For the Use of an Oncologist only

1. **Generic Name and Brand Name**
   Enzalutamide Tablets 160 mg
   Enzandro™ 160

2. **Qualitative and Quantitative Composition**
   Each Film-Coated Tablet Contains:
   Enzalutamide ….…….160 mg
   Excipients……..... q.s.
   Colours: Ferric Oxide USP-NF Yellow, Titanium Dioxide I.P.

3. **Dosage form and Strength**
   Refer section 1&2

4. **Clinical Particulars**

4.1 Therapeutic Indication

- The treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- The treatment of adults with metastatic castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel therapy.

4.2 Posology and Method of Administration

Treatment with enzalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

The recommended dose of Enzalutamide tablets is 160 mg administered orally once daily.

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

Method of Administration

Enzalutamide tablet is for oral use. The film-coated tablets should not be cut, crushed or chewed but should be swallowed whole with water, and can be taken with or without food.

Dose Modifications

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

Concomitant 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 Enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the Enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Concomitant strong CYP3A4 inducers

The concomitant use of strong CYP3A4 inducers should be avoided if possible. If patients must be co-administered a strong CYP3A4 inducer, increase the Enzalutamide dose from 160 mg to 240 mg once daily. If co-administration of the strong CYP3A4 inducer is discontinued, the Enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

Important administration instructions

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

Elderly

No dose adjustment is necessary for elderly patients.

Hepatic impairment

No dose adjustment is necessary for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively). An increased half-life of enzalutamide has however been observed in patients with severe hepatic impairment.

Renal impairment

No dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is advised in patients with severe renal impairment or end-stage renal disease.

4.3 Contraindications

Enzalutamide tablets is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients.

It is also contraindicated in women who are or may become pregnant.

4.4 Special Warnings and Precautions for Use

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

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

Permanently discontinue Enzalutamide tablets in patients who develop a seizure during treatment.

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

Discontinue Enzalutamide tablets in patients who develop PRES.

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

Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions.

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

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

Falls and fractures - Falls and fractures occurred in patients receiving enzalutamide. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for

fractures according to established treatment guidelines and consider use of bone-targeted agents.

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

Embryo-fetal toxicity - The safety and efficacy of enzalutamide have not been established in females. Based on animal reproductive studies and mechanism of action, enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise male patients with female partners who are pregnant or of reproductive potential to use effective contraception during treatment with Enzalutamide tablets and for 3 months after the last dose of Enzalutamide tablets.

Second primary malignancies - Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide-treated patients, and greater than placebo, were bladder cancer (0.3%), adenocarcinoma of the colon (0.2%), transitional cell carcinoma (0.2%) and bladder transitional cell carcinoma (0.1%).

Patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or if other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

Concomitant use with other medicinal products - Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see section 4.2 Posology). A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

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

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

Severe hepatic impairment - An increased half-life of enzalutamide has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged

time to reach steady state concentrations is however anticipated, and the time to maximum pharmacological effect as well as time for onset and decline of enzyme induction may be increased.

Recent cardiovascular disease - The phase 3 studies excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association (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 enzalutamide is prescribed in these patients.

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 enzalutamide.

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

4.5 Drug Interactions

Potential for other medicinal products to affect enzalutamide exposures

CYP2C8 inhibitors- Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of Enzalutamide with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of Enzalutamide tablets with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of Enzalutamide.

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 Cmax was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while Cmax was again unchanged. No dose adjustment is necessary when enzalutamide is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers - Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) with Enzalutamide tablets should be avoided if possible. St John's wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with enzalutamide cannot be avoided, increase the dose of enzalutamide.

Potential for enzalutamide to affect exposures to other medicinal products

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

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

In a clinical study in patients with metastatic CRPC, enzalutamide (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) = 0.882 (90% CI: 0.767, 1.02)] while Cmax decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)].

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. acenocoumarol, warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)

• Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
• Cardiac glycosides (e.g. digoxin)
• Corticosteroids (e.g. dexamethasone, prednisolone)
• HIV antivirals (e.g. indinavir, ritonavir)
• Hypnotics (e.g. diazepam, midazolam, zolpidem)
• Immunosuppressant (e.g. tacrolimus)
• Proton pump inhibitor (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 medicinal products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.

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

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

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

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

Effect of food on enzalutamide exposures

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

4.6 Use In Special Populations

Use in women of childbearing potential and in pregnancy

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

Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant.

Use in lactation

Enzalutamide is not for use in women. The safety and efficacy of enzalutamide have not been established in females. There is no information available on the presence of enzalutamide in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production.

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

Contraception

Based on findings in animal reproduction studies, advise male patients with female partners who are pregnant or of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of enzalutamide tablets. Also, advise to consult a gynecologist if needed.

Fertility

Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs.

Usage in paediatrics

Safety and effectiveness of enzalutamide in paediatric patients have not been established.

Usage in geriatrics

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are asthenia/fatigue, hot flush, hypertension, fractures and fall. Other important adverse reactions include cognitive disorder and neutropenia.

