PACKAGE INSERT

(For the use of a Registered Medical Practitioner or a Hospital)

NAME OF THE MEDICINAL PRODUCT

ABIRACCORD (Abiraterone Acetate Tablets 250 mg)

QUALITATIVE AND QUATITATIVE COMPOSITION

Each tablet contains

Abiraterone acetate USP 250 mg

For a full list of excipients, see *pharmaceutical information – list of excipients*.

PHARMACEUTICAL FORM

Tablet

White to off-white, oval-shaped tablets debossed with A on one side and 250 on other side.

CLINICAL INFORMATION

Indications

Abiraterone acetate tablets are 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 (see *Pharmacodynamic Properties*).
- The treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Dosage and Administration

Dosage

The recommended dosage is 1000 mg (two 500 mg tablets or four 250 mg tablets) as a single daily dose that must not be taken with food. Abiraterone acetate tablets must be taken on an empty stomach, at least one hour before or at least two hours after a meal. Taking the tablets with food increases systemic exposure to abiraterone. The tablets should be swallowed whole with water (see *Pharmacokinetic Properties – Absorption*).

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 for congestive heart failure should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see *Warnings and Precautions – Hypertension, hypokalemia, fluid retention and cardiac failure due to mineralocorticoid excess* and *Hepatotoxicity and Hepatic impairment*).

In patients with pre-existing hypokalemia or those that develop hypokalemia whilst being treated with abiraterone acetate, consider maintaining the patient's potassium level at ≥ 4.0 mM.

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalemia, 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.

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A. 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 (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment* and *Pharmacokinetic Properties – Special populations*). Abiraterone acetate should not be used in patients with severe hepatic impairment (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment* and *Pharmacokinetic Properties – Special populations*).

For patients who develop hepatotoxicity during treatment (alanine aminotransferase (ALT) increases or aspartate aminotransferase (AST) increases above 5 times the upper limit of normal, treatment should be withheld immediately until liver function tests normalize (see *Warnings and Precautions – Hepatotoxicity and Hepatic* impairment). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (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. Reduced doses should not be taken with food (see *Dosage and Administration – Dosage*).

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 with abiraterone acetate.

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 1,000 mg (see *Pharmacokinetic Properties*).

Renal impairment
No dosage adjustment is necessary for patients with renal impairment (see *Pharmacokinetic Properties – Special populations*). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see *Warnings and Precautions*).

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.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients (see *List of Excipients*).
- Women who are or may potentially be pregnant (see *Pregnancy, Breast-feeding and Fertility – Pregnancy*)
- Severe hepatic impairment [Child-Pugh Class C (see *Dosage and Administration, Warnings and precautions* and *Pharmacokinetic Properties*)].

Warnings and Precautions
Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess
Abiraterone acetate may cause hypertension, hypokalemia and fluid retention (see *Adverse Reactions*) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see *Pharmacological Properties – Mechanism of action*). 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, hypokalemia (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. 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. The phase 3 studies conducted with abiraterone acetate 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 New York Heart Association (NYHA) Class III or IV heart failure (Study 301) or Class II to IV heart failure (Study 302) or cardiac ejection fraction measurement of < 50%. In Study 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 (see *Adverse Reactions* and *Pharmacological Properties*).

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 acetate, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalemia 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. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of abiraterone acetate treatment if there is a clinically significant decrease in cardiac function (see *Dosage and Administration*).

Hepatotoxicity and hepatic Impairment
Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see *Adverse Reactions*). Serum transaminase and bilirubin 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 upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment should be interrupted immediately and liver function closely monitored.

Re-treatment may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see *Dosage and Administration – Hepatic impairment*).

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.

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of abiraterone acetate 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). 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 (see *Dosage and Administration – Hepatic impairment* and *Pharmacokinetic Properties – Special populations*). Abiraterone acetate should not be used in patients with severe hepatic impairment (see *Dosage and Administration – Hepatic impairment*, *Contraindications* and *Pharmacokinetic Properties – Special populations*).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see *Adverse Reactions).*

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 acetate is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess*).

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

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.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, 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 (see *Pharmacological Properties – Clinical studies*).

Use in combination with radium 223 dichloride
In a randomized clinical trial in patients with asymptomatic or mildly symptomatic bone- predominant metastatic castration resistant prostate cancer, at the time of unblinding, the addition of radium 223 dichloride to abiraterone acetate plus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture. Radium 223 dichloride is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials.

Intolerance to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicinal product also contains more than 1 mmol (or 27.2 mg) sodium per dose of four tablets. To be taken into consideration by patients on a controlled sodium diet.

Potential risks
Anaemia and sexual dysfunction may occur in men with metastatic castration resistant prostate cancer including those undergoing treatment with abiraterone acetate.

Interactions
Effect of food on abiraterone acetate
Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of Abiraterone acetate given with food have not been established. Abiraterone acetate must not be taken with food (see *Dosage and Administration* and *Pharmacokinetic Properties – Absorption*).

Interactions with other drugs
Potential for other drugs to affect abiraterone exposures
Based on in vitro data, abiraterone is a substrate of CYP3A4.

In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampicin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%.

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

In a clinical 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 AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

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. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecanide, codeine, oxycodone and tramadol (the latter three products requiring CYP2D6 to form their active analgesic metabolites).

In vitro, abiraterone was shown to inhibit the hepatic drug-metabolizing enzyme CYP1A2. However, in a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2

substrate theophylline, no increase in systemic exposure of theophylline was observed.

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. Although these results indicate that no clinically meaningful increases in exposure are expected when abiraterone acetate is combined with drugs that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone acetate. Examples of medicinal products metabolised by CYP2C8 include paclitaxel and repaglinide.

