297mm

210mm

oncogen

Abytiga
Abiraterone Acetate

ایبیٹیگا
(ابیراٹیرون ایسیٹیٹ)

1. NAME OF THE MEDICINAL PRODUCT
Abiraterone Acetate 250mg Film Coated Tablets
Abiraterone Acetate 500mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Abytiga 250mg Film Coated Tablets: Each tablet contains Abiraterone Acetate 250mg.
Abytiga 500mg Film Coated Tablets: Each tablet contains Abiraterone Acetate 500mg.

3. PHARMACEUTICAL FORM
Film-coated tablet.

Abiraterone Acetate 250mg Film Coated Tablets: Purple, oval-shaped, film-coated tablets, debossed with "A" on one side and "250" on other side.
Abiraterone Acetate 500mg Film Coated Tablets: Purple, oval-shaped, film-coated tablets, debossed with "A" on one side and "500" on other side.

4. CLINICAL PARTICULARS
4.1 Therapeutic Indications
Abiraterone Acetate is a CYP17 inhibitor indicated with prednisone or prednisolone for the treatment of

- Metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- Metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Abiraterone Acetate is also indicated in combination with prednisone or prednisolone and androgen deprivation therapy (ADT) for the treatment of patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) who may have received up to 3 months of prior ADT.

4.2 Posology and Method of Administration
Posology
The recommended dose is 1000 mg (two 500 mg tablets or four 250 mg tablets) as a single daily dose that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone.

Dosage of prednisone or prednisolone
For mCRPC, Abiraterone Acetate is used with 10 mg prednisone or prednisolone daily.

For mHSPC, Abiraterone Acetate is used with 5 mg prednisone or prednisolone daily.

Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.

Recommended monitoring
Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk or congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter.

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with Abiraterone Acetate, consider maintaining the patient's potassium level at 4.0mM.

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with Abiraterone Acetate should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

In the event of a missed daily dose of either Abiraterone Acetate, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatotoxicity
For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately. Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (one 500 mg tablet or two 250 mg tablets) once daily. For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued.

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, treatment should be discontinued and patients should not be re-treated.

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

Moderate hepatic impairment (Child-Pugh Class B) has been shown to increase the systemic exposure to abiraterone by approximately four-fold following single oral doses of abiraterone acetate 1000 mg. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of Abrone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abrone should not be used in patients with severe hepatic impairment.

Renal impairment
No dose adjustment is necessary for patients with renal impairment. However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

Paediatric population
There is no relevant use of this medicinal product in the paediatric population, as prostate cancer is not present in children and adolescents.

Method of administration
Abiraterone Acetate is for oral use.
Abiraterone Acetate tablets must be taken as a single dose once daily on an empty stomach. Do not eat food 2 hours before and 1 hour after taking Abytiga. The tablets must be swallowed whole with water. Do not crush or chew tablets.

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients.
- Women who are or may potentially be pregnant.
- Severe hepatic impairment [(Child-Pugh Class C).
- Abiraterone Acetate plus prednisone/prednisolone is not recommended for use in combination with radium Ra 223 dichloride

4.4 Special Warnings and Precautions for Use
Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess
Abiraterone Acetate may cause hypertension, hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia or have underlying cardiovascular conditions while taking Abiraterone Acetate.

Abiraterone Acetate should be used with caution in patients with a history of cardiovascular disease. Before treatment with Abiraterone Acetate, hypertension must be controlled and hypokalemia must be corrected. Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Hepatotoxicity and hepatic impairment
Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies. Serum transaminase and bilirubin levels should be measured prior to starting treatment with Abiraterone Acetate, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with Abiraterone Acetate should be interrupted immediately and liver function closely monitored.

Re-treatment with Abiraterone Acetate may only take place after the return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN.

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, Abiraterone Acetate should be discontinued and patients should not be re-treated with Abiraterone Acetate.

There are no data on the clinical safety and efficacy of multiple doses of Abiraterone Acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. Abiraterone Acetate should be used with caution in patients with moderate hepatic impairment only if the benefit clearly outweighs the possible risk. Abiraterone Acetate should not be used in patients with severe hepatic impairment.

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome.

Corticosteroid withdrawal and coverage of stress situations
Caution is advised and monitoring for adrenocortical insufficiency should occur if patients need to be withdrawn from prednisone or prednisolone. If Abiraterone Acetate is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage of a corticosteroid may be indicated before, during and after the stressful situation.

Hypoglycemia
Cases of hypoglycemia have been reported when Abrone Acetate was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide; therefore, blood sugar should be measured frequently in patients with diabetes.

Use with chemotherapy
The safety and efficacy of concomitant use of Abiraterone Acetate with cytotoxic chemotherapy has not been established.

Combination of abiraterone and prednisone/prednisolone with Ra-223
Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in studies.

It is recommended that subsequent treatment with Ra-223 is not initiated for at least 5 days after the last administration of Abiraterone Acetate in combination with prednisone/prednisolone.

Bone density
Decreased bone density may occur in men with metastatic advanced prostate cancer (castration resistant prostate cancer). The use of Abiraterone Acetate in combination with a glucocorticoid could increase this effect.

