For the Use of an Oncologist only

1. **Generic Name and Brand Name**
   Enzalutamide Capsules 40 mg
   Enzandro™ 40

2. **Qualitative and Quantitative Composition**
   Each hard Gelatin capsule Contains:
   Enzalutamide… 40 mg
   Excipients…..... q.s.
   Approved colours used in Capsule shell

3. **Dosage Form and Strength**

   Refer section 1& 2

4. **Clinical Particulars**

4.1 Therapeutic Indication

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

The recommended dose is 160 mg of enzalutamide (four 40 mg capsules) as a single oral daily dose.
Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.

If a patient misses taking Enzalutamide Capsule at the usual time, take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not take a double dose to make up for the missed dose.
If more than one daily dose is missed, talk to your doctor.

If a patient has a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (3 capsules of 40 mg, 120 mg or 2 capsules of 40 mg, 80 mg) if warranted.
Concomitant use with strong CYP2C8 inhibitors

If a patient requires administration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg/day. It is recommended to avoid concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP2C9, CYP2C19, or CYP3A4, as enzalutamide may decrease their exposure.When simultaneous use of the strong CYP2C8 inhibitor is discontinued, the enzalutamide

dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor.

Method of Administration

Enzalutamide is for oral use. The capsules should be swallowed whole without opening and are not to be chewed or dissolved or opened.

Elderly

No dose adjustment is necessary for older people.
Paediatric population
Enzalutamide is not meant for use in the paediatric population.

Hepatic impairment

No major differences in single-dose pharmacokinetics were observed in subjects with hepatic impairment vs. matched healthy controls. Therefore, no initial dose adjustment is necessary when administering enzalutamide to patients with mild, moderate or severe hepatic impairment. However, an increased half-life of the drug has been observed in patients with severe hepatic impairment and hence caution is advised.

Renal impairment

No significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment compared to patients and volunteers with baseline normal renal function. No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Patient with severe renal impairment and end-stage renal disease have not been assessed and caution is advised..

Important administration instructions

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

4.3 Contraindications

Individual hypersensitivity to the active substance or excipients of the product.
Enzalutamide is not indicated for use by women.

4.4 Special Warnings and Precautions for Use

Risk of seizures
Enzalutamide belongs to a class of antiandrogens that carry a risk of seizures. Caution should be used in administering Enzalutamide Capsule to patients with a history of seizures or other predisposing factors like brain metastases, brain atrophy associated with alcohol use, brain tumor, or patient on lidocaine therapy or any other drugs which can lower the seizure threshold.

Posterior reversible encephalopathy syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) is a clinical/radiological syndrome characterized by symptoms that can include seizure, headache, impaired vision and hypertension, and can be confirmed by magnetic resonance imaging. The list of medications linked to PRES can include traditional cytotoxic chemotherapeutics (e.g., cisplatin, cyclophosphamide, and high-dose corticosteroids), newer agents that target the vascular endothelial growth factor pathway (e.g., bevacizumab, sunitinib, and pazopanib), and supportive care mediations (e.g., granulocyte colony stimulating factors and erythropoietin). Patients treated with enzalutamide could potentially be at risk for PRES. If symptoms suggestive of PRES arise in patients receiving enzalutamide, the drug should be discontinued immediately, and the diagnostic process should be initiated.

Concomitant use with other medicinal products
Enzalutamide is extensively metabolized by CYP2C8. Enzalutamide is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of CYP3A4. If a patient requires coadministration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg/day. It is recommended to avoid concomitant use of enzalutamide with narrow therapeutic index drugs metabolized by CYP2C9, CYP2C19, or CYP3A4, as enzalutamide may decrease their exposure. The effect on CYP3A4 may be clinically relevant as up to 60% of all drugs are metabolized via CYP3A4, and hence additional International Normalized Ratio (INR) monitoring is warranted.
If coadministered with strong CYP2C8 inhibitors such as montelukast, trimethoprim, gemfibrozil, or pioglitazone, plasma levels are likely to be raised. Strong inducers of CYP2C8 may reduce the effectiveness of enzalutamide and hence should be avoided.

Renal impairment
Patient with severe renal impairment and end-stage renal disease have not been assessed and caution is advised.
Severe Hepatic impairment
Enzalutamide is primarily hepatically eliminated, an increased drug half-life has been observed in patients with severe hepatic impairment and hence caution is advised.

Recent cardiovascular disease
A significant increase in the incidence and relative risk (RR) of cardiovascular toxicity in mCRPC treated with new hormonal agents as opposed to a placebo, has been observed, even though the occurrence of all- and grade 3–4 events rose only 14% and 4%, respectively. Follow-ups for the onset of treatment-related cardiovascular events should, therefore, be considered in these patients.

