairment).

## 4.3 CONTRAINDICATIONS

XTANDI is contraindicated in patients with known hypersensitivity to enzalutamide or to any of the excipients in the formulation (Refer to Section 6.1 – List of excipients).

XTANDI is contraindicated in women who are, or may become, pregnant (Refer to Section 4.2 – Dose and method of administration and Section 4.6 – FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy).

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**XTANDI capsules should only be prescribed by a medical practitioner who is experienced with the treatment of prostate cancer and the use of antineoplastic endocrine therapies.**

**The following are clinically significant: seizures** (see Risk of Seizure below and Section 4.8 - Adverse effects (Undesirable effects)), **Posterior Reversible Encephalopathy Syndrome (PRES)** (see Posterior Reversible Encephalopathy Syndrome below and Section 4.8 – Adverse effects (Undesirable effects)) and **drug interactions** (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

### Risk of Seizure

Use of enzalutamide has been associated with seizure. Caution should be used in administering XTANDI to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

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

### Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of 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.

### Falls and Fall-Related Injuries

In the combined data of four randomised clinical trials, falls or injuries related to falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and haematomas. Androgen deprivation therapy has been known to cause bone loss. For patients who fall or have a concomitant recognised risk of falling, it is recommended that the physicians consider additional supportive therapy when appropriate.

### Hypersensitivity Reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, face oedema, tongue oedema, lip oedema, pharyngeal oedema, and rash have been observed with enzalutamide (see Section 4.8 – Adverse effects (Undesirable effects)). Advise patients who experience any symptoms of hypersensitivity to discontinue enzalutamide and promptly seek medical care.

### 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.

### 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 (NYHA) Class 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.

### Hypertension

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

### Risk of Second Malignancy

Across the clinical trial program, the crude incidence of treatment emergent adverse events (TEAEs) corresponding to second primary malignancies (SPM) in the enzalutamide group and placebo/active surveillance group was 2.4% and 1.3%, and the median duration of treatment for patients with SPM was 21.7 months and 13.9 months, respectively. The incidence rate per 100 patient-years of any event of SPM for patients treated with enzalutamide was similar to those in the placebo/active surveillance group (1.9 vs 1.7) in the clinical trial setting.

### Use with Chemotherapy

The safety and efficacy of concomitant use of XTANDI with cytotoxic chemotherapy has not been established.

### Contraception in Males and Females

As it is not known whether XTANDI or its metabolites are present in semen, and there were severe teratogenic effects observed in the animal studies, a condom is required during and for 3 months after treatment with XTANDI 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 (Refer to Section 4.6 – FERTILITY, PREGNANCY AND LACTATION).

### Use in renal impairment

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

### Use in the elderly

No overall differences in safety or effectiveness were observed between elderly patients and younger patients. No dose adjustment is required for the elderly.

### Paediatric use

The safety and efficacy of XTANDI have not been established in children, and therefore it is not recommended for use in those < 18 years of age.

### Effects on laboratory tests

Refer to Section 4.8 – ADVERSE EFFECTS - Laboratory abnormalities.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Effects of other Medicines on XTANDI**

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 the sum of enzalutamide plus the active metabolite increased by 2.17-fold while $C_{max}$ decreased by 18%. 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 (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION).

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 enzalutamide is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of rifampicin (moderate CYP2C8 and strong CYP3A4 inducer). Rifampicin decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on $C_{max}$. No dose adjustment is necessary when enzalutamide is co-administered with inducers of CYP2C8 or CYP3A4.

**Effects of XTANDI on other Medicines**

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). Some transporters may also be induced, e.g. multidrug resistance-associated protein 2 (MRP2) 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. Enzalutamide did not have a clinically meaningful effect on plasma exposure to intravenously administered docetaxel (CYP3A4 substrate).

Interactions 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. 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)
- Immunosuppressants (e.g. cyclosporin, tacrolimus)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolised 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 drugs 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 XTANDI treatment and dose adjustment should be considered as appropriate. In consideration of the

long half-life of enzalutamide (5.8 days, refer to Section 5.2 – PHARMACOKINETIC PROPERTIES), effects on enzymes may persist for one month or longer after stopping XTANDI. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping XTANDI treatment.

Warfarin and coumarin-like anticoagulants

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If XTANDI is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin), additional INR monitoring should be conducted.

CYP1A2, CYP2C8 and CYP2D6 substrates

Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or $C_{max}$ of caffeine (CYP1A2 substrate), pioglitazone (CYP2C8 substrate) or dextromethorphan (CYP2D6 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, CYP2C8 or CYP2D6 substrate is co-administered with XTANDI.

P-gp substrates

*In vitro* data indicate that enzalutamide is not a substrate for, but may be an inhibitor of the efflux transporter P-gp. A mild inhibitory effect of enzalutamide, at steady-state, on P-gp was observed in a study in patients with prostate cancer that received a single oral dose of the probe P-gp substrate digoxin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC and $C_{max}$ of digoxin increased by 33% and 17%, respectively. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with XTANDI and may require dose adjustment to maintain optimal plasma concentrations.

BCRP substrates

At steady-state, enzalutamide did not cause a clinically meaningful change in exposure to the probe breast cancer resistance protein (BCRP) substrate rosuvastatin in patients with prostate cancer that received a single oral dose of rosuvastatin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC of rosuvastatin decreased by 14% while $C_{max}$ increased by 6%. No dose adjustment is necessary when a BCRP substrate is co-administered with XTANDI.

MRP2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 substrates

Based on *in vitro* data, inhibition of MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3), OATP1B1, and OCT1 (systemically) cannot be excluded. Theoretically, induction of OAT3, OATP1B1, OCT1 and MRP2 is also possible, and the net effect is presently unknown. The effects of enzalutamide on these transporters have not been evaluated *in vivo. In vitro* data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OAT1, OATP1B3, or OCT2.

Effect of Food on XTANDI Exposure

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

## 4.6 FERTILITY, PREGNANCY AND LACTATION

### Effects on fertility

Based on its pharmacology and findings in animal studies, male fertility may be impaired by treatment with enzalutamide. Findings in the male reproductive tract of mice, rats and/or dogs treated with enzalutamide included atrophy of the prostate gland, epididymis and seminal vesicles, testicular hypospermia and seminiferous tubule degeneration. These effects were observed at doses below the clinical exposure (based on AUC) and reversed or partially resolved after an 8-week recovery period (Refer to Section 4.4 – Special warnings and precautions for use, Contraception in Males and Females).

### Use in pregnancy – Category X

XTANDI is not indicated for use in women. XTANDI has not been shown to be safe for use in women. XTANDI is contraindicated in women who are or may become pregnant (Refer to Section 4.3 - Contraindications). There are no human data on the use of XTANDI in pregnancy.

Teratogenicity (cleft palate, cervical rib and decreased anogenital distance) and embryofetal lethality were seen in mouse embryofetal development studies at greater than or equal to 10 mg/kg/day (below the AUC at the maximum recommended human dose). This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant.

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

### Use in lactation

XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. XTANDI and/or its metabolites are secreted in rat milk. After oral administration of radiolabelled $^{14}$C-enzalutamide to lactating rats at a dose of 30 mg/kg, the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results have also shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No formal studies of the effects of XTANDI on the ability to drive or use machines have been conducted. Neurological and psychiatric events (such as seizure, amnesia, fatigue, memory impairment, cognitive disorder, and disturbance in attention) associated with XTANDI may affect some patients' ability to drive or operate machinery (Refer to Section 4.8 – ADVERSE EFFECTS).

Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risk of seizure).

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience:

Six randomized, controlled clinical studies enrolled patients with castration-resistant prostate cancer that had progressed on androgen deprivation therapy (LHRH therapy or bilateral orchiectomy). Four studies were placebo-controlled and two studies were bicalutamide-controlled. In the AFFIRM, PREVAIL, Asian PREVAIL, and PROSPER studies, patients received enzalutamide 160 mg or placebo orally once daily. In the TERRAIN and STRIVE studies, patients received enzalutamide 160 mg or bicalutamide 50 mg orally once daily. A randomised, placebo-controlled clinical study was also conducted in patients with metastatic hormone-sensitive prostate cancer (mHSPC) on androgen deprivation therapy (ARCHES). Patients in the ARCHES study received enzalutamide 160 mg or placebo orally once daily. All patients continued androgen deprivation therapy.

The most common adverse reactions (≥ 10%) seen in enzalutamide-treated patients in clinical studies, in decreasing order of frequency are fatigue, nausea, hot flush, diarrhoea, hypertension, fracture, asthenia, and fall. Other important adverse reactions include ischaemic heart disease and seizure.

