To be sold by retail on the prescription of a Registered Medical Practitioner (RMP) only

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Enzalutamide Capsules 40 mg

ENZALUTAGEN-40

1. Generic Name

Enzalutamide Capsules 40 mg

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 & Strength

40 mg Capsules for oral use.

4. Clinical Particulars

4.1 Therapeutic Indications

Enzalutamide capsules was indicated for the treatment of adults with metastatic castration resistant prostate cancer 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.

Posology

The recommended dosage of Enzalutamide capsules is 160 mg administered orally once daily with or without food.

Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

Missed Dose

If a patient misses taking enzalutamide capsules 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.

Dosage Modifications for Adverse Reactions

If a patient experiences a ≥ Grade3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

Dosage Modifications for Drug Interactions

- *Strong CYP2C8 inhibitors*

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

- *Strong CYP3A4 Inducers*

Avoid the coadministration of strong CYP3A4 inducers. If the coadministration of a strong CYP3A4 inducer cannot be avoided, increase the Enzalutamide dosage from 160 mg to 240 mg orally once daily. If the coadministration of the strong CYP3A4 inducer is discontinued, decrease the Enzalutamide dosage to the dosage used prior to initiation of the strong CYP3A4 inducer.

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.

Paediatric population

There is no relevant use of enzalutamide in the paediatric population in the indication of treatment of adult men with CRPC and mHSPC.

Method of administration

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

Important Administration Instructions

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

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients.
- Women who are or may become pregnant.

4.4 Special warnings and precautions for use

Risk of seizure

Use of enzalutamide has been associated with seizure. The decision to continue treatment in patients who develop seizures should be taken case by case.

Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving enzalutamide capsules. 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 enzalutamide capsules in patients who develop PRES is recommended.

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 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. 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 capsules 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 6months) or unstable angina (in the past 3months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥45%, bradycardia or uncontrolled hypertension. This should be taken into account if enzalutamide capsules 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 capsules.

Use with chemotherapy

The safety and efficacy of concomitant use of enzalutamide capsules 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.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide. 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.

4.5 Drug Interactions

Potential for other medicinal products to affect enzalutamide exposures

CYP2C8 inhibitors

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

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

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

Potential for enzalutamide to affect exposures to other medicinal products

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyl transferase (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 (160mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. In a clinical study in patients with metastatic CRPC, enzalutamide (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75mg/m2by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) = 0.882 (90% CI: 0.767, 1.02)] while C_{max} decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)].

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 1monthafter 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, CYP2C19or 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, 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 (160mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while C_{max} decreased by 18%. The AUC and C_{max} of caffeine decreased by 11% and 4%, respectively. No dose adjustment is indicated when a CYP1A2 or CYP2C8 substrate is co-administered with enzalutamide.

P-gp substrates

In vitro data indicate that enzalutamide 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 55days of once daily dosing of 160mg 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 enzalutamide 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 55days 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 enzalutamide.

MRP2, OAT3 and OCT1 substrates

Based on in vitro data, inhibition of 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 (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential

There are no human data on the use of enzalutamide in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant.

Contraception in males and females

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

Pregnancy

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

Breast-feeding

Enzalutamide is not for use in women. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable Effects

Summary of the safety profile

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

Seizure occurred in 0.5% of enzalutamide-treated patients, 0.2% 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.

Tabulated 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.

Adverse reactions identified in controlled clinical trials and post-marketing

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*: erythema multiforme, rash

Musculoskeletal and connective tissue disorders

Dimension: 205x380 mm,
Colour: Black
Spec.: 54 gsm, Maplitho Paper
Folding size: 51.25x95 mm
Reason for change: Change in pack size from 120 Capsules to 112 Capsules and artwork code revised

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.

Description of selected adverse reactions

Seizure

In controlled clinical studies, 24 patients (0.5%) experienced a seizure out of 4403 patients treated with a daily dose of 160mg enzalutamide, whereas four patients (0.2%) 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 9.3months.

