PROSTAXEN

Apalutamide 60 mg tablets

Everest

COMPOSITION

PROSTAXEN Tablet: Each film coated tablet contains Apalutamide INN 60 mg.

INDICATION AND USAGE

Apalutamide is an androgen receptor inhibitor indicated for the treatment of patients with

- metastatic castration-sensitive prostate cancer
- non-metastatic castration-resistant prostate cancer.

PHARMACOLOGY

Apalutamide is an orally administered, selective Androgen Receptor (AR) inhibitor that binds directly to the ligand-binding domain of the AR. Apalutamide prevents AR nuclear translocation, inhibits DNA binding, impedes AR-mediated transcription, and lacks androgen receptor agonist activity. Apalutamide treatment decreases tumor cell proliferation and increases apoptosis leading to potent antitumor activity.

DOSAGE AND ADMINISTRATION

The recommended dose of Apalutamide is 240 mg (four 60 mg tablets) administered orally once daily. Swallow the tablets whole. Apalutamide can be taken with or without food.

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

CONTRAINDICATION

- Hypersensitivity to the active substance
- Women who are or may become pregnant

WARNINGS AND PRECAUTIONS

Seizure

Apalutamide is not recommended in patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, recent stroke (within one year), primary brain tumours or brain metastases. If a seizure develops during treatment with Apalutamide, treatment should be discontinued permanently.

In two randomised studies (SPARTAN and TITAN), seizure occurred in 0.4% of patients receiving apalutamide and in 0.2% of patients treated with placebo. These studies excluded patients with a history of seizure or predisposing factors for seizure.

Falls and fractures

Falls and fractures occurred in patients receiving apalutamide. Patients should be evaluated for fracture and fall risk before starting Apalutamide and should continue to be monitored and managed according to established treatment guidelines and use of bone-targeted agents should be considered.

Ischaemic heart disease

Ischaemic heart disease, including events leading to death, occurred in patients treated with Apalutamide. The majority of patients had cardiac risk factors. Patients should be monitored for signs and symptoms of ischaemic heart disease and management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care.

Concomitant use with other medicinal products

Apalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. Concomitant use of apalutamide 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 of apalutamide with warfarin and coumarin-like anticoagulants should be avoided. If Apalutamide is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

Recent cardiovascular disease

Patients with clinically significant cardiovascular disease in the past 6 months including severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischaemic attacks), or clinically significant ventricular arrhythmias were excluded from the clinical studies. Therefore, the safety of apalutamide in these patients has not been established. If Apalutamide is prescribed, patients with clinically significant cardiovascular disease should be monitored for risk factors such as hypercholesterolaemia, hypertriglyceridaemia, or other cardio-metabolic disorders. Patients should be treated after initiating Apalutamide for these conditions according to established treatment guidelines.

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 Apalutamide.

SIDE EFFECTS

The following clinically significant adverse reactions are observed in clinical trial:

- **Endocrine disorders:** Hypothyroidism
- **Metabolism and nutrition disorders:** hypercholesterolaemia, hypertriglyceridaemia
- **Nervous system disorders:** Dysgeusia, seizure
- **Cardiac disorders:** ischaemic heart disease
- **Vascular disorders:** hot flush, hypertension
- **Gastrointestinal disorders:** diarrhea
- **Skin and subcutaneous tissue disorders:** skin rash, pruritus
- **Musculoskeletal and connective tissue disorders:** fracture, arthralgia, muscle spasm
- **General disorders and administration site conditions:** fatigue
- **Investigations:** weight decreased
- **Injury, poisoning and procedural complications:** fall, fracture

DRUG INTERACTIONS

Effect of Other Drugs on Apalutamide

CYP2C8 plays a role in the elimination of Apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the Cmax of Apalutamide decreased by 21% while AUC increased by 68% following co-administration of Apalutamide 240 mg single dose with gemfibrozil (strong CYP2C8 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), Cmax decreased by 21% while AUC increased by 45%. No initial dose adjustment is necessary when Apalutamide is co-administered with a strong inhibitor of CYP2C8 (e.g., gemfibrozil, clopidogrel) however, a reduction of the Apalutamide dose based on tolerability should be considered .Mild or moderate inhibitors of CYP2C8 are not expected to affect the exposure of Apalutamide.

Medicinal products that inhibit CYP3A4

CYP3A4 plays a role in the elimination of Apalutamide and in the formation of its active metabolite. In a drug-drug interaction study, the Cmax of apalutamide decreased by 22% while AUC was similar following co-administration of Apalutamide as a 240 mg single dose with itraconazole (strong CYP3A4 inhibitor). For the active moieties (sum of apalutamide plus the potency adjusted active metabolite), Cmax decreased by 22% while AUC was again similar. No initial dose adjustment is necessary when Apalutamide is co-administered with a strong inhibitor of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) however, a reduction of the Apalutamide dose based on tolerability should be considered. Mild or moderate inhibitors of CYP3A4 are not expected to affect the exposure of Apalutamide.

Medicinal products that induce CYP3A4 or CYP2C8

The effects of CYP3A4 or CYP2C8 inducers on the pharmacokinetics of apalutamide have not been evaluated in vivo. Based on the drug-drug interaction study results with strong CYP3A4 inhibitor or strong CYP2C8 inhibitor, CYP3A4 or CYP2C8 inducers are not expected to have clinically relevant effects on the pharmacokinetics of apalutamide and the active moieties therefore no dose adjustment is necessary when Apalutamide is co-administered with inducers of CYP3A4 or CYP2C8.

Effect of Apalutamide on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of Apalutamide with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of Apalutamide with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with Apalutamide and evaluate for loss of activity.

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, Apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate).

Concomitant use of Apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with Apalutamide and evaluate for loss of activity if medication is continued.

USE IN SPECIFIC POPULATION

Pregnancy

Apalutamide is contraindicated in women who are or may become pregnant. Based on its mechanism of action, Apalutamide may cause foetal harm when administered during pregnancy. There are no data available from the use of Apalutamide in pregnant women. Animal reproductive studies have not been conducted with Apalutamide.

Breast-feeding

It is unknown whether apalutamide/metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Apalutamide should not be used during breast-feeding.

Females and Males of Reproductive Potential

Contraception in males and females

It is not known whether apalutamide or its metabolites are present in semen. Apalutamide may be harmful to a developing foetus. For patients having sex with female partners of reproductive potential, a condom should be used along with another highly effective contraceptive method during treatment and for 3 months after the last dose of Apalutamide.

Fertility

Based on animal studies, Apalutamide may decrease fertility in males of reproductive potential.

OVERDOSE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop Apalutamide, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PHARMACEUTICAL INFORMATION

STORAGE

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

How Supplied

PROSTAXEN Tablet: Each HDPE container of PROSTAXEN contains 30 film-coated tablets (each tablet contains 60 mg Apalutamide) a silica gel desiccant and polyester coil with a child-resistant closure.

Manufactured by
Everest Pharmaceuticals Ltd.
BSCIC I/A, Kanchpur, Narayanganj, Bangladesh
www.everestpharmabd.com