AFFIRM study: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic castration-resistant prostate cancer (CRPC) who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

**Table 1. Adverse Reactions in AFFIRM**

| | XTANDI (n = 800) | | Placebo (n = 399) | |
|---|---|---|---|---|
| | Grade 1 – 4[1] (%) | Grade 3 – 4 (%) | Grade 1 – 4 (%) | Grade 3 – 4 (%) |
| **General Disorders** | | | | |
| Asthenic Conditions[2] | 50.6 | 9.0 | 44.4 | 9.3 |
| Peripheral Oedema | 15.4 | 1.0 | 13.3 | 0.8 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Back Pain | 26.4 | 5.3 | 24.3 | 4.0 |
| Arthralgia | 20.5 | 2.5 | 17.3 | 1.8 |
| Musculoskeletal Pain | 15.0 | 1.3 | 11.5 | 0.3 |
| Muscular Weakness | 9.8 | 1.5 | 6.8 | 1.8 |
| Musculoskeletal Stiffness | 2.6 | 0.3 | 0.3 | 0.0 |
| **Gastrointestinal Disorders** | | | | |
| Diarrhoea | 21.8 | 1.1 | 17.5 | 0.3 |
| **Vascular Disorders** | | | | |
| Hot Flush | 20.3 | 0.0 | 10.3 | 0.0 |
| Hypertension | 6.4 | 2.1 | 2.8 | 1.3 |
| **Nervous System Disorders** | | | | |
| Headache | 12.1 | 0.9 | 5.5 | 0.0 |
| Dizziness[3] | 9.5 | 0.5 | 7.5 | 0.5 |
| Spinal Cord Compression and Cauda Equina Syndrome | 7.4 | 6.6 | 4.5 | 3.8 |
| Paraesthesia | 6.6 | 0.0 | 4.5 | 0.0 |
| Mental Impairment Disorders[4] | 4.3 | 0.3 | 1.8 | 0.0 |
| Hypoesthesia | 4.0 | 0.3 | 1.8 | 0.0 |
| **Infections and Infestations** | | | | |
| Upper Respiratory Tract Infection[5] | 10.9 | 0.0 | 6.5 | 0.3 |
| Lower Respiratory Tract and Lung Infection[6] | 8.5 | 2.4 | 4.8 | 1.3 |
| **Psychiatric Disorders** | | | | |
| Insomnia | 8.8 | 0.0 | 6.0 | 0.5 |
| Anxiety | 6.5 | 0.3 | 4.0 | 0.0 |
| **Renal and Urinary Disorders** | | | | |
| Haematuria | 6.9 | 1.8 | 4.5 | 1.0 |
| Pollakiuria | 4.8 | 0.0 | 2.5 | 0.0 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Fall | 4.6 | 0.3 | 1.3 | 0.0 |
| Non-pathologic Fractures | 4.0 | 1.4 | 0.8 | 0.3 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Pruritus | 3.8 | 0.0 | 1.3 | 0.0 |
| Dry Skin | 3.5 | 0.0 | 1.3 | 0.0 |
| **Respiratory Disorders** | | | | |
| Epistaxis | 3.3 | 0.1 | 1.3 | 0.9 |

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

PREVAIL study: Chemotherapy-naïve Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy

PREVAIL enrolled 1717 patients with metastatic prostate cancer that progressed on an LHRH analogue or after bilateral orchiectomy and had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 16.6 months with XTANDI and 4.6 months with placebo. The most common adverse reaction leading to treatment discontinuation was fatigue, which occurred in 0.2% of the XTANDI-treated patients compared to 0.9% of placebo-treated patients.

Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

**Table 2. Adverse Reactions in PREVAIL**

| | **XTANDI (n = 872)** | | **Placebo (n = 845)** | |
|---|---|---|---|---|
| | **Grade 1 – 4[1] (%)** | **Grade 3 – 4 (%)** | **Grade 1 – 4 (%)** | **Grade 3 – 4 (%)** |
| **General Disorders** | | | | |
| Asthenic Conditions[2] | 46.9 | 3.4 | 33.0 | 2.8 |
| Peripheral Oedema | 11.5 | 0.2 | 8.2 | 0.4 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Back Pain | 28.6 | 2.5 | 22.4 | 3.0 |
| Arthralgia | 21.4 | 1.6 | 16.1 | 1.1 |
| **Gastrointestinal Disorders** | | | | |
| Constipation | 23.2 | 0.7 | 17.3 | 0.4 |
| Diarrhoea | 16.8 | 0.3 | 14.3 | 0.4 |
| **Vascular Disorders** | | | | |
| Hot Flush | 18.0 | 0.1 | 7.8 | 0.0 |
| Hypertension | 14.2 | 7.2 | 4.1 | 2.3 |
| **Nervous System Disorders** | | | | |
| Headache | 11.0 | 0.2 | 7.0 | 0.4 |
| Dizziness[3] | 11.3 | 0.3 | 7.1 | 0.0 |
| Dysgeusia | 7.6 | 0.1 | 3.7 | 0.0 |
| Mental Impairment Disorders[4] | 5.7 | 0.0 | 1.3 | 0.1 |
| Restless Legs Syndrome | 2.1 | 0.1 | 0.4 | 0.0 |
| **Respiratory Disorders** | | | | |
| Dyspnea[5] | 11.0 | 0.6 | 8.5 | 0.6 |
| **Infections and Infestations** | | | | |
| Upper Respiratory Tract Infection[6] | 16.4 | 0.0 | 10.5 | 0.0 |
| Lower Respiratory Tract and Lung Infection[7] | 7.9 | 1.5 | 4.7 | 1.1 |
| **Psychiatric Disorders** | | | | |
| Insomnia | 8.2 | 0.1 | 5.7 | 0.0 |
| **Renal and Urinary Disorders** | | | | |
| Haematuria | 8.8 | 1.3 | 5.8 | 1.3 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Fall | 12.7 | 1.6 | 5.3 | 0.7 |
| Non-pathologic Fractures | 8.8 | 2.1 | 3.0 | 1.1 |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased Appetite | 18.9 | 0.3 | 16.4 | 0.7 |
| **Investigations** | | | | |
| Weight Decreased | 12.4 | 0.8 | 8.5 | 0.2 |

| | XTANDI (n = 872) | | Placebo (n = 845) | |
|---|---|---|---|---|
| | Grade 1 – 4[1] (%) | Grade 3 – 4 (%) | Grade 1 – 4 (%) | Grade 3 – 4 (%) |
| **Reproductive System and Breast Disorders** | | | | |
| Gynaecomastia | 3.4 | 0.0 | 1.4 | 0.0 |

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

TERRAIN Study: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

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

**Table 3. Adverse Reactions in TERRAIN**

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

| | XTANDI (N = 183) | | Bicalutamide (N = 189) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **Investigational** | | | | |
| Weight Loss | 11 | 0.5 | 7.9 | 0.5 |

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

PROSPER Study: XTANDI versus Placebo in Non-metastatic CRPC Patients

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

Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

**Table 4. Adverse Reactions in PROSPER**

| | XTANDI (N = 930) | | Placebo (N = 465) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased Appetite | 9.6 | 0.2 | 3.9 | 0.2 |
| **Nervous System Disorders** | | | | |
| Dizziness[2] | 12 | 0.5 | 5.2 | 0 |
| Headache | 9.1 | 0.2 | 4.5 | 0 |
| Cognitive and Attention Disorders[3] | 4.6 | 0.1 | 1.5 | 0 |
| **Vascular Disorders** | | | | |
| Hot Flush | 13 | 0.1 | 7.7 | 0 |

| | XTANDI (N = 930) | | Placebo (N = 465) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| Hypertension | 12 | 4.6 | 5.2 | 2.2 |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 11 | 0.3 | 8.6 | 0 |
| Constipation | 9.1 | 0.2 | 6.9 | 0.4 |
| **General Disorders and Administration Site Conditions** | | | | |
| Asthenic Conditions[4] | 40 | 4.0 | 20 | 0.9 |
| **Investigations** | | | | |
| Weight Decreased | 5.9 | 0.2 | 1.5 | 0 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Fractures[5] | 9.8 | 2.0 | 4.9 | 1.7 |
| Fall | 11 | 1.3 | 4.1 | 0.6 |
| **Psychiatric Disorders** | | | | |
| Anxiety | 2.8 | 0.2 | 0.4 | 0 |

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

ARCHES Study: XTANDI versus Placebo in Metastatic HSPC Patients

ARCHES randomized 1150 patients with mHSPC, of whom 1146 received at least one dose of study drug. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). At the time of analysis, the median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo. Seventy-six percent (76%) of patients remained on treatment with XTANDI and 58% of patients remained on placebo at the time of analysis.

Grade 3 or higher adverse events were reported in 24% of patients treated with XTANDI and 26% of patients treated with placebo. The primary reason for study drug discontinuation in both treatment groups was disease progression. Disease progression was approximately 3-fold lower in patients in the XTANDI group (11.3%) compared to the placebo group (29.7%). Discontinuation due to adverse events as the primary reason were reported in 4.9% of XTANDI-treated patients and 3.6% of placebo-treated patients. The most common adverse events for the XTANDI group (0.9% each) that were the primary reason leading to study drug discontinuation were anemia (0.5% in the placebo group), decreased appetite (0.7% in the placebo group), diarrhoea (0.3% in the placebo group) and fatigue (0.7% in the placebo group).