Seizure occurred in 0.5% of enzalutamide-treated patients, 0.1% of placebo-treated patients and 0.3% in bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide-treated patients.

List of adverse reactions

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

Blood and lymphatic system disorders- *Uncommon*: leucopenia, neutropenia; *Not known**: thrombocytopenia

Immune system disorders- *Not known**: face oedema, tongue oedema, lip oedema, pharyngeal oedema

Psychiatric disorders- *Common*: anxiety; *Uncommon*: visual hallucination

Nervous system disorders- *Common*: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome; *Uncommon*: cognitive disorder, seizure [¥]; *Not known**: posterior reversible encephalopathy syndrome

Cardiac disorders- *Common:* ischemic heart disease[†]; *Not known**: QT-prolongation

Vascular disorders- *Very common*: hot flush, hypertension

Gastrointestinal disorders- *Not known**: nausea, vomiting, diarrhoea

Skin and subcutaneous tissue disorders- *Common*: dry skin, pruritus; *Not known** : rash

Musculoskeletal and connective tissue disorders- *Very common*: fractures[‡]; *Not known**: myalgia, muscle spasms, muscular weakness, back pain

Reproductive system and breast disorder - *Common*: gynaecomastia

General disorders and administration site conditions: *Very common*: asthenia, fatigue

Injury, poisoning and procedural complications- *Very common*: fall

* Spontaneous reports from post-marketing experience
¥ 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.
† As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarction, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.
‡ Includes all preferred terms with the word 'fracture' in bones.

Other adverse reactions included constipation, arthralgia, decreased appetite, peripheral edema, musculoskeletal pain, musculoskeletal stiffness, dizziness, spinal cord compression and Cauda Equina syndrome, paresthesia, hypoesthesia, mental impairment disorders, upper respiratory tract infection (nasopharyngitis, sinusitis, rhinitis, pharyngitis laryngitis), lower respiratory tract and lung infection (pneumonia, bronchitis), weight decreased, hyperglycemia, hypermagnesemia, hyponatremia and hypercalcemia, insomnia, anxiety, hematuria, pollakiuria, pruritus, dry skin and epistaxis, vertigo.

Post-marketing experience included skin and subcutaneous tissue disorders such as severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP).

Description of selected adverse reactions

Seizure

In controlled clinical studies, 22 patients (0.5%) experienced a seizure out of 4168 patients treated with a daily dose of 160 mg enzalutamide, whereas three patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

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

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

Ischemic heart disease

In randomised placebo-controlled clinical studies, ischemic heart disease occurred in 3.7% of patients treated with enzalutamide plus ADT compared to 1.5% of patients treated with placebo plus ADT. Fifteen (0.4%) patients treated with enzalutamide and 2 (0.1%) patients treated with placebo had an ischemic heart disease event that led to death.

4.9 Overdose

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

5. Pharmacological properties

5.1 Mechanism of Action

Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the

association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity. A major metabolite, N-desmethyl enzalutamide, exhibited similar in vitro activity to enzalutamide.

5.2 Pharmacodynamic properties

Cardiac electrophysiology

The effect of enzalutamide 160 mg/day at steady-state on the QTc interval was evaluated in 796 patients with metastatic CRPC. No large difference (i.e., greater than 20 ms) was observed between the mean QT interval change from baseline in patients treated with enzalutamide and that in patients treated with placebo, based on the Fridericia correction method. However, small increases in the mean QTc interval (i.e., less than 10 ms) due to enzalutamide cannot be excluded due to limitations of the study design.

Clinical Studies

Enzalutamide versus Placebo in Metastatic CRPC Following Chemotherapy

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

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

A statistically significant improvement in overall survival was demonstrated at the prespecified interim analysis at the time of 520 deaths in patients in the enzalutamide arm compared to patients in the placebo arm (Table 1).

Table 1. Overall Survival of Patients Treated with Either Enzalutamide or Placebo in AFFIRM

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

NR = Not reached.

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

† Hazard Ratio is derived from a stratified proportional hazards model. Hazard Ratio < 1 favors enzalutamide

Enzalutamide versus Placebo in Chemotherapy-naïve Metastatic CRPC

In PREVAIL, 1717 chemotherapy-naïve patients were randomized 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral metastases, patients with a history of mild to moderate heart failure (NYHA class I or II), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression) and the initiation of a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

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

A statistically significant improvement in overall survival was demonstrated at the prespecified interim analysis, conducted after 540 deaths, in patients treated with enzalutamide compared to those treated with placebo (Table 2). Forty percent of enzalutamide -treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival

analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis. At the updated analysis, 52% of enzalutamide -treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. Enzalutamide was used as a subsequent therapy in 2% of enzalutamide -treated patients and 29% of placebo-treated patients.

Table 2. Overall Survival of Patients Treated with Either Enzalutamide or Placebo in PREVAIL

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

NR = Not reached.
* The data cut-off date is 16 Sep 2013.
† P-value is derived from an unstratified log-rank test.
‡ Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors enzalutamide.
§ The data cut-off date is 01 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥ 765.