The mechanism by which enzalutamide may lower the seizure threshold is not known but could be related to data from Invitro 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 3.9% of patients treated with enzalutamide plus ADT compared to 1.5% patients treated with placebo plus ADT. Fifteen (0.4%) patients treated with enzalutamide and 2 (0.1%) patients treated with placebo had an ischemic heart disease event that led to death.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above ADRs associated with the use of the above drugs. If such reactions are encountered, please report to the Hetero either by filling of Suspect Adverse Drug Reactions Reporting Form **(form.heteroworld.com)** or by **Hetero Helpline No.1800-120-8689** and for all India safety cases and complaints, please write to **drugsafetyindia@heterodrugs.com.**

4.9 Overdote

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 5.8days. 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.

5.2 Pharmacodynamic properties

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

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

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

In a single arm trial (9785-CL-0410)of patients previously treated with at least 24weeks of abiraterone (plus prednisone), 22.4% had a ≥50% decrease from baseline in PSA levels. According to prior chemotherapy history, the results proportion of patients with a ≥50% decrease in PSA levels were 22.1% and 23.2%, for the no prior chemotherapy and prior chemotherapy patient groups, respectively.

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

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

5.3 Pharmacokinetic properties

Enzalutamide achieves steady-state by Day 28 and its AUC accumulates approximately 8.3-fold relative to a single dose.

At steady-state, the mean (% CV) maximum concentration (C_{max}) for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23%) and 12.7 µg/mL (30%), respectively, and the mean (% CV) minimum concentrations (C_{min}) are 11.4 µg/mL (26%) and 13.0 µg/mL (30%), respectively. Enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 (0.2 times the approved recommended dosage) to 360 mg (2.25 times the approved recommended dosage).

Absorption

The median T_{max} is 1 hour (0.5 to 3 hours) following a single 160 mg dose of capsules.

Effect of Food

There was no clinically meaningful effect on enzalutamide or N-desmethyl enzalutamide pharmacokinetics following the administration of enzalutamide with a high-fat meal (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat).

Distribution

The mean (% CV) volume of distribution after a single oral dose is 110 L (29%).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism.

The mean apparent clearance (CL/F) of enzalutamide after a single dose is 0.56 L/h (0.33 to 1.02 L/h). The mean terminal half-life (t1/2) for enzalutamide after a single oral dose is 5.8 days (2.8 to 10.2 days). The mean terminal t1/2 for Ndesmethyl enzalutamide is approximately 7.8 to 8.6 days.

Metabolism

Enzalutamide is metabolized by CYP2C8 and CYP3A4. CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Carboxylesterase 1 metabolizes N-desmethyl enzalutamide and enzalutamide to the inactive carboxylic acid metabolite.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of enzalutamide were observed based on age (41 to 92 years), race (White, Chinese, and Japanese), body weight (46 kg to 163 kg), mild to moderate renal impairment (CLcr ≥ 30 mL/min) and hepatic impairment (Child-Pugh A, B, and C). Severe renal impairment and end stage renal disease (CLcr < 30 mL/min) have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP2C8 Inhibitors on Enzalutamide: The coadministration of Enzalutamide 160 mg with gemfibrozil (strong CYP2C8 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}.

Effect of CYP3A4 and CYP2C8 Inducers on Enzalutamide: The coadministration of Enzalutamide 160 mg after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}.

Effect of CYP3A4 Inhibitors on Enzalutamide: The coadministration of Enzalutamide 160 mg after multiple oral doses of itraconazole (strong CYP3A4 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}.

Effect of Enzalutamide on Other Drugs:

The coadministration of Enzalutamide 160 mg orally once daily with midazolam (a sensitive CYP3A4 substrate) decreased midazolam AUC by 86% and C_{max} by 77%.