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

**Table 5. Adverse Reactions in ARCHES**

| | XTANDI (N = 572) | | Placebo (N = 574) | |
|---|---|---|---|---|
| | Grade 1-4[1] (%) | Grade 3-4 (%) | Grade 1-4 (%) | Grade 3-4 (%) |
| **Metabolism and Nutrition Disorders** | | | | |
| Decreased Appetite | 4.9 | 0.2 | 2.6 | 0 |
| **Nervous System Disorders** | | | | |
| Restless Legs Syndrome | 2.4 | 0 | 0.3 | 0 |
| **Vascular Disorders** | | | | |
| Hot Flush | 27.1 | 0.3 | 22.3 | 0 |
| Hypertension | 8.0 | 3.3 | 5.6 | 1.7 |
| **General Disorders and Administration Site Conditions** | | | | |
| Asthenic conditions[2] | 24.1 | 1.7 | 19.5 | 1.6 |
| **Musculoskeletal and Connective Tissue Disorders** | | | | |
| Musculoskeletal Pain | 6.3 | 0.2 | 4.0 | 0.2 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Fractures[3] | 6.5 | 1.0 | 4.2 | 1.0 |

1. CTCAE v 4.03
2. Includes asthenia and fatigue
3. Defined by MedDRA v21.0 high level group term of "fractures"

ENZAMET Study: XTANDI versus Non-Steroidal Anti-Androgen in Metastatic HSPC Patients

ENZAMET randomized 1125 patients with mHSPC, of whom 1121 received at least one dose of study drug. Patients received either XTANDI at a dose of 160 mg once daily (N = 563) or NSAA (non-steroidal anti-androgen bicalutamide, nilutamide, or flutamide) (N = 558). Patients were allowed up to 6 cycles of concomitant docetaxel (at the start of study with up to 2 cycles prior to study). At the time of analysis, the median duration of treatment was 29.5 months (range: 0.1 to 58.4 months) with XTANDI and 22.1 months (range: 0.0 to 58.6 months) with NSAA. Sixty-four percent (64%) of patients remained on treatment with XTANDI and 36% of patients remained on treatment with NSAA at the time of analysis.

Grade 3 or 4 adverse events were reported in a higher percentage of patients who received docetaxel in each arm; in the enzalutamide arm, 60% of patients treated with docetaxel vs 55% without docetaxel, and in the NSAA arm, 52% of patients treated with docetaxel vs 35% without docetaxel. Discontinuations due to serious adverse events were reported in 11% of XTANDI-treated patients and 9% of NSAA-treated patients. The most common serious adverse event leading to study drug discontinuation was seizure which occurred in 0.9% of the XTANDI-treated patients compared to none in the NSAA-treated patients.

Table 6 shows Grade 3 and Grade 4 adverse reactions reported in ENZAMET that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the NSAA arm.

**Table 6. Grade 3 and Grade 4 Adverse Reactions in ENZAMET**[1]

| | XTANDI | | | NSAA | | |
|---|---|---|---|---|---|---|
| | **With Docetaxel N = 243 (%)** | **Without Docetaxel N = 320 (%)** | **Total N = 563 (%)** | **With Docetaxel N = 235 (%)** | **Without Docetaxel N = 323 (%)** | **Total N = 558 (%)** |
| **Vascular Disorders** | | | | | | |
| Hypertension | 7.4 | 7.8 | 7.6 | 4.7 | 4.3 | 4.5 |
| **Blood and Lymphatic System Disorders** | | | | | | |
| Neutrophil count decreased | 12.3 | 0.3 | 5.5 | 6.4 | 0.3 | 2.9 |
| **General Disorders and Administration Site Conditions** | | | | | | |
| Fatigue | 5.8 | 5.3 | 5.5 | 0.9 | 0.6 | 0.7 |
| **Nervous System Disorders** | | | | | | |
| Syncope | 4.1 | 3.4 | 3.7 | 1.7 | 0.6 | 1.1 |

1. CTCAE v 4.03

Summary of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category in each system organ class. 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); and not known (cannot be estimated from the available data).

**Table 7. Adverse Reactions Summary**

| **MedDRA System Organ Class**[1] | **Adverse Reaction (Preferred Term)** | **Frequency Category** |
|---|---|---|
| **Blood and lymphatic system disorders** | Neutropenia<br>Leukopenia | uncommon<br>uncommon |
| **Cardiac disorders** | Ischaemic Heart Disease[2] | common |
| **Gastrointestinal disorders** | Nausea | not known[9] |
| | Diarrhoea | not known[9] |
| | Vomiting | not known[9] |
| **General disorders and administration site conditions** | Fatigue | very common |
| | Asthenia | very common |
| **Immune system disorders** | Face oedema[3]<br>Tongue oedema[4]<br>Lip oedema[5]<br>Pharyngeal oedema | not known[9] |
| **Injury, poisoning and procedural complications** | Fracture[6] | very common |
| | Fall | very common |
| **Nervous system disorders** | Headache | common |
| | Cognitive Disorders[7] | common |
| | Restless Legs Syndrome | common |
| | Seizure[8] | uncommon |

| MedDRA System Organ Class[1] | Adverse Reaction (Preferred Term) | Frequency Category |
|---|---|---|
| | Posterior Reversible Encephalopathy Syndrome | not known[9] |
| **Psychiatric disorders** | Anxiety | common |
| | Visual Hallucination | uncommon |
| **Reproductive system and breast disorders** | Gynaecomastia | common |
| **Skin and subcutaneous tissue disorders** | Pruritus | common |
| | Dry Skin | common |
| | Rash | not known[9] |
| **Vascular disorders** | Hot Flush | very common |
| | Hypertension | very common |

1. MedDRA v. 21.1
2. As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischaemic 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 ischaemia, and arteriosclerosis coronary artery
3. Includes events of face edema and swelling face
4. Includes events of swollen tongue and tongue oedema
5. Includes events of lip swelling and lip oedema
6. Includes all preferred terms with the word 'fracture' in bones
7. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention
8. 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
9. Adverse reactions of an unknown frequency have been identified during post approval use of enzalutamide. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure

Post Marketing Experience

The following adverse events, which are not listed above, have been reported in association with enzalutamide use during worldwide post-marketing experience:

*Musculoskeletal and connective tissue disorders*: myalgia, muscle spasms, muscular weakness, back pain.

*Skin and connective tissue disorders*: 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.

Description of Selected Adverse Reactions

*Seizures*

In controlled clinical studies, 24 patients (0.5%) experienced a seizure out of 4403 patients treated with a daily dose of 160 mg enzalutamide, whereas four patients (0.2 %) receiving placebo and one patient (0.3%) receiving bicalutamide experienced a seizure. In the patients who experienced seizure when treated with enzalutamide, there was one case of seizure where the patient experienced

complications resulting in death. In the controlled clinical studies, patients with prior seizures or other risk factors for seizures were excluded (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risk of seizure).

Patients who are taking concomitant medicines (strong CYP2C8 inhibitors) that increase the blood levels of enzalutamide may be at increased risk of seizure (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION; and Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In the single-arm UPWARD study to assess incidence of seizure in patients with predisposing factors for seizure (whereof 1.7% had a history of seizures), and 8 of 366 (2.2%) patients treated with XTANDI experienced a seizure. The median duration of treatment was 9.3 months.

*Laboratory abnormalities*
Table 8 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled Phase 3 placebo-controlled studies.

**Table 8. Laboratory Abnormalities**

| | **XTANDI (N = 3173)** | | **Placebo (N = 2282)** | |
|---|---|---|---|---|
| | **Grade 1-4 (%)** | **Grade 3-4 (%)** | **Grade 1-4 (%)** | **Grade 3-4 (%)** |
| **Hematology** | | | | |
| Neutrophil count decreased | 19.8 | 0.9 | 16.7 | 0.4 |
| White blood cell decreased | 16.5 | 0.4 | 9.8 | 0.2 |
| **Chemistry** | | | | |
| Hyponatremia | 13.1 | 1.4 | 8.6 | 1.5 |
| Hyperglycemia | 83.2 | 3.2 | 75.0 | 3.1 |
| Hypermagnesemia | 16.1 | 0.1 | 12.9 | 0 |
| Hypercalcemia | 6.8 | 0.1 | 4.5 | 0 |

*Infections*
In the AFFIRM trial, 1% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. In the PREVAIL trial, 1 patient in each treatment group (0.1%) had an infection resulting in death.

*Hallucinations*
In the AFFIRM trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. In the PREVAIL trial, 1 patient in each treatment group (0.1%) reported an event of Grade 1 hallucination. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

## Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

### 4.9 OVERDOSE

There is no antidote for XTANDI. In the event of an overdose, treatment with XTANDI 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 following an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### Mechanism of action

Enzalutamide is an androgen receptor signalling inhibitor that blocks the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently, inhibits nuclear translocation of these receptors and inhibits the binding of androgen receptor to DNA. *In vitro*, enzalutamide treatment decreased proliferation and induced prostate cancer cell death. Decreased tumour growth was seen in a mouse prostate cancer xenograft model. In preclinical studies enzalutamide lacked androgen receptor agonist activity against several prostate cancer cell lines. The active metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide in the inhibition of testosterone binding to the androgen receptor.

#### Clinical trials

Efficacy of enzalutamide was established in three randomised placebo-controlled multicentre 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 [luteinising hormone-releasing hormone (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. Additionally, efficacy in patients with mHSPC was also established in one randomized, placebo-controlled multicentre phase 3 clinical study (ARCHES). All patients continued on a LHRH analogue or had bilateral orchiectomy.