A statistically significant improvement in rPFS was demonstrated in patients treated with Enzalutamide compared to patients treated with placebo (Table 3).

Table 3. Radiographic Progression-free Survival of Patients Treated with Either Enzalutamide or Placebo in PREVAIL

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

NR = Not reached.
Note: As of the cut-off date for the rPFS analysis, 1633 patients had been randomized.
* P-value is derived from an unstratified log-rank test.
† Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors enzalutamide.

5.3 Pharmacokinetic properties

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

The pharmacokinetics of enzalutamide and its major active metabolite (N-desmethyl enzalutamide) were evaluated in patients with metastatic CRPC and healthy male volunteers. The plasma enzalutamide pharmacokinetics are adequately described by a linear two-compartment model with first-order absorption.

The mean terminal half-life (t1/2) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption

Oral absorption of film-coated enzalutamide tablets was evaluated in healthy male volunteers after a single 160 mg dose of enzalutamide film-coated tablets, and pharmacokinetic modelling and simulation were used to predict the pharmacokinetic profile at steady state. Based on these predictions, as well as other supportive data, the median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 2 hours (range 0.5 to 6 hours).

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.

Food has no clinically significant effect on the extent of absorption. In clinical trials, enzalutamide 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*.

Biotransformation

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, both of which play a role in the formation of the active metabolite. In vitro, N-desmethyl enzalutamide is metabolised to the carboxylic acid metabolite by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the carboxylic acid metabolite. N-desmethyl enzalutamide was not 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.

Elimination

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

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

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

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

Linearity

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

Renal impairment

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

Hepatic impairment

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

Elderly

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

Body Weight and Age

Population pharmacokinetic analyses showed that weight (range: 46 to 163 kg) and age (range: 41 to 92 yrs.) do not have a clinically meaningful influence on the exposure to enzalutamide.

Gender

The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

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

Studies in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to fetuses. After oral administration of radiolabeled ^{14}C-enzalutamide to rats on day 14 of pregnancy at a dose of 30 mg/kg (~ 1.9 times the maximum dose indicated in humans), the maximum radioactivity in the fetus was reached 4 hours after administration and was lower than that in the maternal plasma with tissue/plasma ratio

of 0.27. The radioactivity in the fetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

Studies in lactating rats have shown that enzalutamide and/or its metabolites are secreted in rat milk. After oral administration of radiolabeled ^{14}C-enzalutamide to lactating rats at a dose of 30 mg/kg (~ 1.9 times the maximum dose indicated in humans), the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results also have shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

Enzalutamide was negative for genotoxicity in a standard battery of in vitro and in vivo tests. In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg per day (AUC_{24h} ~317 µg·h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC_{24h} ~322 µg·h/mL) in mCRPC patients receiving 160 mg, daily.

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

Enzalutamide was not phototoxic *in vitro.*

7. Description

ENZANDRO 160 is supplied for oral administration, as a film coated tablet of Enzalutamide. Each film coated tablet of ENZANDRO 160 contains Enzalutamide 160 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Refer Pack

8.3 Packaging information

Refer Pack

8.4 Storage and handing instructions

Refer Pack

Special precautions for disposal and other handling: Enzalutamide should not be handled by persons other than the patient or his caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, enzalutamide may harm a developing fetus. Women who are or may become pregnant should not handle broken or damaged enzalutamide tablets without protection, e.g. gloves. The film-coated tablets should not be chewed, cut or crushed. Any unused medicinal product or waste material should be disposed off in accordance with local requirements.

9. Patient Counselling Information

- Instruct patients to take their dose at the same time each day (once daily). Enzalutamide can be taken with or without food.
- Patients receiving a GnRH analog should be informed that they need to maintain this treatment during the course of treatment with Enzalutamide.
- Patients should be informed that Enzalutamide has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients that Enzalutamide may cause dizziness, mental impairment, paresthesia, hypoesthesia, and falls.
- Patients should be informed that they should not interrupt, modify the dose, or stop Enzalutamide without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Patients should be informed of the common side effects associated with Enzalutamide: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension.
- Inform patients that Enzalutamide may be harmful to a developing fetus. Patients should also be informed that they should use a condom if having sex with a pregnant woman. A condom and another effective method of birth control should be used if the patient is having sex with a woman of child-bearing potential. These measures are required during and for three months after treatment with Enzalutamide.

10. Details of manufacturer

Refer Pack for manufacturer details.

Marketed by:
Abbott Healthcare Pvt. Ltd.
Angel Space, Bldg. No D-4,
Gala No 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor,
201 to 206 & 211 to 216, 2nd Floor,
Pimplas, Bhiwandi, Dist. Thane,
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11. Details of permission or licence number with date

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12. Date of revision

Version 4.0, dated 26th August 2025

For Product Complaints/Adverse events or Queries please write to **webmasterindia@abbott.com**