Prior use of ketoconazole
Lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Intolerance to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction
Effect of food on abiraterone
Administration of Abiraterone Acetate with food significantly increases the absorption of abiraterone. Instruct patients to not eat food 2 hours before and 1 hour after taking Abiraterone Acetate. If taken with food causes increased exposure and may result in adverse reactions.

Interactions with other drugs
Potential for other drugs to affect abiraterone exposures
Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with Abiraterone Acetate are to be avoided, or used with careful evaluation of clinical efficacy.

In a study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential for Abiraterone Acetate to affect exposures to other drugs
Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8.

Caution is advised when Abiraterone Acetate is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide.

4.6 Fertility, pregnancy and lactation
Pregnancy
Abiraterone Acetate is contraindicated in women who are or may potentially be pregnant.

There are no human data on the use of Abiraterone Acetate in pregnancy and Abiraterone Acetate is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the fetus.

It is not known if abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of child-bearing potential, a condom is required along with another effective contraceptive method.

Breast-feeding
The safety and efficacy of Abiraterone Acetate have not been established in females. There is no information available on the presence of abiraterone in human milk, or on the effects on the breastfed child or milk production.

4.7 Effects on Ability to Drive and Use Machines
No studies on the effects of Abiraterone Acetate on the ability to drive or use machines have been performed. It is not anticipated that Abiraterone Acetate will affect the ability to drive and use machines.

4.8 Undesirable Effects
Summary of the safety profile
In an analysis of adverse reactions of studies with Abiraterone Acetate, adverse reactions that were observed in ≥10% of patients were peripheral oedema, hypokalaemia, hypertension, urinary tract infection and increase alanine aminotransferase and/or aspartate aminotransferase. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

Abiraterone Acetate may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions.

Tabulated list of adverse reactions
In studies of patients with metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, Abiraterone Acetate was administered at a dose of 1000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: very common; common; uncommon; rare; very rare and not known.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse reactions identified in studies and post-marketing

System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Immune system disorders	not known: anaphylactic reactions
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation
Vascular disorders	very common: hypertension

297mm

210mm

Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased[b] rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash
Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased
** Fractures includes osteoporosis and all fractures with the exception of pathological fractures
[a] Spontaneous reports from post-marketing experience
[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

4.9 Overdose
Human experience of overdose with Abiraterone Acetate is limited.

There is no specific antidote. In the event of an overdose, administration of Abiraterone Acetate should be stopped and general supportive measures undertaken, including monitoring for arrhythmias. Liver function also should be assessed.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic Properties
Pharmacotherapeutic group: Other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action
Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumor tissues. It catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results 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 LHRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Treatment with Abiraterone Acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects
Abiraterone Acetate decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer.

Use of Spironolactone
Patients in clinical trials with Abiraterone Acetate were not allowed to use spironolactone as spironolactone binds to the androgen receptor and may increase PSA levels.

5.2 Pharmacokinetic Properties
General introduction
Following administration of abiraterone acetate, the pharmacokinetics of abiraterone has been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted in vivo to abiraterone, an androgen biosynthesis inhibitor.

Absorption
Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 17-fold increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking Abiraterone Acetate with meals has the potential to result in highly variable exposures. Therefore, Abiraterone Acetate must not be taken with food. Abiraterone Acetate tablets must be taken as a single dose once daily on an empty stomach. Abiraterone Acetate must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Abiraterone Acetate. The tablets must be swallowed whole with water.

Distribution and protein binding
The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Metabolism
Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43% of total radioactivity.

Elimination
The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-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).

Special populations
Renal impairment
The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable hemodialysis schedule, versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1000 mg dose did not increase in patients with end-stage renal disease on dialysis.

Administration of Abiraterone Acetate in patients with renal impairment including severe renal impairment does not require dose reduction.

Hepatic impairment
The pharmacokinetics of abiraterone acetate was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1,000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dose adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dosage adjustment can be predicted. Abiraterone Acetate should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk. Abiraterone Acetate should not be used in patients with severe hepatic impairment. For patients who develop hepatotoxicity during treatment with Abiraterone Acetate, suspension of treatment and dosage adjustment may be required.

Effects on the QT interval
In a cardiovascular safety study in patients with metastatic advanced prostate cancer there were no significant effects of abiraterone acetate on the cardiac QT/QTc interval.

6. Pharmaceutical Particulars

6.1 Pack Sizes
For 250mg tablets: 10x 12's (120) tablets.
Alu/PVDC blisters having 12 tablets in each blister and packed in unit carton with leaflet.
For 500mg tablets: 5x 12's (60) tablets.
Alu/PVDC blisters having 12 tablets in each blister and packed in unit carton with leaflet.

6.2 Storage Conditions
Store below 30°C. Protect from sunlight and moisture.

6.3 Dosage and Instructions
As directed by physician.
Keep out of reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔

For adverse event reporting, kindly email us at
pharmacovigilance@oncogenpharma.com.pk

7. MANUFACTURER
Manufactured by:
oncogen
Oncogen Pharma (Pvt.) Limited.
Plot No: WH-26 & 27-A3, Korangi Creek
Industrial Park (KCIP), Karachi 75190, Pakistan.
www.oncogenpharma.com.pk