Coadministration of Enzalutamide 160 mg orally once daily with warfarin (a sensitive CYP2C9 substrate) decreased Swarfarin AUC by 56% and Cmax by 17%.

Coadministration of Enzalutamide 160 mg orally once daily with omeprazole (a sensitive CYP2C19 substrate) decreased omeprazole AUC by 72% and C_{max} by 62%.

No clinically meaningful changes in exposure of pioglitazone (a sensitive CYP2C8 substrate), caffeine (a sensitive CYP1A2 substrate), or dextromethorphan (a sensitive CYP2D6 substrate) were observed following coadministration with Enzalutamide.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Enzalutamide induces CYP2B6 at clinically achievable concentrations.

Transporter Systems: Enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for P-glycoprotein or BCRP.

Enzalutamide and N-desmethyl enzalutamide are inhibitors of P-glycoprotein and BCRP. The major inactive carboxylic acid metabolite does not inhibit P-glycoprotein.

6. Nonclinical Properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, Impairment of Fertility

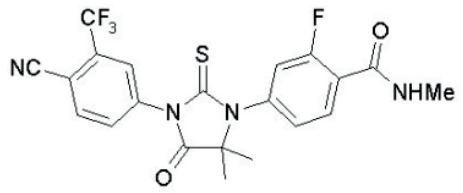
A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the in vitro mouse lymphoma thymidine kinase (Tk) gene mutation assay or the in vivo mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with enzalutamide. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

7. Description

Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5- dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide. The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



8. Pharmaceutical Particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

24 months

8.3 Packing Information

HDPE Container Pack of 112 Capsules

8.4 Storage and handling instructions

Store protected from moisture, at a temperature not exceeding 30°C.

Keep the container tightly closed.

Dispense in original container.

Do not use if seal over bottle opening is broken or missing.

9. Patient Counselling Information

Advise the patient to read the approved patient labelling:

Seizure

Inform patients 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 to contact their healthcare provider right away if they have loss of consciousness or seizure.

Posterior Reversible Encephalopathy Syndrome (PRES)

Inform patients to contact their healthcare provider right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision.

Hypersensitivity

Inform patients that enzalutamide may be associated with hypersensitivity reactions that include swelling of the face, lip, tongue, or throat. Advise patients who experience these types of symptoms of hypersensitivity to discontinue enzalutamide and promptly contact their healthcare provider.

Ischemic Heart Disease

Inform patients that enzalutamide has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur.

Falls and Fractures

Inform patients that enzalutamide is associated with an increased incidence of dizziness/vertigo, falls, and fractures.

Advise patients to report these adverse reactions to their healthcare provider.

Hypertension

Inform patients that enzalutamide is associated with an increased incidence of hypertension.

Dosing and Administration

Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with enzalutamide.

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.

Inform patients that they should not interrupt, modify the dose, or stop enzalutamide without first consulting their healthcare provider.

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.

Embryo-Fetal Toxicity

Inform patients that enzalutamide can be harmful to a developing fetus and can cause loss of pregnancy.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of enzalutamide. Advise male patients to use a condom if having sex with a pregnant woman.

Infertility

Inform male patients that enzalutamide may impair fertility.

10. Details of Manufacturer

Hetero Labs Limited (Unit-I)

Village: Kalyanpur, Chakkan Road, Tehsil: Baddi,
Distt.: Solan, Himachal Pradesh-173 205.

11. Details of permission or licence number with date

MNB/06/328 dated 29-03-2022

12. Date of revision

24-08-2024

GENYGI

Marketed by:
Genygi Life Sciences Private Limited
SS - 29, Second Floor, Aditya Mega Mall,
Plot # 9D, Delhi - 110032

2067932-02

Dimension: 205x380 mm,
Colour: Black
Spec.: 54 gsm, Maplitho Paper
Folding size: 51.25x95 mm
Reason for change: Change in pack size from 120 Capsules to 112 Capsules and artwork code revised