Zytix

Abiraterone Acetate

COMPOSITION

Zytix Tablet: Each tablet contains Abiraterone Acetate INN 250 mg.

DESCRIPTION

Abiraterone Acetate is a CYP17 inhibitor.

CLINICAL PHARMACOLOGY

Mode of Action

Abiraterone Acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals. Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Abiraterone decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor serum testosterone levels in patients receiving Abiraterone. Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

Pharmacokinetics

Following administration of Abiraterone Acetate, the pharmacokinetics of abiraterone and Abiraterone Acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). In clinical studies, Abiraterone Acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption

Following oral administration of Abiraterone Acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1000 mg dose of Abiraterone Acetate.

At the dose of 1000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1000 mg.

Systemic exposure of abiraterone is increased when Abiraterone Acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$were approximately 7- and 5-fold higher, respectively, when Abiraterone Acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when Abiraterone Acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking Abiraterone with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of Abiraterone is taken and for at least one hour after the dose of Abiraterone is taken.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. In vitro studies show that at clinically relevant concentrations, Abiraterone Acetate and abiraterone are not substrates of P- glycoprotein (P-gp) and that Abiraterone Acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

Following oral administration of 14C-Abiraterone Acetate as tablets, Abiraterone Acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide Abiraterone Sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide Abiraterone Sulphate and SULT2A1 is involved in the formation of Abiraterone Sulphate.

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of 14C-Abiraterone Acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged Abiraterone Acetate and abiraterone (approximately 55% and 22% of the administered dose respectively).

Indications

Zytix (abiraterone acetate) is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

-In patients with mCRPC who progressed on ADT and had not received prior cytotoxic chemotherapy.

-In patients with mCRPC who progressed on ADT and had received docetaxel chemotherapy.

DOSAGE AND ADMINISTRATION

The recommended dose of Abiraterone is 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of Abiraterone is taken and for at least one hour after the dose of Abiraterone is taken. The tablets should be swallowed whole with water.

For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the Abiraterone starting dose to 250 mg once daily. Abiraterone for patients who develop hepatotoxicity during treatment, hold Abiraterone until recovery. Retreatment may be initiated at a reduced dose. Abiraterone should be discontinued if patients develop severe hepatotoxicity.

DOSE MODIFICATION GUIDELINES

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of Abiraterone to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue Abiraterone and do not retreat patients with Abiraterone. Avoid Abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C), as Abiraterone has not been studied in this population and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with Abiraterone (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with Abiraterone .Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, retreatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with Abiraterone. The safety of Abiraterone retreatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

CONTRAINDICATIONS

Abiraterone is contraindicated in women who are or may become pregnant.

PRECAUTIONS

Mineralocorticoid excess: Use Abiraterone with caution in patients with a history of cardiovascular disease. The safety of Abiraterone in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly.

Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity: Increases in liver enzymes have lead to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt or discontinue Abiraterone dosing as recommended.

Food Effect: Abiraterone must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when Abiraterone Acetate is taken with meals.

OVERDOSE

There have been no reported cases of an overdose with Abiraterone. Based on the known effects of the drug, symptoms of an overdose on this drug may include: hot flushes, muscle and joint discomfort, fluid retention, heart rhythm problems, heart failure, liver problems.

If the overdose was recent, a healthcare provider may administer activated charcoal or "pump the stomach" to help reduce the amount of the medication that is absorbed into the bloodstream. Treatment will also involve supportive care, which consists of treating the symptoms that occur as a result of the overdose. Supportive treatment for a Abiraterone overdose may include close monitoring of the heart and liver.

ADVERSE EFFECTS

The most common adverse reactions (≥5%) are joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia and upper respiratory tract infection.

DRUG INTERACTIONS

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of Abiraterone with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate.

PHARMACEUTICAL INFORMATION

Storage condition: Store in cool and dry place, away from light. Keep out of the reach of children.

Presentation & Packaging

Zytix Tablet: Each commercial box contains 1 x 6's tablets of Abiraterone Acetate in Alu-Alu blister pack.

Manufactured By
BEACON
Pharmaceuticals Limited
Mymensingh, Bangladesh

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