Enzalunix

Enzalutamide INN

COMPOSITION

Enzalunix 40 Tablet: Each film coated tablet contains Enzalutamide INN 40 mg.

Enzalunix 80 Tablet : Each film coated tablet contains Enzalutamide INN 80 mg.

Therapeutic class: Anti-Cancer

CLINICAL PHARMACOLOGY

Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors; and consequently, inhibits nuclear translocation of androgen receptors and their interaction with DNA. A major metabolite, N-desmethyl Enzalutamide, exhibited similar in vitro activity to Enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

Pharmacodynamics

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.

Pharmacokinatics

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.

Absorption

Following oral administration of Enzalutamide capsules (160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma Enzalutamide concentrations (C_{max}) is 1 hour (range 0.5 to 3 hours). At steady-state, the plasma mean C_{max} values for Enzalutamide and N-desmethyl Enzalutamide are 16.6 µg/mL (23% CV) and 12.7 µg/mL (30% CV), respectively, and the plasma mean predose trough values are 11.4 µg/mL (26% CV) and 13.0 µg/mL (30% CV), respectively. Following a single dose administration of 160 mg Enzalutamide in healthy male volunteers, Enzalutamide extent of absorption (AUC) was comparable between Enzalutamide tablet and Enzalutamide capsule, but the mean C_{max} was 10% - 28% lower than that of Enzalutamide capsules. The steady-state pharmacokinetic profiles (AUC and C) of Enzalutamide and N-desmethyl Enzalutamide are similar for Enzalutamide tablet and Enzalutamide capsule. With the daily dosing regimen, Enzalutamide steady-state is achieved by Day 28, and Enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in Enzalutamide plasma concentrations are low (mean peak-to-trough ratio of 1.25). At steady-state, Enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 to 360 mg. A single 160 mg oral dose of Enzalutamide was administered to healthy volunteers with a high fat meal or in the fasted condition. A high-fat meal did not alter the AUC to Enzalutamide or N-desmethyl Enzalutamide.

Distribution and Protein Binding

The mean apparent volume of distribution (V/F) of Enzalutamide in patients after a single oral dose is 110 L (29% CV). Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl Enzalutamide is 95% bound to plasma proteins. *In vitro*, there was no protein binding displacement between Enzalutamide and other highly protein bound drugs (Warfarin, Ibuprofen, and Salicylic Acid) at clinically relevant concentrations.

Metabolism

Following single oral administration of ^{14}C-Enzalutamide 160 mg, plasma samples were analyzed for Enzalutamide and its metabolites up to 77 days post dose. Enzalutamide, N desmethyl Enzalutamide, and a major inactive carboxylic acid metabolite accounted for 88% of the ^{14}C-radioactivity in plasma, representing 30%, 49%, and 10%, respectively, of the total ^{14}C-$AUC_{0\text{-}inf}$.

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism. Following single oral administration of ^{14}C-Enzalutamide 160 mg, 85% of the radioactivity is recovered by 77 days post dose: 71% is recovered in urine (including only trace amounts of Enzalutamide and N-desmethyl Enzalutamide), and 14% is recovered in feces (0.4% of dose as unchanged Enzalutamide and 1% as N-desmethyl Enzalutamide). The mean apparent clearance (CL/F) of Enzalutamide in patients after a single oral dose is 0.56 L/h (range 0.33 to 1.02 L/h). The mean terminal half-life ($t_{1/2}$) for Enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days). Following a single 160 mg oral dose of Enzalutamide in healthy volunteers, the mean terminal $t_{1/2}$ for N-desmethyl Enzalutamide is approximately 7.8 to 8.6 days.

THERAPEUTIC INDICATIONS

Enzalutamide is indicated for the treatment of patients with:

Non-Metastatic Castration-resistant prostate cancer (nmCRPC)

Metastatic Castration-resistant prostate cancer (mCRPC)

Metastatic castration-sensitive prostate cancer (mCSPC)

DOSAGE & ADMINISTRATION

Dosing Information: The recommended dose of Enzalutamide is 160 mg (two 80 mg tablets or four 40 mg tablets) administered orally once daily.

Method of administration: Enzalutamide can be taken with or without food. Swallow tablets whole. Do not cut, crush, or chew the tablets.

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Seizure: Seizure occurred in 0.5% of patients receiving Enzalutamide. In patients with predisposing factors, seizures were reported in 2.2% of patients. Permanently discontinue Enzalutamide in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue Enzalutamide 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. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue Enzalutamide and promptly seek medical care. Permanently discontinue Enzalutamide for serious hypersensitivity reactions.

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

Falls and Fractures: Falls and Fractures occurred in 11% and 10% of patients receiving Enzalutamide, respectively. Evaluate patients for fracture and fall risk and treat patients with bone-targeted agents according to established guidelines.

Embryo-Fetal Toxicity: Enzalutamide can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception.

SIDE EFFECTS

Serious side effects:

1. Seizure.
2. Posterior Reversible Encephalopathy Syndrome (PRES).
3. Allergic reactions.
4. Heart disease.
5. Falls and fractures.

The most common side effects:

1.Weakness or feeling more tired than usual
2. Back pain
3. Hot flashes
4. Constipation
5. Joint pain
6. Decreased appetite
7. Diarrhea
8. High blood pressure

SPECIFIC POPULATIONS

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.

Lactation: 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.

Females and Males of Reproductive Potential Contraception

Males

Based on findings in animal reproduction studies, 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.

Infertility

Males

Based on animal studies, Enzalutamide may impair fertility in males of reproductive potential.

Pediatric Use

Safety and effectiveness of Enzalutamide in pediatric patients have not been established.

Geriatric Use

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Patients with Renal Impairment

No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL <30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

DRUG INTERACTIONS

1. Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to Enzalutamide. If co-administration is necessary, reduce the dose of Enzalutamide.

2. Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to Enzalutamide. If co-administration is necessary, increase the dose of Enzalutamide.

3. Avoid CYP3A4, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index, as Enzalutamide may decrease the plasma exposures of these drugs. If Enzalutamide is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

OVERDOSAGE

In the event of an overdose, stop treatment with Enzalutamide and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at <240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdose.

PHARAMCEUTICAL INFORMATION

Storage Condition:

Store below 30°C and dry place, away from light. Keep out of the reach of children.

Presentations & Packings:

Enzalunix 40 Tablet: Each commercial box contains 120 tablets in a HDPE Pot.

Enzalunix 80 Tablet: Each commercial box contains 60 tablets in a HDPE Pot.

Only for Export

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON® Medicare Limited
Dhaka, Bangladesh

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