Androgen deprivation therapy may prolong the QT interval
In patients with a history 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 before prescribing Enzalutamide Capsule.

Use with chemotherapy
The safety and efficacy of concomitant use of Enzalutamide Capsule with cytotoxic chemotherapy has not been established. The combination of docetaxel and enzalutamide is feasible, although higher rates of neutropenia and neutropenic fever,

than anticipated, were observed. Reductions in docetaxel exposure with enzalutamide coadministration were not considered clinically meaningful.

Hypersensitivity reactions
Hypersensitivity reactions manifested by symptoms including, but not limited to, tongue oedema, lip oedema and pharyngeal oedema have been reported with enzalutamide.

Excipients
Enzalutamide contains a type of sugar called lactose. If you have an intolerance to some sugars, contact your doctor before taking this medicine**.**

4.5 Drug Interactions

CYP2C8 and CYP3A4 inhibitors
In the drug interaction study with CYP2C8 and CYP3A4 inhibitors, coadministration of gemfibrozil (strong CYP2C8 inhibitor) increased the composite AUC∞ of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold, and coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC∞ by 1.3-fold. Based on these findings, it is recommended to avoid CYP2C8 inhibitor, however if a patient requires coadministration of a strong CYP2C8 inhibitor with enzalutamide, then the enzalutamide dose should be reduced to 80 mg once daily.

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 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 from 160 mg to 240 mg once daily, Enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer.

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, it reduces the plasma exposure to CYP3A4 substrate like midazolam, CYP2C9 substrate like warfarin, and CYP2C19 substrate like omeprazole. 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) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

P-gp substrates
In in vitro experiments, enzalutamide and N-desmethyl enzalutamide were shown to be inhibitors of P-gp. 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 Capsule and may require dose adjustment.

BCRP, MRP2, OAT3 and OCT1 substrates

Enzalutamide is not a substrate of P-gp or the breast cancer resistance protein (BCRP). Inhibition of multidrug resistance-associated protein 2 (MRP2), BCRP and OATP1B1 could not be excluded based on in vitro data. Theoretically, induction of these transporters is also possible, and the net clinical effect is presently unidentified.

Medicinal products which prolong the QT interval

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Enzalutamide Capsule with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA i.e. Fast sodium (Na) channel blockers like Quinidine, procainamide, disopyramide or class III i.e. Potassium (K) channel blockers like amiodarone, sotalol, dofetilide, ibutilide, other antiarrhythmic medicinal products, and methadone, moxifloxacin, antipsychotics, etc., should, therefore, be carefully evaluated.

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)
· Anticoagulants (e.g. acenocoumarol, warfarin)
· Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
· Antipsychotics (e.g. haloperidol)
· 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)
· Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
· Thyroid agents (e.g. levothyroxine)

Effect of food on enzalutamide exposures

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

4.6 Use in special populations

Use in women of childbearing potential and in pregnancy

Enzalutamide is not indicated for use by women.

Use in lactation

Enzalutamide is not indicated for use by women.

Contraception

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

Fertility

Animal studies suggest that enzalutamide could affect the reproductive system in male rats and dogs.

4.7 Effects on ability to drive and use machines

No studies on the effects of Enzalutamide on the ability to drive or use machines have been performed. It is anticipated that Enzalutamide may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported. Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines.

4.8 Undesirable effects

Summary of the adverse events

Adverse reactions observed during clinical studies are listed below by frequency category.

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

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

MedDRA System organ class	Adverse reaction and frequency
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 (see sections 4.4 and 4.5)
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*: erythema multiforme, 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 infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.

‡ Includes all preferred terms with the word 'fracture' in bones.

Also, some other not known adverse reactions identified are as below:
thrombocytopenia, tongue oedema, lip oedema, pharyngeal oedema, posterior reversible encephalopathy syndrome, QT-prolongation, nausea, vomiting, diarrhea, rash, myalgia, muscle spasms, muscular weakness, and back pain,

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

Enzalutamide is a rationally designed androgen receptor antagonist that blocks androgen receptor (AR) binding, nuclear translocation, and co-activator recruitment more effectively than the androgen receptor antagonists currently in use. Enzalutamide is also unique in that it prevents DNA binding, induces apoptosis, and has no agonist activity when AR is overexpressed.

5.3 Pharmacokinetic properties

Enzalutamide is poorly water soluble. The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. In a reported dose-escalation study, enzalutamide half-life was 5.8 days, steady state was achieved by day 28, accumulation was 8.3-fold, exposure was approximately dose proportional from 30–360 mg/day, and inter-subject variability was ≤30 %. In the multiple-dose period, enzalutamide was absorbed rapidly on day 84, with the median tmax ranging from 0.00 to 2.07 h, which was similar to the median tmax in the single-dose period. The mean CL/F was 0.61 L/h, also similar to the CL/F during the single-dose period. In general, dosing for 1 month was required to reach steady state, and the daily fluctuations in plasma concentrations were low (mean peak-to-trough ratio, 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite, N-desmethylenzalutamide that is equally as active as enzalutamide and circulates at approximately the same plasma concentration as enzalutamide.

