For the use only of an Oncologist or a Hospital or a Laboratory

℞

ABIRATERONE ACETATE TABLETS IP 250 MG

ABSTET® अब्स्टेट

COMPOSITION
Each tablet contains
Abiraterone Acetate IP 250 mg

PHARMACEUTICAL FORM
Tablets

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents.
ATC code: L02BX03

Mechanism of Action
Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor that inhibits 17 a-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 (see **Special Warnings and Precautions for Use** section).

Androgen sensitive prostatic carcinoma responds to treatment that decreases and rogen levels. Androgen deprivation therapies, such as treatment with gonadotropin releasing hormone [GnRH) agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

Pharmacokinetic Properties
Absorption
Following oral administration of abiraterone acetate to patients with metastatic castration-resistant prostate cancer [CRPC], the median time to reach maximum plasma abiraterone concentrations is 2 hours. Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and AUC0-∞ 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 it was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Therefore, no food should be consumed for at least 2 hours before the dose of abiraterone is taken and for at least 1 hour after the dose of abiraterone is taken (see **Posology and Method of Administration and Special Warnings and Precautions for Use** sections).

Distribution
Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution is 19,669 L.

Metabolism
Following oral administration abiraterone acetate is rapidly hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterase 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 accounts for about 43% of exposure each.

Excretion
In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma is 12 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

Special Populations
Patients with hepatic impairment
Increased systemic exposure and prolonged mean half-life is reported after a single oral 1,000 mg dose of abiraterone given under fasting conditions to subjects with mild and moderate baseline hepatic impairment. The pharmacokinetics of abiraterone were examined in subjects with baseline severe (N=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. 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 (see **Posology and Method of Administration and Special Warnings and Precautions for Use** sections).

Patients with renal impairment
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 (see **Posology and Method of Administration** section).

Geriatrics
No overall differences in safety or effectiveness were observed between these elderly patients and younger patients (see **Posology and Method of Administration** section).

CLINICAL PARTICULARS
Therapeutic Indications
Abiraterone is indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

Posology and Method of Administration
General Recommendations
The recommended dose of abiraterone is 1,000 mg (four 250 mg tablets) 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 2 hours before and 1 hour after the dose of abiraterone (see **Pharmacokinetic Properties and Special Warnings and Precautions for Use** section).The tablets should be swallowed whole with water. Do not crush or chew tablets.

Dosage Modifications
Hepatic impairment
No dose adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduction of the abiraterone dose to 250 mg once daily is recommended. However, there are no clinically significant data on the dose of 250 mg once daily in patients with moderate hepatic impairment, therefore caution is advised. In patients with moderate hepatic impairment monitor serum transaminases (alanine transaminase [ALT], aspartate transaminase [AST], and bilirubin prior to the start of treatment, every week for the first month of treatment, every 2 weeks for the following 2 months of treatment and monthly thereafter If elevations in ALT and/or AST are >5X upper limit of normal (ULN) or total bilirubin are >3X ULN in patients with baseline moderate hepatic impairment, discontinue abiraterone and do not re-treat patients with abiraterone (see **Special Warnings and Precautions for Use and Pharmacokinetic Properties** section).
Do not use Abiraterone in patients with baseline severe hepatic impairment (Child - Pugh Class C). (see **Pharmacokinetic Properties and Special Warnings and Precautions for Use** section).

Hepatotoxicity
- For patients who develop hepatotoxicity during treatment with abiraterone (ALT and/or AST >5X ULN or total bilirubin >3X ULN), interrupt treatment with abiraterone (see **Special Warnings and Precautions for Use** section). Treatment may be restarted at a reduced dose (e.g. 750 mg or 500 mg once daily) following return of liver function tests to the patient's baseline or to AST and ALT ⩽ 2.5X ULN and total bilirubin ⩽ 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every 2 weeks for three months and monthly thereafter.
- If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with abiraterone. The safety of abiraterone re-treatment of patients who develop AST or ALT ⩾ 20X ULN and/or bilirubin ⩾ 10X ULN is unknown
(see **Special Warnings and Precautions for Use** section).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see **Pharmacokinetic properties** section). However, there is no clinical experience in patients with prostate cancer and severe renal impairment, therefore caution is advised in these patients

Pediatrics
There is no relevant use of this medicinal product in the pediatric population.

Geriatrics
No dosage adjustment is recommended. But, the sensitivity for the medication in this type of patients cannot be neglected.