In the active treatment arm, XTANDI was administered orally at a dose of 160 mg daily. In the four clinical studies (ARCHES, PROSPER, AFFIRM and PREVAIL), 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 prostate specific antigen (PSA) serum concentration independently do not always predict clinical benefit. Therefore, in the four studies, it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

ARCHES study (patients with metastatic HSPC)

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

The following patient demographics and baseline characteristics were balanced between the two treatment arms. 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. Sixty-seven percent (67%) of patients treated with XTANDI and 65% of patients who received placebo had a Gleason score of ≥ 8. Thirty-seven percent (37%) of patients had a low volume of disease and 63% of patients had a high volume of disease. High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Eighty-two percent (82%) of patients had no prior docetaxel treatment; 2% of patients had 1 to 5 cycles of docetaxel and 16% of patients had 6 prior cycles of docetaxel treatment. 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.

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 the time of randomization through 24 weeks after study drug discontinuation), whichever occurred first. XTANDI demonstrated a statistically significant 61% reduction in the risk of an rPFS event compared to placebo. Consistent rPFS results were also observed in patients with high or low volume of disease, and patients with and without prior docetaxel therapy. At the pre-specified final analysis for overall survival (OS), 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. Efficacy results for rPFS and OS from ARCHES are summarized in Table 9, Figure 1 and Figure 2.

**Table 9. Summary of Efficacy Results in ARCHES (Intent-to-Treat Analysis)**

| | **XTANDI (N = 574)** | **Placebo (N = 576)** |
|---|---|---|
| **Radiographic Progression-free Survival** | | |
| Number of events (%) | 91 (15.9) | 201 (34.9) |
| Median, months (95% CI)[1] | NR (NR, NR) | 19.0 (16.6, 22.2) |

| | | |
|---|---|---|
| Hazard ratio (95% CI)[2] | 0.39 (0.30, 0.50) | |
| P-value[3] | p < 0.0001 | |
| **Overall Survival**[4] | | |
| Number of events (%) | 154 (26.8) | 202 (35.1) |
| Median, months (95% CI)[1] | NR (NR, NR) | NR (49.7, NR) |
| Hazard ratio (95% CI)[2] | 0.66 (0.53, 0.81) | |
| P-value[3] | p < 0.0001 | |

NR = Not reached

1. Based on Kaplan-Meier estimates
2. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
3. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no)
4. Based upon a pre-specified final analysis with data cutoff date of 28 May 2021

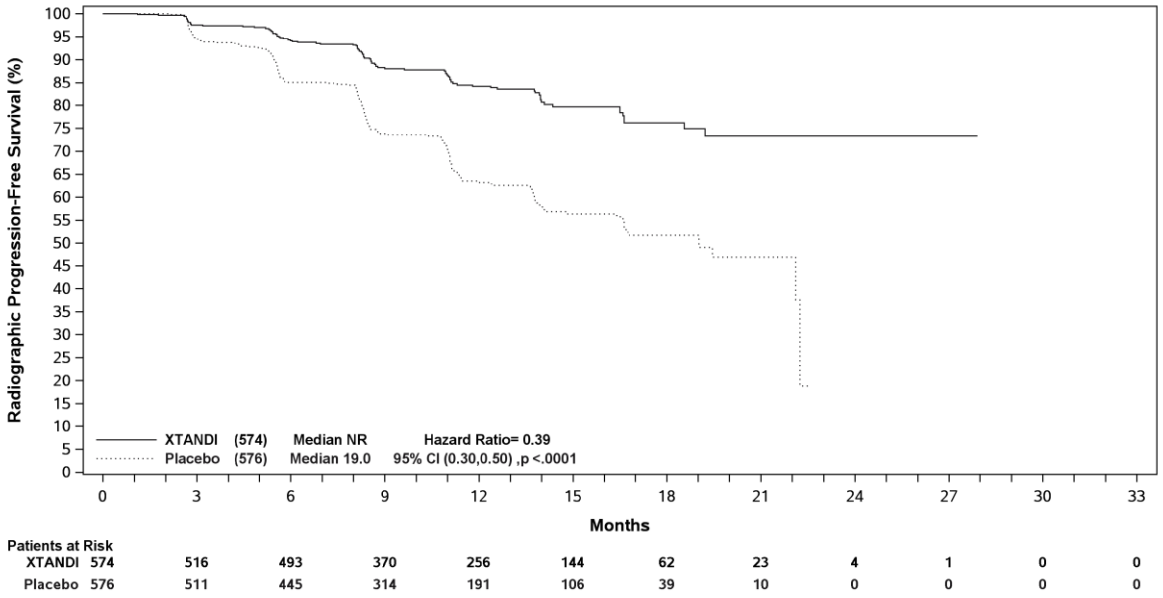



**Figure 1. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)**

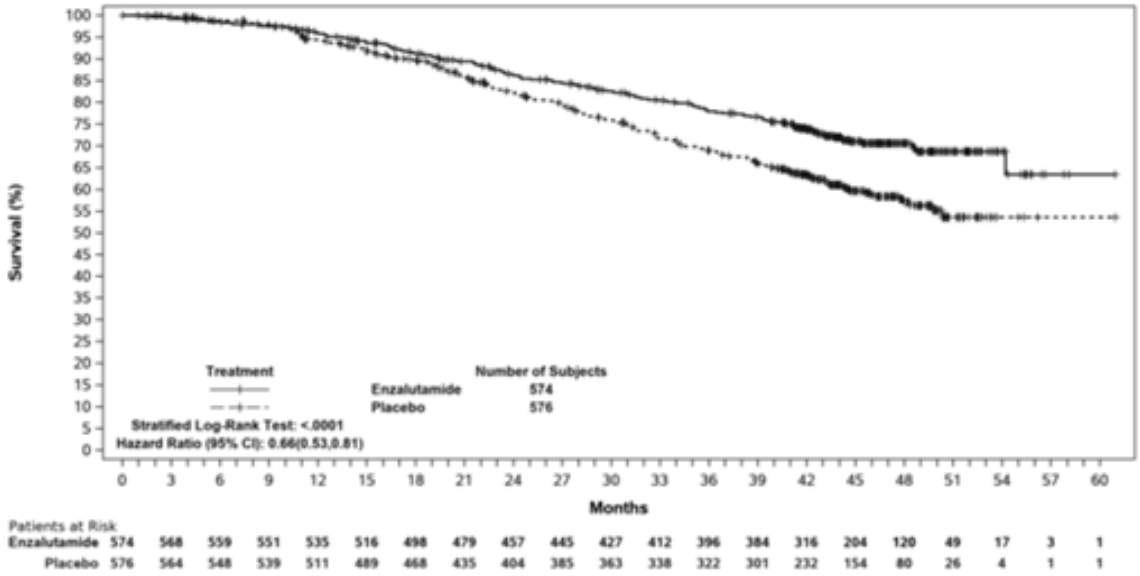



**Figure 2. Kaplan-Meier Curves of overall survival in the ARCHES study (intent-to-treat analysis)**

The major efficacy outcome was supported by multiple secondary endpoints. A statistically significant 72% reduction in risk of initiation of a new antineoplastic therapy was demonstrated for patients in the XTANDI arm compared to patients in the placebo arm (HR = 0.28 [95% CI: 0.20, 0.40]; $p < 0.0001$). A statistically significant improvement of 19.3% in objective response rate (percentage of patients with complete or partial response in their soft tissue disease) was demonstrated with an Objective Response Rate (OSS) (calculated as percentage of patients with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease) of 83.1% for patients in the XTANDI arm compared to 63.7% for patients in the placebo arm (95% CI: 10.4, 28.2; $p < 0.0001$). Time to First Symptomatic Skeletal Event (SSE) (time from randomization to the occurrence of the first symptomatic skeletal event) was associated with a 48% reduction in the risk of a patient experiencing an SSE compared with patients in the placebo arm [HR = 0.52, 95% CI: 0.33, 0.80; nominal p = 0.0026].

<u>ENZAMET study (patients with metastatic HSPC)</u>

The ENZAMET study enrolled 1125 patients with mHSPC randomized 1:1 to receive treatment orally once daily with XTANDI 160 mg (N = 563) or NSAA (N = 562). All patients in the trial received a LHRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high), concomitant antiresorptive therapy (yes vs no), comorbidities (ACE-27: 0 to 1 vs 2 to 3) and planned use of a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomization (yes vs no). Patients were required to have confirmation of metastatic prostate cancer by positive bone scan or metastatic lesions on CT or MRI scan. Patients continued treatment until evidence of clinical progression via CT, MRI or whole body bone scan.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomization was 69 years in the XTANDI group and 68 years in the NSAA group (treated with bicalutamide, nilutamide, or flutamide). The majority of patients had an ECOG performance status score of 0 (72%) and a Gleason score of ≥ 8 (58%). Forty-eight percent (48%) of patients had a low volume of disease and 52% of patients had a high volume of disease.

High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Ten percent (10%) of patients had concomitant antiresorptive therapy; 75% had no or mild comorbidities (ACE-27 score of 0 to 1) and 45% had a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomization.

At the time of analysis, the median follow-up for OS was 33.8 months. The interim analysis demonstrated a statistically significant 33% reduction in the risk of death for patients treated with XTANDI compared to conventional NSAA treatment [HR of 0.67 (95% CI: 0.52, 0.86; p = 0.0018)].

