# Abiron 250

Abiraterone Acetate USP

**COMPOSITION:**

**Abiron 250 Tablet:** Each tablet contains Abiraterone Acetate USP 250 mg.

**PHARMACOLOGY:**

Abiraterone Acetate is converted in vivo to Abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-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 17 α-hydroxy derivatives by 17 α-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 Acetate decreased serum testosterone and other androgens in patients in the placebo-controlled clinical trial. It is not necessary to monitor the effect of Abiraterone Acetate on serum testosterone levels. 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:**

**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 1,000 mg dose of Abiraterone Acetate. At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 993 ± 639 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC). Systemic exposure of Abiraterone is increased when Abiraterone Acetate is administered with food. In healthy subjects Abiraterone Cmax and AUC0-∞ were approximately 7- and 5-fold higher, respectively, when a single dose of Abiraterone Acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17-and 10-fold higher, respectively, when a single dose of Abiraterone Acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone AUC0-∞ was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of Abiraterone Acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 491 calories) compared to overnight fasting. Systemic exposures of Abiraterone in patients with metastatic CRPC, after repeated dosing of Abiraterone Acetate were similar when Abiraterone Acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days. Given the normal variation in the content and composition of meals, taking Abiraterone Acetate with meals has the potential to result in increased and highly variable exposures. Therefore, Abiraterone Acetate must be taken on an empty stomach, either one hour before or two hours after a meal. The tablets should be swallowed whole with water.

**Distribution**

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.

**Metabolism**

Following oral administration of 14C- Abiraterone Acetate as capsules, 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 14CAbiraterone 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:**

Abiraterone Acetate is indicated in combination with Prednisone for the treatment of patients with

- Metastatic castration-resistant prostate cancer (CRPC)
- Metastatic high-risk castration-sensitive prostate cancer (CSPC)

**DOSAGE AND ADMINISTRATION:**

Recommended Dose For Metastatic CRPC: The recommended dose of Abiraterone Acetate is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with Prednisone 5 mg orally twice daily. Recommended Dose For Metastatic High-Risk CSPC: The recommended dose of Abiraterone Acetate is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with Prednisone 5 mg administered orally once daily. Important Administration Instructions :ontains 1x10's tablets in blister pack. Patients receiving Abiraterone Acetate should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Abiraterone Acetate must be taken on an empty stomach, at least one hour before or at least two hours after a meal. The tablets should be swallowed whole with water. Do not crush or chew tablets.

**DOSE MODIFICATIONS:**

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the Abiraterone Acetate starting dose to 250 mg once daily.
- For patients who develop hepatotoxicity during treatment, hold Abiraterone Acetate until recovery. Retreatment may be initated at a reduced dose. Abiraterone Acetate should be discontinued if patients develop severe hepatotoxicity.
- Avoid concomitant strong CYP3A4 inducers (e.g., Phenytoin, Carbamazepine, Rifampin, Rifabutin, Rifapentine, Phenobarbital) during Abiraterone Acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the Abiraterone Acetate dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued. Or, as directed by the registered physician.

**CONTRAINDICATIONS:**

It is contraindicated in any patient who has shown a hypersensitivity reaction to the drug or to any of the excipients.

**WARNING & PRECAUTIONS:**

Abiraterone Acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Patients should be monitored for hypertension, hypokalemia, and fluid retention at least once a month. Hypertension and hypokalemia should be controlled and corrected before and during treatment with Abiraterone. Patients should be monitored for symptoms and signs of adrenocortical insufficiency. Serum transaminases (ALT and AST) and bilirubin levels should be measured prior to starting treatment with Abiraterone, every two weeks for the first three months of treatment and monthly thereafter.

**ADVERSE REACTIONS:**

The most common adverse reactions are fatigue, arthalgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache.

**USE IN SPECIAL POPULATION:**

**Pediatric Use:** The safety and effectiveness in pediatric patients have not been established.

**Use in Pregnancy:** The safety and efficacy of Abiraterone Acetate have not been established in females. The drug can cause fetal harm and potential loss of pregnancy.

**Use in Lactation:** There is no information available on the presence of Abiraterone Acetate in human milk, or on the effects on the breastfed child or milk production.

**DRUG INTERACTIONS:**

**Drugs That Inhibit Or Induce CYP3A4 Enzymes**

Based on in vitro data, Abiraterone Acetate is a substrate of CYP3A4. In a dedicated drug interaction trial, co-administration of Rifampin, a strong CYP3A4 inducer, decreased exposure of Abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during Abiraterone Acetate treatment. If a strong CYP3A4 inducer must be co-administered, increase the Abiraterone Acetate dosing frequency. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of Abiraterone.

**Effects Of Abiraterone On Drug Metabolizing Enzymes**

Abiraterone Acetate is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of Dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when Dextromethorphan was given with Abiraterone Acetate 1,000 mg daily and Prednisone 5 mg twice daily. Avoid co-administration of Abiraterone Acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., Thioridazine). If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug. In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of Pioglitazone (CYP2C8 substrate) was increased by 46% when Pioglitazone was given together with a single dose of 1,000 mg Abiraterone Acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with Abiraterone Acetate.

**OVERDOSE:**

There is no specific antidote. In the event of an overdose, Abiraterone Acetate should be stopped, general supportive measures are undertaken, including monitoring for arrhythmias and cardiac failure and assess liver function.

**STORAGE:**

Do not store above 25° C. Protect from light. Keep out of the reach of children.

**PACKAGING:**

**Abiron 250 Tablet:** Each HDPE container of Abiron 250 contains 28 tablets, a silica gel desiccant and polyester coil with a child resistent closure.

*Manufactured by:*

ZISKA PHARMA **Ziska Pharmaceuticals Ltd.**

Kaliakoir, Gazipur, Bangladesh

Version: 00

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