Contraindications
Abiraterone is not indicated for women.
Abiraterone is contraindicated in the following conditions:
- Hypersensitivity to the active substance or to any of the products excipients.
- Women who are or may potentially be pregnant (see **Pregnancy and Lactation** section).
- Severe hepatic impairment [Child-Pugh Class C] (see Pharmacokinetic Properties and **Special Warnings and Precautions for Use** sections).

For the use only of an Oncologist or a Hospital or a Laboratory

℞

ABIRATERONE ACETATE TABLETS IP 250 MG

ABSTET® अब्स्टेट

Special Warnings and Precautions for Use
Hypertension, Hypokalemia and Fluid Retention Due to Excess of Mineralocorticoid
Abiraterone may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Undesirable Effects section). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions.
Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia.
Use abiraterone with caution in patients with a history of cardiovascular disease. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with abiraterone.

Adrenocortical Insufficiency
Adrenocortical insufficiency was reported in patients receiving abiraterone in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.
Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. 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
- It is recommended to measure the serum transaminases (ALT and AST) and bilirubin levels prior to the start of abiraterone treatment, every 2 weeks for the first 3 months of treatment and monthly thereafter.
- In patients with baseline moderate hepatic impairment receiving a reduced abiraterone dose of 250 mg, measure 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 at any time AST or ALT rise above 5 times the ULN, or the bilirubin rises above 3 times the ULN, interrupt abiraterone treatment and closely monitor liver function. Re-treatment with abiraterone at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT ⩽ 2.5X ULN and total bilirubin ⩽ 1.5X ULN (see **Posology and Method of Administration** section).
- The safety of abiraterone re-treatment of patients who develop AST or ALT ⩾ 20X ULN and/or bilirubin ⩾ 10X ULN is unknown.

Increased Abiraterone Exposures with Food
Abiraterone must be taken on an empty stomach. No food should be consumed for at least 2 hours before and 1 hour after the dose of abiraterone (see **Pharmacokinetic Properties** and **Posology and Method of Administration** section) .The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed.

Drug Interactions
Effects of Abiraterone on Drug Metabolizing Enzymes
Abiraterone is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6 and CYP2C8. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 like dextromethorphan, drugs with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.
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.

Drugs that Inhibit or Induce CYP3A4 Enzymes
Based on *in vitro* data, abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during abiraterone treatment.

Abiraterone and Grapefruit or Grapefruit Juice
Concomitant ingestion of grapefruit juice with CYP3A4 substrates with extensive first-pass metabolism and a narrow therapeutic range can increase the risk of adverse effect of these drugs.
Pregnancy and Lactation
Pregnancy Category X.
Abiraterone is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with abiraterone (see **Contraindications** section). Women who are pregnant or women who may become pregnant should not handle abiraterone without protection, eg. gloves.
It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing, or to discontinue the drug taking into account the importance of the drug to the mother.

Effects on Ability to Drive and Use Machines
Abiraterone may have no or negligible influence on the ability to drive or use machines.

Undesirable Effects
The most common adverse effects reported with abiraterone usage in clinical studies in addition to those mentioned in section **Special Warnings and Precautions for Use** were joint swelling, muscle discomfort, hypokalemia, edema, hot flush, diarrhea, urinary tract infection, cough, fractures, hypertension, fluid retention, arrhythmia, chest pain or chest discomfort, cardiac failure, frequent urination, nocturia, dyspepsia and upper respiratory tract infection.
The most common adverse drug reactions that resulted in drug discontinuation were increased aspartate aminotransferase; alanine aminotransferase levels, urosepsis and cardiac failure

Overdose
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.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable

Shelf Life: Please refer to carton/label.

Storage
Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep out of reach of children.

Special Precautions for Disposal and Other Handling
Based on its mechanism of action, abiraterone may harm a developing fetus; therefore, women who are pregnant or may be pregnant should not handle abiraterone without protection, e.g., gloves (see **Pregnancy and Lactation and Contraindications** section).
Any unused medicinal product or waste material should be disposed off in accordance with local requirements.

Nature and Contents of Container
ABSTET®(Abiraterone Acetate Tablets IP 250 mg) is available in pack sizes; 30, 60 &120 tablets in HDPE container.

Marketed by:
Biocon Biologics India Limited
Biocon House, Semicon Park,
Electronics City, Phase - II,
Bengaluru - 560 100, India.

Leaflet revised **July 2019**

® - Registered trademark

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com**

BF/LL/3670/01

C03001-03