PACKAGE INFORMATION LEAFLET
ABIRAT 250
(Abiraterone Acetate Tablets USP 250mg)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or Nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or Nurse. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet

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1. What Abiraterone Acetate Tablets is and what it is used for
Abiraterone is indicated with prednisone or prednisolone for:

• The treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)

• 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

• The treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

2. Before you take Abiraterone Acetate Tablets
Do not take Abiraterone Acetate Tablets
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may potentially be pregnant.
- If you have Severe hepatic impairment [Child-Pugh Class C].
- Abiraterone with prednisone or prednisolone is contraindicated in combination with Ra-223.

Warnings and precautions

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess

Abiraterone 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 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 (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The Phase 3 studies conducted with Abiraterone acetate excluded patients with uncontrolled hypertension, clinically significant heart diseases evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class (NYHA) III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011and 302) or cardiac ejection fraction measurement of < 50%. In studies 3011 and 302, patients with atrial fibrillation, or other cardiac arrhythmia requiring medical therapy were excluded.

Safety in patients with left ventricular ejection fraction (LVEF) < 50% or NYHA Class III or IV heart failure (in study 301)or NYHA Class II to IV heart failure (in studies 3011 and 302) was not established.

Before treating patients with a significant risk for congestive heart failure (e.g. a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischaemic heart disease), consider obtaining an assessment of cardiac function(e.g. echocardiogram). Before treatment with Abiraterone, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with Abiraterone treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function .Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies. Serum transaminase levels should be measured prior to starting treatment, 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 ULN, treatment should

be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level.

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

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of Abiraterone in this population.

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). The use of Abiraterone should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abiraterone 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 are withdrawn from prednisone or prednisolone. If Abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids maybe indicated before, during and after the stressful situation.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer. The use of Abiraterone 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.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently inpatients with diabetes.

Hypoglycaemia

Cases of hypoglycaemia have been reported when Abiraterone plus prednisone/prednisolone 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 with cytotoxic chemotherapy has not been established.

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.

This medicinal product contains less than 1 mm ol (23 mg) sodium per dose of two tablets, that is to say essentially ‘sodium-free'.

Potential risks

Anaemia and sexual dysfunction may occur in men with metastatic prostate cancer including those undergoing treatment with Abiraterone.

Skeletal muscle effects

Cases of myopathy and rhabdomyolysis have been reported in patients treated with Abiraterone acetate. Most cases developed within the first 6 months of treatment and recovered after Abiraterone acetate withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with my apathy/rhabdomyolysis.

Interactions with other medicinal products

Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to Abiraterone.

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 clinical trials.

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

Interaction with other medicinal products and other forms of interaction

Effect of food on Abiraterone acetate

Administration with food significantly increases the absorption of Abiraterone acetate. The efficacy and safety when given with food have not been established therefore this medicinal product must not be taken with food.

Interactions with other medicinal products

Potential for other medicinal products to affect Abiraterone exposures

In a clinical pharmacokinetic interaction study of healthy subjects pre treated with a strong CYP3A4 inducer rifampicin, 600 mg daily for 6 days followed by a single dose of Abiraterone acetate 1,000 mg, the mean plasma AUC∞ of Abiraterone was decreased by 55%. Strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's worth [Hypericum perforatum]) during treatment are to be avoided, unless there is no therapeutic alternative.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co- administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of Abiraterone.

Potential to affect exposures to other medicinal products

Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8. In a study to determine the effects of Abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow the rapeuticindex that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and theAUCs 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 1,000 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 metabolised by CYP2C8 include pioglitazone and repaglinide.

In vitro, the major metabolites Abiraterone sulphate and N-oxide Abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicinal products eliminated by OATP1B1.

There are no clinical data available to confirm transporter based interaction.

Use with products known to prolong QT interval

Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering Abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes suchas class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone

Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with Abiraterone is not recommended.

Fertility, pregnancy and lactation

Women of childbearing potential

There are no human data on the use of Abiraterone in pregnancy and this medicinal product is not for use in women of child bearing potential.