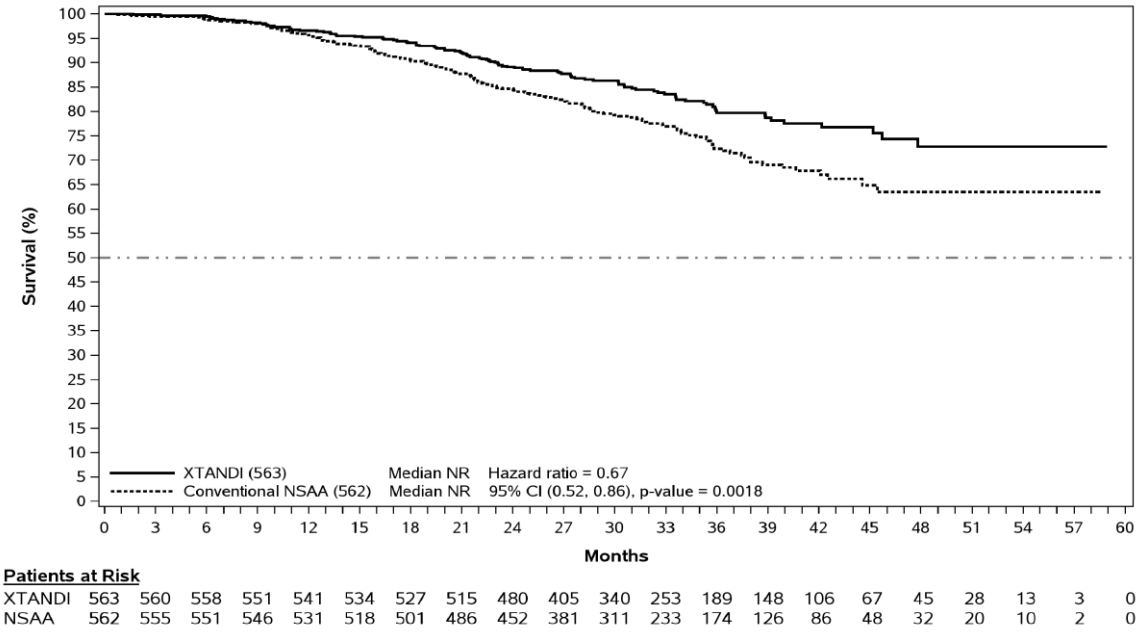



**Figure 3. Kaplan-Meier Curves of Overall Survival in ENZAMET (intent-to-treat analysis)**

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 randomised 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 randomisation 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 randomisation 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 10).

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).

**Table 10. 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 favouring 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

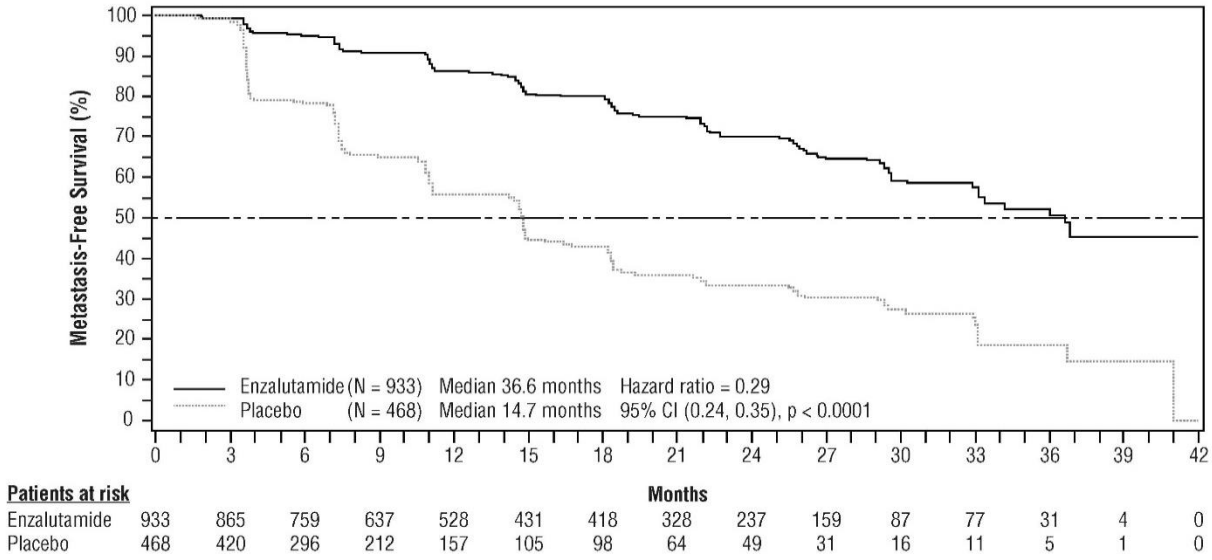



**Figure 4. Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)**

At the final analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomised to receive enzalutamide compared with patients randomised 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]. 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.

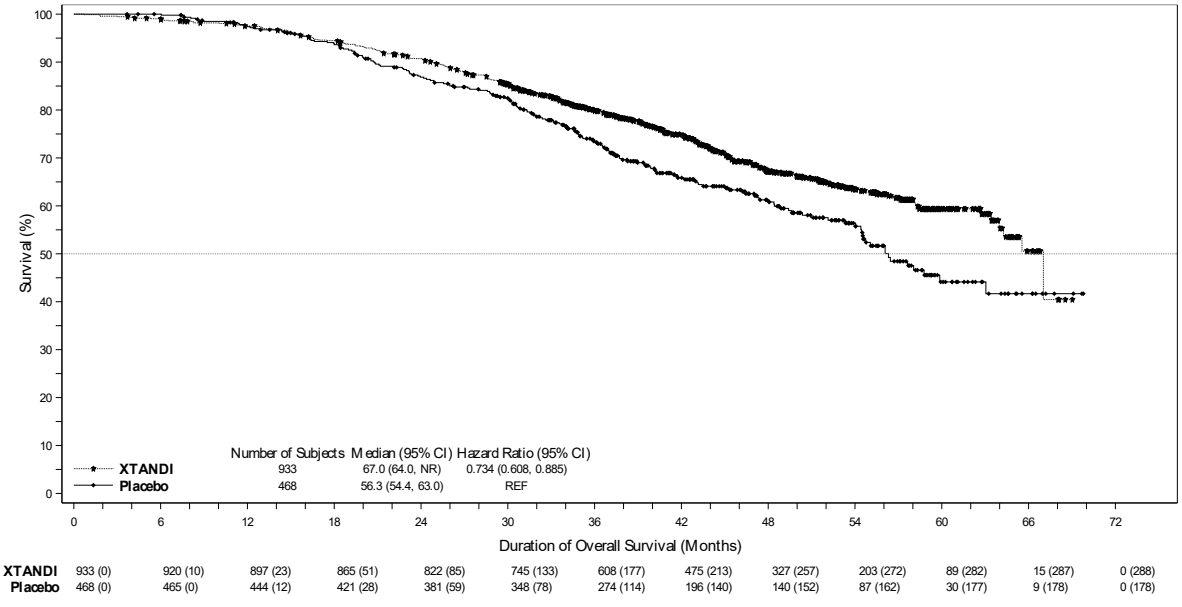



**Figure 5. Kaplan-Meier Curves of overall survival in the PROSPER study (intent-to-treat analysis)**

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.

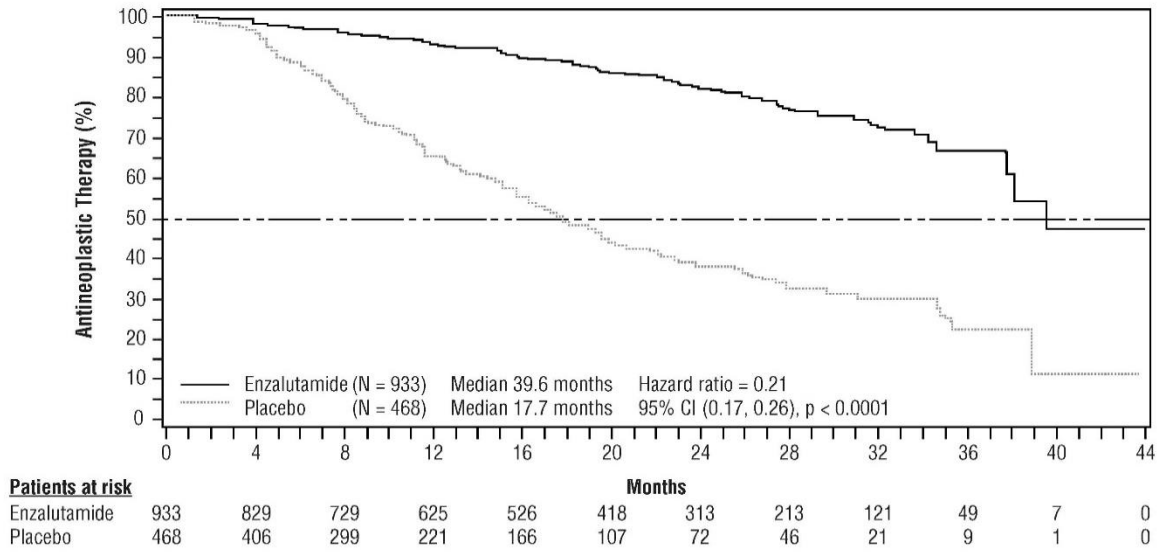



**Figure 6. Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)**

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 PSA progression, radiographic 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 prespecified patient subgroups.

