STORAGE:-
Store protected from light and moisture, at a temperature not exceeding 30°C.
Keep all medicines out of the reach and sight of children.

Marketed by :

APRAZER

Aprazer Healthcare Pvt. Ltd.
B-256, 2nd Floor, Naraina Phase-1, New Delhi-110028, India
Web.: www.aprazerhealthcare.com
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Manufactured in India by:
BDR Pharmaceuticals Int'l Pvt. Ltd.
R. S. No. 578, Near Effluent Channel
Road, Vill. Luna, Tal. Padra, Dist. Vadodara-391 440. Gujarat.

BDR/Abirakast 250 mg/PI/01

References:

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8) Adis R&D Profile**; Abiraterone Acetate;** Drugs R&D 2010; 10(4):261-2691179-6901/10/0004-0261.
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9) Marian Geldof et al; **Presystemic Disposition of Abiraterone** Acetate; International society for the study of xenobiotics.

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PACKAGE LEAFLET: PRESCRIBING INFORMATION

To be sold on the prescription of an oncologist only.

ABIRATERONE ACETATE TABLETS IP 250 MG

ABIRAKAST®

250

COMPOSITION:-
Each uncoated tablet contains:
Abiraterone Acetate IP……..250 mg
Excipients……..... ...q.s.

DOSAGE FORM:-
Tablet

INDICATION:-
In combination with prednisone for the treatment of patients with metastatic castration-resistant prostrate cancer who have received prior chemotherapy containing docetaxel.

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

DOSE & METHOD OF ADMINISTRATION:-
The normal dose of Abiraterone acetate is 1,000 mg, (250 mg x 4 Tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Food consumption should be avoided for at least two hours before the dose of Abiraterone acetate is taken and for at least one hour after the dose of Abiraterone acetate is taken. Patients with moderate hepatic dysfunction should receive 250 mg daily. For patients who develop hepatotoxicity during treatment, withdraw Abiraterone acetate until recovery. Retreatment may be initiated at a reduced dose. Abiraterone acetate should be discontinued if patients develop severe hepatotoxicity.

USE IN SPECIAL POPULATIONS:-
A. Pregnancy
Pregnancy Category X
For women who are or may become pregnant while receiving the drug are advised to avoid the abiraterone acetate. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be aware of the potential hazard to the foetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with Abiraterone acetate.

B. Nursing Mothers
Nursing women are advised to avoid the Abiraterone acetate. It is not known if Abiraterone acetate is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Abiraterone acetate, either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the Nursing women.

C. Paediatric Use
Abiraterone acetate is not indicated in children.

D. Geriatric Use
There was no difference observed in safety or effectiveness between elderly patients and younger patients during the clinical trials.

E. Patients with Hepatic Impairment
For the patients having mild hepatic impairment (Child-Pugh Class A) no dose adjustment is required. Whereas, for patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduction in the dose is recommended, of Abiraterone acetate to 250 mg once daily. Abiraterone acetate should be avoided in patients with baseline severe hepatic impairment (Child-Pugh Class C)

F. Patients with Renal Impairment
Patients with renal impairment do not require the dose adjustment.

CONTRAINDICATIONS:-
Abiraterone acetate is contraindicated in women who are or may become pregnant.

WARNINGS:-
A. Adrenocortical insufficiency: Clinical trials have shown Adrenocortical insufficiency in patients receiving Abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.
B. Food Effect: Up to 10 fold increment in AUC (area under the curve) is noted when Abiraterone acetate is taken with meals.
C. Hepatotoxicity: Increase in liver enzymes may occur, necessicating drug discontinuation or dose modification.
D. Mineralocorticoid excess: Abiraterone acetate is likely to cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition

PRECAUTIONS:-
A. Adrenocortical insufficiency: Increased dosage of corticosteroids may be indicated before, during and after stressful situations.
B. Food Effect: Food consumption should be avoided for at least two hours before the dose of Abiraterone acetate is taken and for at least one hour after the dose of Abiraterone acetate is taken.
C.Hepatotoxicity: Before starting the treatment with Abiraterone acetate, serum transaminases (ALT and AST) and bilirubin levels should be measured, every two weeks for the first three months of treatment and monthly thereafter.
D.Mineralocorticoid excess: Before treatment, control hypertension and correct hypokalemia. Blood pressure, serum potassium and symptoms of fluid retention must be monitored at least monthly.