Contraception in males and females

It is not known whether 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.

Studies in animals have shown reproductive toxicity.

Pregnancy

Abiraterone is not for use in women and is contraindicated in women who are or may potentially be pregnant.

Breast-feeding

Abiraterone is not for use in women.

Fertility

Abiraterone affected fertility in male and female rats, but these effects were fully reversible

Overdose

Human experience of overdose with Abiraterone is limited.

There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

4. Possible side effects

Summary of the safety profile

In an analysis of adverse reactions of composite Phase 3 studies with Abiraterone acetate, adverse reactions that were observed in ≥10% of patients were peripheral oedema, hypokalaemia, hypertension urinary tract infection, and alanine amino transferase increased and/or aspartate aminotransferase increased. Other important adverse reactions include, cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

Abiraterone may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamics consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly inpatients treated with Abiraterone acetate than in patients treated with placebo: hypokalaemia 18% vs.8%, hypertension22% vs. 16% and fluid retention (peripheral oedema) 23% vs. 17%, respectively

In patients treated with Abiraterone acetate versus patients treated with placebo: CTCAE (version 4.0) Grades 3 and 4 hypokalaemia were observed in 6%versus 1%, CTCAE (version 4.0) Grades 3 and 4 hypertension were observed in 7% versus 5%, and fluid retention(peripheral oedema) Grades 3 and 4 were observed in 1% versus 1% of patients, respectively.

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 1,000 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon(≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data).

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

Table 1: Adverse reactions identified in clinical 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: hypertriglyceridemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis
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
Skin and subcutaneous 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.

The following CTCAE (version 4.0) Grade 3 adverse reactions occurred in patients treated with Abiraterone acetate: hypokalaemia 5%; urinary tract infection 2%; alanine aminotransferase increased and/or aspartate aminotransferase increased 4%; hypertension 6%; fractures 2%; peripheral oedema, cardiac failure, and atrial fibrillation 1% each. CTCAE(version 4.0) Grade 3 hypertriglyceridemia and angina pectoris occurred in < 1% of patients. CTCAE (version 4.0)Grade 4 urinary tract infection, alanine aminotransferase increased and/or aspartate aminotransferase increased, hypokalaemia, cardiac failure, atrial fibrillation, and fractures occurred in < 1% of patients.

A higher incidence of hypertension and hypokalaemia was observed in the hormone sensitive population (study 3011).Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8%and 20.2% in studies 301 and 302, respectively.

Hypokalaemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2%and 14.9% in 301 and 302, respectively).

The incidence and severity of adverse events was higher in the subgroup of patients with baseline ECOG2 performance status grade and also in elderly patients (≥75 years).

Description of selected adverse reactions

Cardiovascular reactions

The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50%.

All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3studies in patients taking Abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2.6% vs.2.0%, tachycardia 1.9% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs.0.5%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with Abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 6% of patients who received Abiraterone acetate, typically during the first 3 months after starting treatment.

In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with Abiraterone acetate. Ten patients who received Abiraterone acetate were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, Abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patientstreated with Abiraterone acetate.

Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of Abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with Abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 XULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were excluded.

In the 301 trial, patients with baseline ALT and AST ≥ 2.5 x ULN in the absence of liver metastases and > 5 x ULN in the presence of liver metastases were excluded.

In the 302 trial, patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2.5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline. Patients with elevations of ALT or AST > 20 x ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity is not understood.

5. How to store Abiraterone Acetate Tablets

Store below 30°C.

6. Contents of the pack and other information

What Abiraterone Acetate Tablets contains

Each film coated tablet contains: Abiraterone acetate USP 250 mg

Excipients: Lactose monohydrate, Croscarmellose sodium, Hypromellose (2910) 15mPa.s, Sodium Lauryl sulfate, Microcrystalline cellulose (silicified), Silica colloidal anhydrous, Magnesium stearate and Opadry II White.

Composition of *Opadry II White*: Polyvinyl Alcohol –Part hydrolysed, Titanium dioxide, Macrogol 3350, Talc.

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