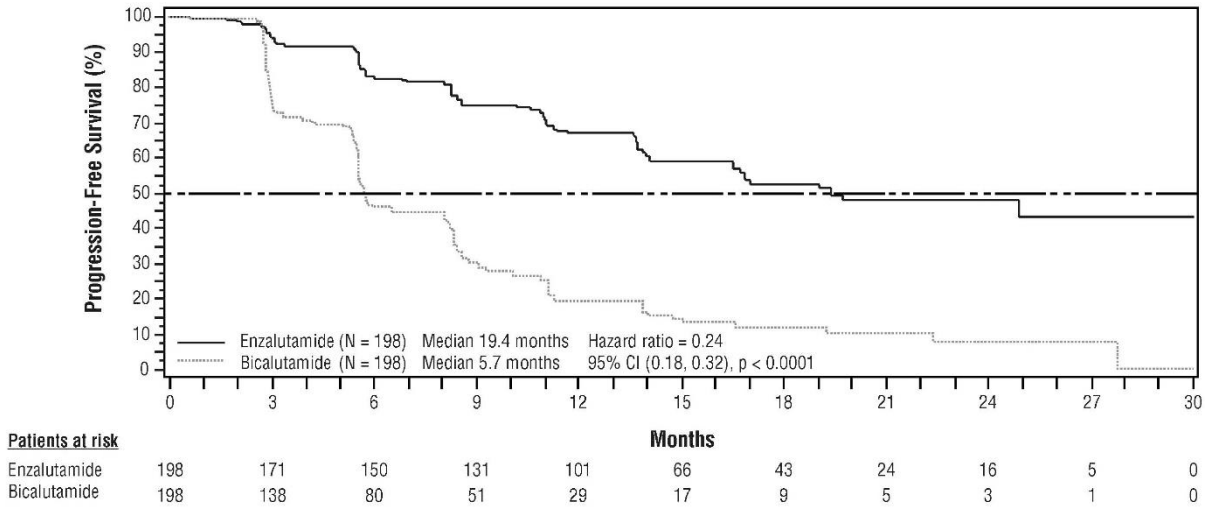



**Figure 7. Kaplan-Meier Curves of progression-free survival in the STRIVE study (intent-to-treat analysis)**

TERRAIN Study (chemotherapy-naïve patients)

TERRAIN enrolled 375 chemotherapy- and anti-androgen-therapy naïve patients who were randomised to receive either enzalutamide orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Median progression-free survival (PFS) was 15.7 months for patients on enzalutamide vs. 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), P < 0.0001] (Figure 8). PFS 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.

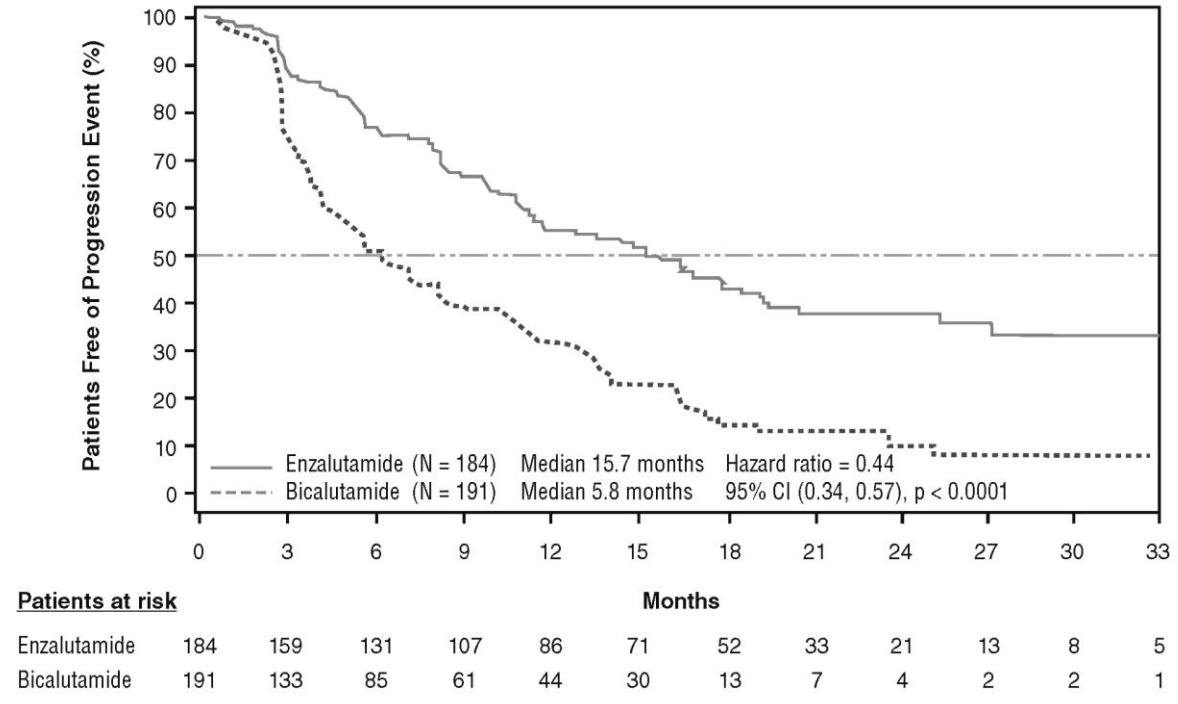



**Figure 8. Kaplan-Meier Curves of Progression-Free Survival in the TERRAIN Study (Full Analysis Set)**

PREVAIL Study (chemotherapy-naïve patients with metastatic CRPC)

A total of 1717 asymptomatic or mildly symptomatic chemotherapy-naïve patients were randomised 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 medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal related event, or clinical progression) and the initiation of either a cytotoxic chemotherapy or an investigational agent, or until unacceptable toxicity.

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% of 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 Tumours (RECIST v 1.1) criteria (for soft tissue lesions). Analysis of rPFS utilised 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), $p < 0.0001$] (Table 11). Of note, 40.4% of enzalutamide-treated patients and 70.5% of placebo-treated patients received subsequent therapies with a demonstrated survival benefit.

An updated overall survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 11). At the updated analysis, 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic castration resistant prostate cancer which 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.

(Table 11 and Figures 9 and 10). The 5-year OS rate was 26% for the enzalutamide arm compared to 21% for the placebo arm.

**Table 11. 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%) |
| Estimated median, 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 | |
| Number of deaths (%) | 0.835 (0.75, 0.93) | |

[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 favours enzalutamide

NR = Not reached

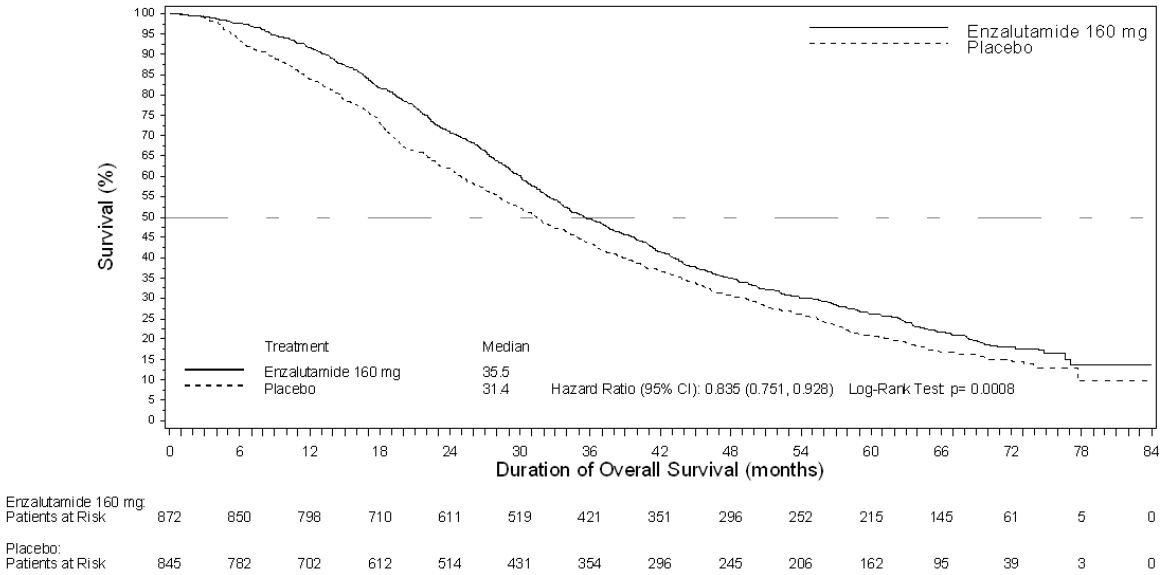



**Figure 9. Kaplan-Meier curves of overall survival based on 5-year survival analysis in the PREVAIL study (intent-to-treat analysis)**