DRUG INTERACTIONS:-
A. Effects of Abiraterone on Drug Metabolizing Enzymes
Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Co-administration of Abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine) must be avoided. If alternative treatments cannot be used, Caution should be exercised and dose reduction of concomitant drug considered.

B. Drugs that Inhibit or Induce CYP3A4 Enzymes
In vitro data suggest that, Abiraterone acetate 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, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Strong inhibitors and inducers of CYP3A4 during Abiraterone acetate treatment should be avoided or used with proper precaution.

C. 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 for adverse effects of these drugs.

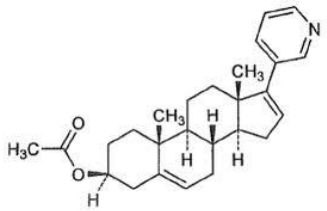
D. Abiraterone and thioridazine
It is possible that concentration of thioridazine may increase, concomitant use should be avoided, if it cannot be avoided then thioridazine dosage must be reduced.

UNDESIRABLE EFFECTS:-
The most usual undesirable effects (≥ 5%) are joint swelling or discomfort, hypokalemia (low blood potassium), edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection.
The most common adverse drug reactions (≥5%) reported in clinical studies were 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.
The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure.

OVEDOSAGE:-
Abiraterone acetate during clinical studies, found to have no reports of overdose.
There is no specific antidote. In the case of an overdose, stop Abiraterone acetate, and undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and liver function.

PHARMACODYNAMIC & PHARMACOKINETIC PROPERTIES:-

DESCRIPTION:
Abiraterone acetate, 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene being a prodrug gets converted to Abiraterone, in vivo, an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17, 20-lyase (CYP17), which is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. Its empirical formula is $C_{26}H_{33}NO_2$, with a molecular weight of 391.6. The structural formula is:



Pharmacotherapeutic group: Anti-Neoplastic
ATC Code: L02BX03

PHARMACODYNAMIC:
Mechanism of Action
Abiraterone acetate is indicated for use in combination with prednisone for the treatment of patients with metastatic CRPC who have received prior docetaxel-containing chemotherapy. Abiraterone acetate is converted in vivo to abiraterone which is an androgen biosynthesis inhibitor that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). Inhibition of CYP17 results in reduction of androgen synthesis in the testes, adrenal glands, and prostate tissue, resulting in reduced serum levels of testosterone and other androgens.
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.

PHARMACOKINETIC
Absorption: After oral administration, peak plasma concentrations of abiraterone are reached in 1.5–4 hours (mean 2). Administration with food increases systemic exposure of abiraterone. The maximum concentration (C_{max}) was 7-fold higher after administration with a low-fat meal (7% fat, 300 calories) and 17-fold higher after administration with a high-fat meal (57% fat, 825 calories) when compared to a fasted state. Likewise the AUC was 5-fold higher after the low-fat meal and 10-fold higher after the high-fat meal.

Distribution: The plasma protein binding of abiraterone in human plasma is >99%. The mean volume of distribution is approximately 19,669 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation: In man, Abiraterone acetate (AA) is rapidly hydrolysed to Abiraterone(ABT). The major human circulating metabolites are sulphated ABT (ABT-S) and the N-oxide of ABT-S. The metabolic stability of ^{14}C-AA and -ABT was investigated in vitro in human stomach mucosa, human and dog intestinal subcellular fractions, human blood and human hepatocytes. In combination with in vitro phenotyping data, illustrating that esterase-mediated hydrolysis of AA occurs in gastro-intestinal tissue. Hence, not AA but ABT is the main entity being absorbed from the intestine ,which is further sulphated and oxidised to ABT-S and N-oxide ABT-S, mainly in the liver.

Elimination: The mean half-life of abiraterone in plasma is approximately 10.3 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1,000 mg, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone.

SHELF LIFE
Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.

PACKAGING INFORMATION:-
HDPE container containing 120 tablets packed in a mono carton along with pack insert.