Zaluta

Enzalutamide INN

COMPOSITION

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

PHARMACOLOGICAL INFORMATION

Therapeutic Class: Anti-Cancer agent.

PHARMACOLOGICAL ACTIONS

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.

PHARMACOKINETICS

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 tablets (160 mg daily) in patients with metastatic CRPC, the median time to reach maximum plasma Enzalutamide concentrations (Cmax) is 1 hour (range 0.5 to 3 hours).

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-$AUC_{0\text{-}inf}$. In vitro, human CYP2C8 and CYP3A4 are responsible for the metabolism of Enzalutamide. Based on in vivo and in vitro data, CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl Enzalutamide). In vitro data suggest that carboxylesterase 1 metabolizes N-desmethyl Enzalutamide and Enzalutamide to the inactive carboxylic acid metabolite. In vitro, N-desmethyl Enzalutamide is not a substrate of human CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5.

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 ($t_{½}$) 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:

• Castration-resistant prostate cancer (CRPC)

• Metastatic castration-sensitive prostate cancer (mCSPC).

DOSAGE & ADMINISTRATION

Recommended Dosage

The recommended dose of Enzalutamide is 160 mg (two 80 mg tablets or four 40 mg tablets) administered orally once daily. Enzalutamide can be taken with or without food

Swallow tablets or tablets whole. Do not chew, dissolve, or open the tablets. Do not cut, crush, or chew the tablets

Dose Modification

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

CONTRAINDICATIONS

None.

SIDE EFFECTS

• Seizure

• Posterior Reversible Encephalopathy Syndrome (PRES

• Hypersensitivity

• Ischemic Heart Disease

• Falls and Fractures

USE IN SPECIFIC POPULATIONS

Pregnancy

The safety and efficacy of Enzalutamide have not been established in females. 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

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

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

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.

DRUG INTERACTIONS

Drugs that Inhibit CYP2C8

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 with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of Enzalutamide

Drugs that Induce CYP3A4

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

Effect of Enzalutamide on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, Enzalutamide reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). 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

OVERDOSE

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.

PHARMACEUTICAL INFORNATION

Storage

Store below 30^{0}C and dry place, away from light and moisture. Keep out of the reach of children.

PACKING

Zaluta Tablet: Each Commercial box contains 30 tablets in Alu-Alu blister pack.

Manufactured By

BEACON® Pharmaceuticals Limited

Bhaluka, Mymensingh, Bangladesh

LF38201

জ্যালুটা

এনজ্যালুটামাইড আইএনএন

উপাদানঃ

জ্যালুটা ট্যাবলেটঃ প্রতিটি ফিল্ম কোটেড ট্যাবলেটে আছে এনজ্যালুটামাইড আইএনএন যা ৪০ মিগ্রা।

নির্দেশনাঃ

এনজ্যালুটামাইড ক্যাসট্রেশন রেজিস্ট্যান্ট প্রোস্টেট ক্যান্সার (CRPC), মেটাস্ট্যাটিক ক্যাসট্রেশন সেনসেটিভ প্রোস্টেট ক্যান্সার (mCSPC) রোগীদের জন্য নির্দেশিত।

সেবনমাত্রা ও বিধিঃ

প্রতিদিন একবার ১৬০ মিগ্রা (চারটি ৪০ মিগ্রা ট্যাবলেট) এনজ্যালুটামাইড মুখে সেবন করতে হবে। এনজ্যালুটামাইড খাদ্য গ্রহণের সঙ্গে বা ব্যতীত সেবন করা যায়।

নির্দিষ্ট জনসংখ্যার উপর ব্যবহারঃ

গর্ভাবস্থায় ব্যবহারঃ

এনজ্যালুটামাইড নারীদের ক্ষেত্রে নির্দেশিত নয়। এনজ্যালুটামাইড গর্ভবতী নারীদের ক্ষেত্রে নির্দেশিত নয়।

স্তন্যদানকালীন সময়ে ব্যবহারঃ

মাতৃদুগ্ধে এনজ্যালুটামাইড উপস্থিতি, দুগ্ধ সেবনকারী শিশুর ওপর প্রভাব এবং মাতৃদুগ্ধ উৎপাদনের সক্ষমতার ব্যাপারে কোন তথ্য নেই। স্তন্যদানকালীন নারীদের ক্ষেত্রে এনজ্যালুটামাইড নির্দেশিত নয়।

পুরুষদের ক্ষেত্রে ব্যবহারঃ

প্রাণির ওপর পরীক্ষালব্ধ তথ্যের ভিত্তিতে এনজ্যালুটামাইড পুরুষের প্রজনন ক্ষমতার হানি করতে পারে। এনজ্যালুটামাইডের কার্যকরণ এবং প্রাণির ওপর পরীক্ষালব্ধ তথ্যের ভিত্তিতে, এনজ্যালুটামাইড সেবনকালে এবং এনজ্যালুটামাইডের সর্বশেষ ডোজের পরবর্তী তিন মাস পর্যন্ত পুরুষদের কার্যকরি গর্ভনিরোধ ব্যবহারের পরামর্শ দেয়া হয়।

শিশুদের ক্ষেত্রে ব্যবহারঃ

শিশু রোগীদের ক্ষেত্রে এনজ্যালুটামাইডের নিরাপদ ব্যবহার এখনও প্রতিষ্ঠিত হয়নি।

বয়স্কদের ক্ষেত্রে ব্যবহারঃ

এনজ্যালুটামাইডের ক্লিনিকাল পরীক্ষার ভিত্তিতে, বয়স্ক ও যুবকদের ক্ষেত্রে এর কার্যকারিতার সামগ্রিক পার্থক্য পরিলক্ষিত হয়নি।

প্রতিনির্দেশনাঃ

নাই

পার্শ্বপ্রতিক্রিয়াঃ

- খিচুনী
- পোস্টারিয়োর রিভারসিভল এনছেপালোপ্যাথি সিনড্রোম (PRES)
- অতিসংবেদনশীলতা
- ইস্কেমিক হার্ট ডিজিজ
- হাড়ে চির ধরা

সংরক্ষণঃ

৩০^0 সে. তাপমাত্রার নিচে, শুকনো স্থানে, আলো ও আর্দ্রতা থেকে দূরে রাখুন। সকল ওষুধ শিশুদের নাগালের বাইরে রাখুন।

সরবরাহঃ

জ্যালুটা ট্যাবলেটঃ প্রতিটি বাণিজ্যিক মোড়কে আছে ৩০ টি ট্যাবলেট অ্যালু-অ্যালু ব্লিস্টার প্যাকে।

বিস্তারিত ইংরেজী অংশে দেখুন

প্রস্তুতকারক

বীকন ফার্মাসিউটিক্যালস্ লিমিটেড

ভালুকা, ময়মনসিংহ, বাংলাদেশ