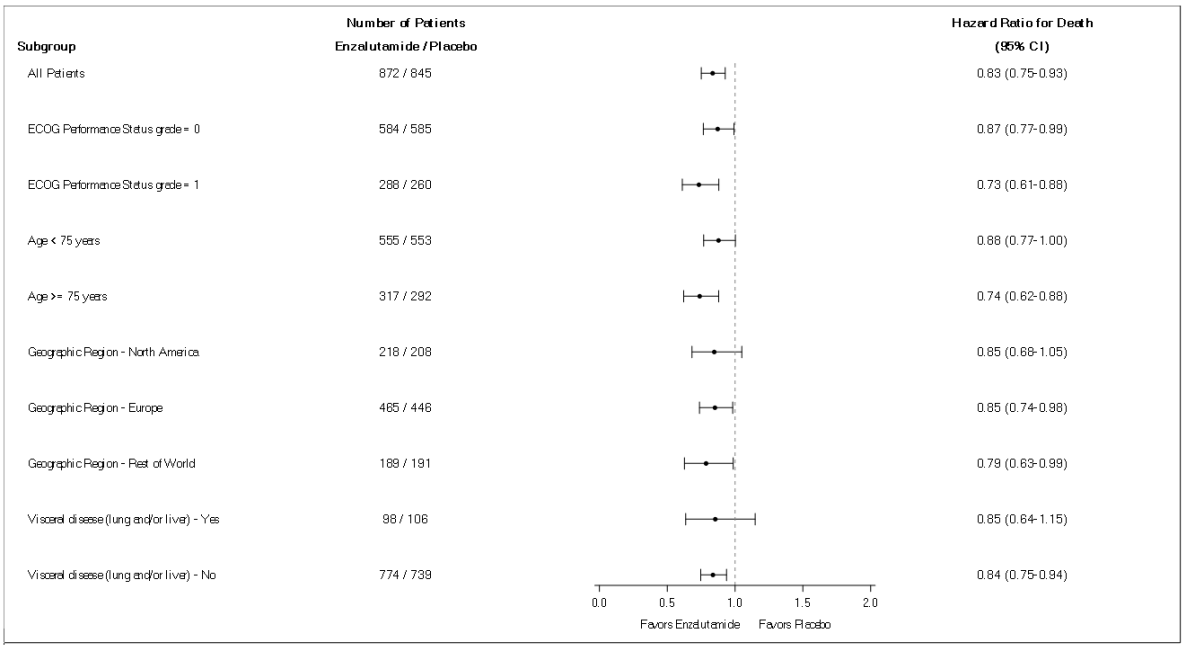
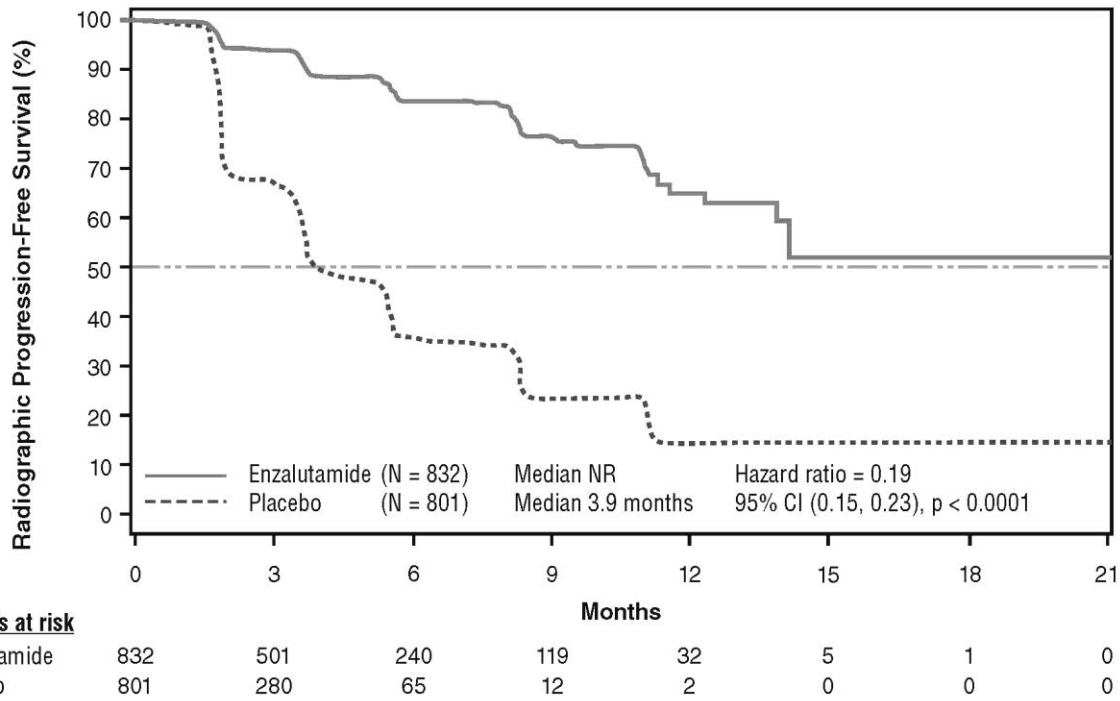



**Figure 10. 5-year overall survival analysis by subgroup: Hazard ratio and 95% confidence interval in the PREVAIL study (intent-to-treat analysis)**

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.




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

**Figure 11. Kaplan-Meier curves of radiographic progression-free survival in the PREVAIL study (intent-to-treat analysis**)

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 27% [HR = 0.526, (95% CI: 0.421, 0.656), $p < 0.0001$], 21.6% of enzalutamide-treated patients reported a skeletal-related event versus 18.5% of placebo-treated patients, an absolute difference of 3.1% events. 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 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.

AFFIRM Study (patients with metastatic CRPC who previously received chemotherapy)
The efficacy and safety of XTANDI 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 randomised, placebo-controlled, multicentre phase 3 clinical trial (AFFIRM). A total of 1199 patients were randomised 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed but not required to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients randomised 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. Following progression, 41% of study drug arm and 61.7% of placebo arm received ≥1 further systemic treatment; therefore, the observed survival data and Kaplan-Meier curve reflect a median duration of treatment of 8 months of enzalutamide vs. 3 months of placebo followed by additional treatments.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41 – 92) and the racial distribution was 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 randomisation). Most (91%) patients had metastases in bone and 23% had visceral lung and/or liver involvement. At study entry, 41% of randomised 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 and medications 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 XTANDI compared to placebo (Table 12 and Figures 12 and 13).

**Table 12. Overall Survival of Patients treated with either XTANDI 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) | |

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 favours XTANDI

NR = Not reached

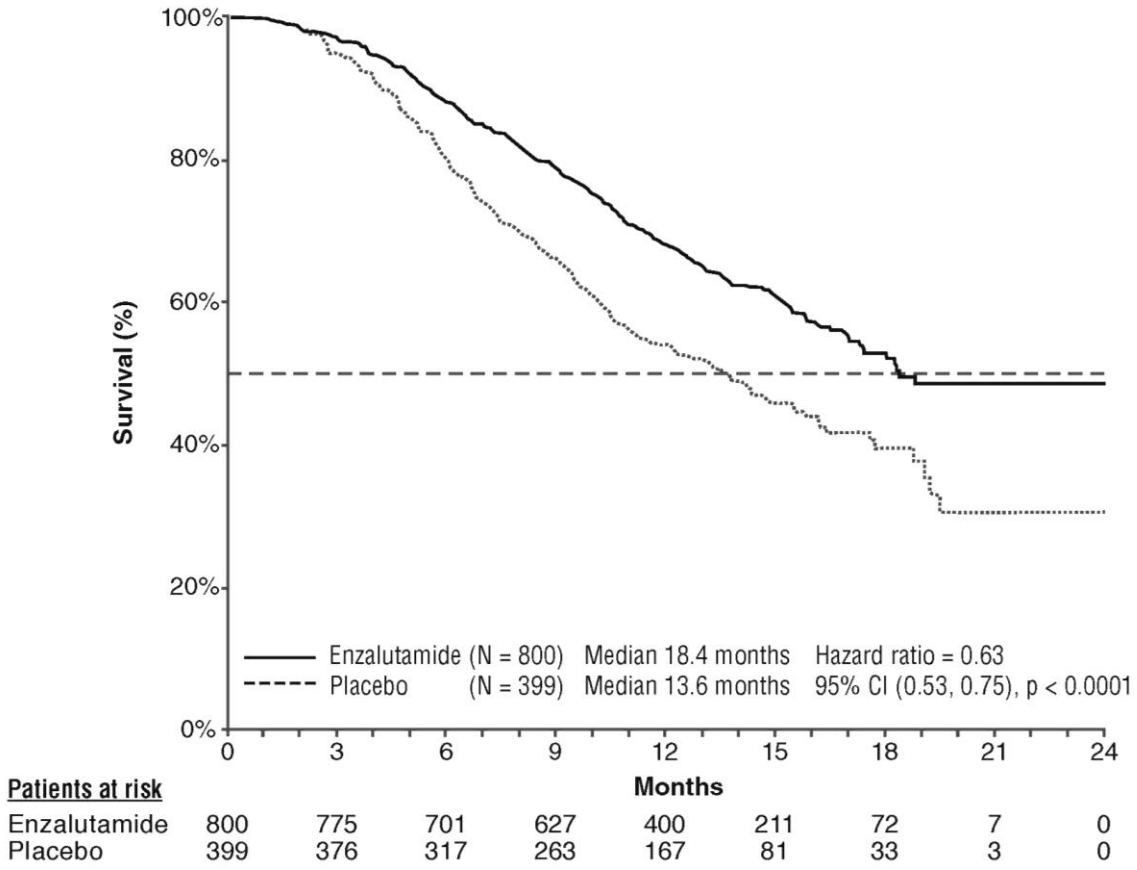
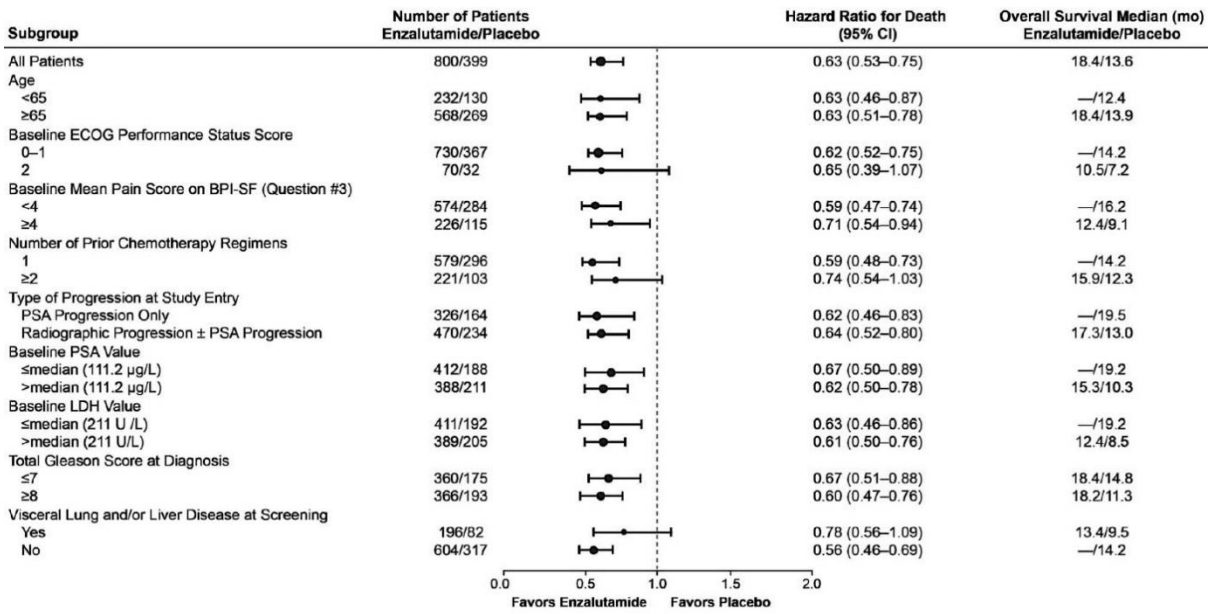



