To be sold by retail on the prescription of "Oncologist" only

Abiraterone Acetate IP Tablets 500mg

Abura-500
आबुरा-५००

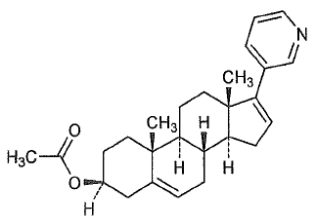
COMPOSITION
Abiraterone Acetate IP Tablets 500 mg
Each film Coated tablet contains
Abiraterone Acetate IP 500 mg

DESCRIPTION

Abiraterone acetate, the active ingredient is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/ C17, 20-lyase). Each tablet contains either 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5, 16-dien-3-yl acetate and its structure is:

Abiraterone acetate has a molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

DOSAGE FORM AND STRENGTHS



Each Film coated tablet consists of 500 mg of Abiraterone acetate for twice daily oral administration.

INDICATIONS
Abiraterone is indicated in combination with prednisone for the treatment of patients with metastatic castration resistant prostate cancer who have received prior chemotherapy containing docetaxel.

Abiraterone is indicated for the treatment of metastatic castration resistant prostate cancer in adult men who are symptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated with prednisone or prednisolone.

DOSAGE AND METHOD OF ADMINISTRATION
Recommended Dose for metastatic CRPC
The recommended dose of Abiraterone is 1,000 mg (two 500 mg tablets) orally once daily with prednisone 5 mg orally twice daily.

Recommended Dose for metastatic high-risk CSPC
The recommended dose of Abiraterone is 1,000 mg (two 500 mg tablets) orally once daily with prednisone 5 mg administered orally once daily.

Important Administration Instructions
Patients receiving Abiraterone should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Abiraterone 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. Do not crush or chew tablets.

Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity
Hepatic Impairment
In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of Abiraterone to 250 mg once daily. 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 re-treat patients with Abiraterone.

Do not use Abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C).

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, re-treatment 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.

Permanently discontinue Abiraterone for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

Dose Modification Guidelines for Strong CYP3A4 Inducers
Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during Abiraterone treatment.

If a strong CYP3A4 inducer must be co-administered, increase the Abiraterone 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.

USE IN SPECIFIC POPULATIONS

Pregnancy
Based on findings from animal studies and the mechanism of action, Abiraterone is contraindicated for use in pregnant women because the drug can cause fetal harm and potential loss of pregnancy. Abiraterone is not indicated for use in females.

There are no human data on the use of Abiraterone in pregnant women. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose.

Lactation
Abiraterone is not indicated for use in women. 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.

Females and Males of Reproductive Potential
Contraception
Males
Based on findings in animal reproduction studies and its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 weeks after the final dose of Abiraterone.
Infertility

Based on animal studies, Abiraterone may impair reproductive function and fertility in males of reproductive potential Abiraterone.

Pediatric Use
Safety and effectiveness of Abiraterone in pediatric patients have not been established.

Geriatric Use
No overall differences in safety or effectiveness were observed between these elderly patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment
No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of Abiraterone to 250 mg once daily. Do not use Abiraterone in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X

ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue Abiraterone treatment.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required.

Patients with Renal Impairment
No dosage adjustment is necessary for patients with renal impairment.

CONTRAINDICATIONS
Pregnancy
Abiraterone can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS
Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with Abiraterone.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of Abiraterone in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure has not been established because these patients were excluded from these randomized clinical trials.

Adrenocortical Insufficiency
Adrenal insufficiency occurred in 0.3% of 2230 patients taking Abiraterone and in 0.1% of 1763 patients taking placebo in the combined data of the 5 randomized, placebo-controlled clinical studies. Adrenocortical insufficiency was reported in patients receiving Abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress.

Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with Abiraterone. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity
In post marketing experience, there has been Abiraterone -associated severe hepatic toxicity, including fulminant hepatitis, acute liver failure and deaths.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes
Based on *in vitro* data, Abiraterone 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 treatment. If a strong CYP3A4 inducer must be co-administered, increase the Abiraterone dosing frequency.

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 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.

UNDESIRABLE EFFECTS
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess
- Adrenocortical Insufficiency
- Hepatotoxicity

The most common adverse effects reported with abiraterone usage in clinical studies in addition to those mentioned above were joint swelling, joint discomfort, arthritis, arthralgia, joint swelling, and joint stiffness, muscle discomfort, edema, edema peripheral, pitting edema, and generalized edema, edema, hypertension, diarrhea, dyspepsia, urinary tract infection, upper respiratory tract infection, cough, nocturia, fractures, arrhythmia, chest pain or chest discomfort, cardiac failure, rash, hematuria, nasopharyngitis, insomnia and constipation.

The following additional adverse reactions have been identified during post approval use of abiraterone with prednisone.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.

Hepatobiliary Disorders: fulminant hepatitis, including acute hepatic failure and death.

OVERDOSAGE
Human experience of overdose with Abiraterone is limited.There is no specific antidote. In the event of an overdose, stop Abiraterone, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

PHARMACODYNAMICS AND PHARMACOKINETICS

Pharmacodynamics
Mechanism of Action
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 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 clinical trial. It is not necessary to monitor the effect of Abiraterone 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
Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic CRPC. *In vivo*, abiraterone acetate is converted to abiraterone. 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 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% increases in the mean AUC).
Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food.

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 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. The tablets should be swallowed whole with water.

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.

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 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).

Patients with Hepatic Impairment
The pharmacokinetics of abiraterone was examined in subjects with baseline mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh Class A and B, 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.

The systemic exposure (AUC) of abiraterone increased by approximately 7-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function. In addition, the mean protein binding was found to be lower in the severe hepatic impairment group compared to the normal hepatic function group, which resulted in a two-fold increase in the fraction of free drug in patients with severe hepatic impairment.

Patients with Renal Impairment
The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function.

INCOMPATIBILITIES
Not applicable.

PACKING INFORMATION
60's HDPE bottle

STORAGE AND HANDLING INFORMATION
Storage: store below 30ºC.

KEEP OUT OF REACH FOR CHILDREN

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division, Unit-II,
Sy.no. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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