Absorption

Absorption after single- and multiple-dose oral administration, the tmax generally occurred around 1 h post dose, showing that enzalutamide is rapidly absorbed. Based on excretion of metabolites in urine and feces in the mass balance and biotransformation study, the extent of absorption of enzalutamide after oral administration is at least 84.2 %.

Maximum plasma concentrations (Cmax) 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 Cmax 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, enzalutamide was administered without regard to food.

Distribution

The mean Vz/F of enzalutamide in patients (110 L) was approximately 2.6 times greater than the volume of total body water (42 L), and approximately 37 times greater than the plasma volume (3 L), suggesting extensive extravascular distribution of the drug. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.
Enzalutamide is highly bound (97 to 98%) to plasma proteins, primarily albumin. The active metabolite is about 95% plasma proteins bound. There was no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) in vitro.

Biotransformation

As confirmed in a drug interaction study, in vitro studies indicated that enzalutamide is mainly metabolized by CYP2C8, with minor CYP3A4/5 involvement. In a 14C-enzalutamide mass balance study, a total of seven metabolites were identified. The two main metabolites in circulation are the active N-desmethyl enzalutamide (M2), which in vitro is equally active as enzalutamide, and the inactive carboxylic acid metabolite (M1). The mean steady-state Ctrough concentrations are similar for enzalutamide and its active metabolite N-desmethyl enzalutamide, and therefore both substances contribute to pharmacological activity. The inactive carboxylic metabolite accounts for approximately 75 % of the exposure. N-desmethyl enzalutamide (M2) is metabolized by carboxylesterase 1 to the carboxyl metabolite (M1). No CYP enzymes involved in further metabolism were identified.

Elimination

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h. In feces, 0.39 % of the dose was recovered as unchanged parent enzalutamide. Given that overall recovery in excreta was 84.6 % of the 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 at least 84.2 % of the dose was absorbed.
Linearity
The steady-state Ctrough values for enzalutamide and N-desmethyl enzalutamide in individual patients remained constant during more than 1 year of long-term therapy, demonstrating time-linear pharmacokinetics once steady state was achieved. At steady state, enzalutamide showed no major deviations from dose proportionality over the daily dose range of 30–360 mg. In patients, %CV for AUCt, Ctrough, and Cmax was ≤30 %, demonstrating low inter-subject variability.

Renal impairment

Renal excretion was an insignificant elimination pathway for enzalutamide and N-desmethyl enzalutamide. Patient with severe renal impairment and end-stage renal disease have not been assessed and hence caution is advised.

Hepatic impairment

Enzalutamide was primarily eliminated by hepatic metabolism.
In a reported study, the pharmacokinetic data were obtained from two non-randomized, open label, single-dose, phase 1 studies conducted in patients with mild (Child-Pugh class A, n = 6) or moderate (Child-Pugh class B, n = 8) hepatic impairment or severe (Child-Pugh class C, n = 8) hepatic impairment and their corresponding matched healthy controls; Subjects with hepatic impairment had liver cirrhosis (n = 19) or chronic hepatitis (n = 3). All subjects received a single oral dose of 160 mg enzalutamide under fasting conditions, with blood samples collected pre-dose and up to 49 days post-dose.

Hepatic impairment did not have a significant effect on the total exposure to enzalutamide or its active metabolite. However t1/2 was 2x in patients with severe hepatic impairment compared to healthy controls (10.4 days compared to 4.7 days), this could be attributed possibly to an increased tissue distribution. It is reported that following a single oral 160 mg dose of enzalutamide, the AUC and Cmax for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, the AUC and Cmax of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively, and the AUC and Cmax 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 Cmax in subjects with mild impairment increased by 14% and 19%, respectively, the AUC and Cmax in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, and the AUC and Cmax in subjects with severe hepatic impairment increased by 34% and decreased by 27%, respectively, compared to healthy control subjects.

Elderly

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

Race

Most patients in the reported clinical trials (>84%) were Caucasian. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

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 40 is supplied for oral administration, as a hard gelatin capsule of Enzultamide. Each hard gelatin capsule of Enzandro 40 contains Enzultamide 40 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. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- 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 D4,
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, Dist. Thane, Bhiwandi - 421 302,
Maharashtra, India.

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11. Details of permission or licence number

Refer Pack for Permission/license details.

12. Date of revision

Version 3.0, dated 19th August 2025

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