**Figure 12. Kaplan-Meier curves of overall survival in the AFFIRM study (intent-to-treat analysis)**




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

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

In addition to the observed improvement in overall survival, key secondary endpoints (radiographic progression-free survival, and time to first skeletal-related event) favoured XTANDI 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 XTANDI 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.

The median time to first skeletal-related event was 16.7 months for patients treated with XTANDI 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.

**9785-CL-0410 study (enzalutamide post abiraterone in patients with metastatic CRPC)**

The study was a single-arm study in 214 patients with progressing metastatic CRPC who received enzalutamide (160 mg once daily) after at least 24 weeks of treatment with abiraterone acetate plus prednisone. Median rPFS (radiologic progression free survival, the study´s primary endpoint) was 8.1 months (95% CI: 6.1, 8.3). Median OS was not reached. PSA Response (defined as ≥ 50% decrease from baseline) was 22.4% (95% CI: 17.0, 28.6).

For the 69 patients who previously received chemotherapy, median rPFS was 7.9 months (95% CI: 5.5, 10.8). PSA Response was 23.2% (95% CI: 13.9, 34.9).

For the 145 patients who had no previous chemotherapy, median rPFS was 8.1 months (95% CI: 5.7, 8.3). PSA Response was 22.1% (95% CI: 15.6, 29.7).

Although there was a limited response in some patients from treatment with enzalutamide after abiraterone, the reason for this finding is currently unknown. The study design could neither identify the patients who are likely to benefit, nor the order in which enzalutamide and abiraterone should be optimally sequenced.

Elderly

Of the 4403 patients in the controlled clinical trials who received enzalutamide, 3451 patients (78%) were 65 years and over and 1540 patients (35%) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients.

## 5.2 PHARMACOKINETIC PROPERTIES

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 circulates at approximately the same plasma concentration as enzalutamide.

### Absorption

Maximum plasma concentrations ($C_{max}$) 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 medicinal products (warfarin, ibuprofen and salicylic acid) *in vitro*.

### Metabolism

Enzalutamide is extensively metabolised. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolised by CYP2C8 and to a lesser extent by CYP3A4/5 (Refer to Section 4.5 - Interactions with other medicines and other forms of interactions), both of which play a role in the formation of the active metabolite. N-desmethyl enzalutamide was not metabolised 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 (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

*In vitro*, small amounts of N-desmethyl enzalutamide are metabolised to the carboxylic acid metabolite by carboxylesterase 1 which also plays a minor role in the metabolism of enzalutamide to the inactive carboxylic acid metabolite. Carboxylesterase 2 does not appear to play a role in the metabolism of either enzalutamide or N-desmethyl enzalutamide.

### Excretion

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).

### 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.

### Pharmacokinetic Characteristics in Special Populations

Patients with hepatic impairment: The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N = 6), moderate (N = 8) or severe (N = 8) hepatic impairment (Child Pugh Class A, B and 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 $C_{max}$ of enzalutamide in subjects with severe hepatic impairment increased by 34% and decreased by 27%, respectively, compared to healthy control subjects.

Patients with 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 haemodialysis or continuous ambulatory peritoneal dialysis.

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

Paediatric use: The pharmacokinetics of enzalutamide in paediatric patients have not been established.

Gender and race: The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated. Most patients in the randomised 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.

## 5.3 PRECLINICAL SAFETY DATA

### Genotoxicity

Enzalutamide did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay with mouse lymphoma cells or the *in vivo* mouse micronucleus assay.

### Carcinogenicity

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/day, which resulted in combined exposure levels (based on AUC), for enzalutamide plus its active metabolite M2, approximately half the clinical exposure in metastatic CRPC patients receiving 160 mg daily.

Daily oral dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of neoplastic findings (compared to control) that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumours in the testes in males; benign granulosa cell tumour in the of ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes.

Benign Leydig cell tumours are generally not considered relevant to humans based on experience with other anti-androgens. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out.

The urothelial papilloma and carcinoma of the urinary bladder observed at the 100 mg/kg/day dose in male rats are considered secondary to the continuous irritation caused by the increased accumulation of urinary crystal/calculi in the rat urinary bladder possibly due to its horizontal structure. The finding is not expected to occur in humans due to the upright positioning of the

bladder. Prolonged irritation by urinary crystalluria or calculi may dispose rats to urothelial hyperplasia and/or tumour formation, however the incidence of bladder calculi reported in the clinical trials of enzalutamide was comparable between enzalutamide and the placebo groups.

The combined exposure levels (based on AUC) achieved in this study, for enzalutamide and its active metabolite M2 in rats were less than or similar to those in prostate cancer patients receiving 160 mg daily.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

XTANDI contains the following inactive ingredients: caprylocaproyl macrogolglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerol, purified water, titanium dioxide. The soft capsules also contain OPACODE WB monogramming ink NSP-78-17827 BLACK.

## 6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See also Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

## 6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

## 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25$^{o}$C

## 6.5 NATURE AND CONTENTS OF CONTAINER

XTANDI 40 mg capsules are supplied in a cardboard wallet incorporating a PVC/PCTFE/aluminium blister of 28 soft capsules. Each carton contains 4 wallets (112 soft capsules).

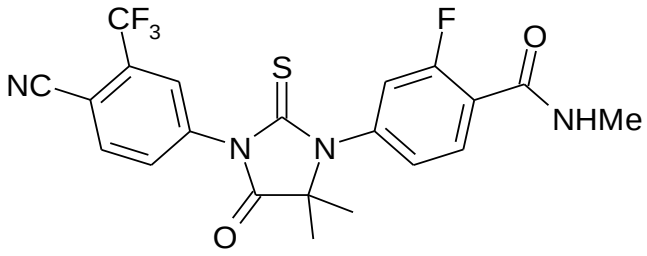
## 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

## 6.7 PHYSICOCHEMICAL PROPERTIES

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

### Chemical structure




Chemical name: 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.

Molecular formula: $C_{21}H_{16}F_4N_4O_2S$

### CAS number

915087-33-1

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

## 8 SPONSOR

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Suite 2.01, 2 Banfield Road Macquarie Park NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
Website: www.astellas.com/au

## 9 DATE OF FIRST APPROVAL

1 July 2014

## 10 DATE OF REVISION

30 June 2023

### SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **4.2** | Changed “fetus” to “foetus” to reflect Australian spelling |
| **4.5** | Addition of drug-drug interaction results from study 9785-CL-0018 |
| **4.6** | Changed “fetus” to “foetus” to reflect Australian spelling |
| **4.8** | Updated the ordering of the most common adverse reactions<br>Updated list of other important adverse reactions |

| | |
|---|---|
| | Update number of patients experienced seizure in controlled clinical studies<br>Changed “ischemic” to “ischaemic” to reflect Australian spelling |
| **5.1** | Addition of final OS results from the ARCHES study and removal of the interim OS results<br>Adjustment in the description of subjects ≥ 65 and ≥ 75 years of age and that received enzalutamide<br>Updated Kaplan-Meier Curves of overall survival in the PROSPER study figure |
| **5.2** | Adjustment to the percentage of patients in the randomized clinical studies that were Caucasian |