420 x 400 mm

Front

ENZALUTAMIDE

ANEZAL

40 mg Capsule
Androgen Receptor Antagonist

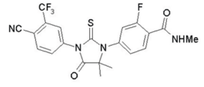
℞

FORMULATION

Each capsule contains:
Enzalutamide..... 40 mg

PRODUCT 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 C21H16F4N4O2S. The structural formula is:



Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

PHARMACODYNAMICS

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
Once daily dosing of 160 mg Enzalutamide in addition to ADT reduced PSA levels to undetectable levels (< 0.2 ng/mL) in 68% of patients with mCSPC (ARCHES).
Based on the efficacy results after once daily dosing of 160 mg Enzalutamide, no exposure response relationship for the efficacy endpoint of overall survival could be identified. In addition, there was no clinically meaningful exposure-response relationship for adverse effects (e.g. fatigue, flushing, headache, or hypertension) within the limited exposure range for 160 mg/day.
Cardiac Electrophysiology
At the recommended dosage, Enzalutamide does not cause large mean increases (i.e., > 20 msec) in the QT interval.

PHARMACOKINETICS

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 (Cmax) 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 (Cmin) 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 Tmax is 1 hour (0.5 to 3 hours) following a single 160 mg dose of capsules and 2 hours (0.5 to 6 hours) following a single 160 mg dose of tablets.
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 N desmethyl 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.

INDICATIONS

Enzalutamide is indicated for the treatment of patients with:
• castration-resistant prostate cancer (CRPC)
• metastatic castration-sensitive prostate cancer (mCSPC)

DOSAGE AND ROUTE OF ADMINISTRATION

Recommended Dosage
The recommended dosage of Enzalutamide is 160 mg administered orally once daily with or without food. Swallow capsules or tablets whole. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets.
Dosage Modifications for Adverse Reactions
If a patient experiences a ≥ Grade 3 or an intolerable adverse reaction, withhold Enzalutamide 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.
Dosage Modifications for Drug Interactions
Strong CYP2C8 Inhibitors
Avoid the coadministration of strong CYP2C8 inhibitors. If the coadministration of a strong CYP2C8 inhibitor cannot be avoided, reduce the Enzalutamide dosage to 80 mg once daily. If the coadministration of the strong inhibitor is discontinued, increase the Enzalutamide dosage to the dosage 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.
Important Administration Instructions
Patients receiving Enzalutamide should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Seizure
Seizure occurred in 0.5% of patients receiving Enzalutamide in seven randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 1776 days after initiation of Enzalutamide. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.
In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) Enzalutamide-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with Enzalutamide after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with Enzalutamide. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.
Advise patients of the risk of developing a seizure while receiving Enzalutamide and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue Enzalutamide in patients who develop a seizure during treatment.
Posterior Reversible Encephalopathy Syndrome (PRES)
There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue Enzalutamide 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 patients receiving Enzalutamide. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.
In the combined data of four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with Enzalutamide compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10% of patients treated with Enzalutamide and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with Enzalutamide and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 days) for patients treated with Enzalutamide. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.
Embryo-Fetal Toxicity
The safety and efficacy of Enzalutamide have not been established in females. Based on animal reproductive studies and mechanism of action, Enzalutamide can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with Enzalutamide and for 3 months after the last dose of Enzalutamide.

PREGNANCY AND LACTATION

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

Back

Data
Animal Data
In an embryo-fetal developmental toxicity study in mice, Enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).
In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg Enzalutamide administration on gestation day 14, Enzalutamide and/or its metabolites were present in the fetus at a Cmax that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.
Breast-feeding:
Risk Summary
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.
Data
Following a single oral administration in lactating rats on postnatal day 14, Enzalutamide and/or its metabolites were present in milk at a Cmax that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

INTERACTION WITH OTHER MEDICINAL PRODUCTS

Effect of other drugs on Enzalutamide:
Strong CYP2C8 Inhibitors
The coadministration of Enzalutamide with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of Enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of Enzalutamide. Avoid the coadministration of Enzalutamide with strong CYP2C8 inhibitors. If the coadministration of Enzalutamide with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of Enzalutamide.
Strong CYP3A4 Inducers
The coadministration of Enzalutamide with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of Enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of Enzalutamide. Avoid the coadministration of Enzalutamide with strong CYP3A4 inducers. If the coadministration of Enzalutamide with a strong CYP3A4 inducer cannot be avoided, increase the dosage of Enzalutamide.
Effect of Enzalutamide on other drugs:
Certain CYP3A4, CYP2C9, or CYP2C19 Substrates
Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of Enzalutamide decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates, which may reduce the efficacy of these substrates. Avoid the coadministration of Enzalutamide with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

ADVERSE DRUG REACTIONS

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.

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 edema, tongue edema, lip edema, 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, diarrhea
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.
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 160 mg 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 9.3 months.
The mechanism by which Enzalutamide may lower the seizure threshold is not known but could be related to data from in vitro studies showing that Enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.
Ischemic Heart Disease
In randomised placebo-controlled clinical studies, ischemic heart disease occurred in 3.9% 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.

OVERDOSAGE AND TREATMENT

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.

SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

No such special precautions are needed for disposal and handeling of the drug.

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE

Dosage Form: Capsule
Packaging Available: Alu/ PVC Blister Pack x 14's (Box of 56's)

CAUTION STATEMENT

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

FDA Reg. No.: DRP-14170-03
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