Pregnancy, Breast-feeding and Fertility

Pregnancy

Abiraterone acetate is not for use in women.

Abiraterone acetate is contraindicated in women who are or may potentially be pregnant (see *Contraindications*).

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 (see *Pharmacological Properties – Mechanism of action* and *Non-Clinical Information – Reproductive Toxicology*).

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 childbearing potential, a condom is required along with another effective contraceptive method.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle abiraterone acetate without protection, e.g., gloves.

Breast-feeding

Abiraterone acetate is not for use in women.
It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.

Fertility

Abiraterone affected fertility in male and female rats, but these effects were fully reversible (see *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines

Abiraterone acetate has no or negligible influence on the ability to drive or use machines.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of abiraterone acetate based on the comprehensive assessment of the available adverse event information. A causal relationship with abiraterone acetate usually cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In an analysis of adverse reactions of composite Phase 3 studies with abiraterone acetate tablets, adverse reactions that were observed in ≥ 10% of patients were hypertension, peripheral edema, hypokalemia, urinary tract infection, and aspartate aminotransferase increased and/or alanine aminotransferase increased.

Abiraterone acetate tablets may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate tablets than in patients treated with placebo: hypokalemia 18% versus 8%, hypertension 22% versus 16% and fluid retention (peripheral oedema) 23% versus 17%, respectively. In patients treated with abiraterone acetate tablets, CTCAE (version 3.0) Grades 3 and 4 hypokalemia were observed in 6% and 2% of patients, CTCAE (version 3.0) Grades 3 and 4 hypertension were observed in 8% and 5% of patients, and grades 3 and 4 fluid retention edema were observed in 1% and 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 (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralcorticoid excess*).

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, abiraterone acetate tablets were administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisolone (5 or 10 mg daily).

Adverse reactions that occurred at a rate of ≥ 1% (all grades) are shown in Table 1.

Table 1: Adverse Reactions in ≥ 1% of Patients in Clinical Studies[a]

	Abiraterone Acetate 1000 mg daily with prednisone or prednisolone n=2659[b]		
System Organ Class Adverse Reaction	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions			
Edema peripheral	20	<1	0
Metabolism and Nutrition Disorders			
Hypokalemia	20	5	<1
Hypertriglyceridemia	1	<1	0
Infections and Infestations			
Urinary tract infection	10	2	<1
Hepatobiliary Disorders			
ALT increased and/or AST increased[c]	13	4	<1
Vascular Disorders			
Hypertension	21	6	0
Injury, Poisoning and Procedural Complications			
Fractures[d]	7	2	<1
Cardiac Disorders			
Cardiac failure[e]	1	<1	<1
Angina pectoris	2	<1	0
Arrhythmia	1	0	0
Atrial fibrillation	3	1	<1
Tachycardia	2	<1	0
Renal and Urinary Disorders			
Hematuria	7	1	0
Gastrointestinal Disorders			
Dyspepsia	6	0	0

[a] All patients were using an LHRH agonist or had undergone orchiectomy.
[b] n=patients assessed for safety.
[c] ALT increased and/or AST increased includes ALT increased, AST increased, and hepatic function abnormal.
[d] Fractures includes osteoporosis and all fractures with the exception of pathological fracture.
[e] Cardiac failure includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased.

The adverse reaction, adrenal insufficiency, occurred in phase 3 clinical studies at a rate of 0.3% in patients taking abiraterone acetate tablets and at a rate of 0.1% in patients taking placebo.

Cardiovascular effects

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 agonists, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the phase 3 studies in patients taking abiraterone acetate tablets versus patients taking placebo were as follows: hypertension 14.5% vs. 10.5%, 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

Drug-associated hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate tablets. 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 tablets, 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 tablets. Ten patients who received abiraterone acetate tablets 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 tablets was withheld or discontinued. In two instances marked increases in liver function tests occurred (see *Warnings and Precautions*). 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 abiraterone acetate tablets, 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%) patients treated with abiraterone acetate tablets. 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 tablets). 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 tablets 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 X ULN 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 (see *Dosage and Administration – Hepatic impairment*). 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.

Post-marketing experience

Adverse reactions identified during the post-marketing experience based on spontaneous reports with abiraterone acetate tablets are described below. The frequencies are provided according to the following convention:

Uncommon	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and <1/1000

System Organ Class: Respiratory, thoracic and mediastinal disorders

Rare: Allergic alveolitis

System Organ Class: Musculoskeletal and connective tissue disorders

Uncommon: Rhabdomyolysis, Myopathy

System Organ Class: Hepatobiliary disorders

Rare: Hepatitis fulminant, Acute hepatic failure

System Organ Class: Cardiac disorders

Very rare: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions).

Overdose

Human experience of overdose with abiraterone acetate 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, hypokalemia and for signs and symptoms of fluid retention. Liver function also should be assessed.

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. 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 tumour tissues. CYP17 catalyses 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 (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess*).

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 tumour. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Clinical efficacy
The efficacy and safety of abiraterone acetate tablets in patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on androgen deprivation therapy was demonstrated in two randomized, placebo-controlled, multicenter Phase 3 clinical trials. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials. Concurrent use of spironolactone was not allowed during the study period.

Study 1
Patients with metastatic CRPC who had received prior docetaxel chemotherapy:
A total of 1195 patients were randomized 2:1 to receive either abiraterone acetate tablets orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient s baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39 to 95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0 to 1 and 45% had a Brief Pain Inventory-Short Form score of >4 (patient s reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival (OS) in patients treated with abiraterone acetate tablets compared to patients in the placebo arm (Table 5 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 5).

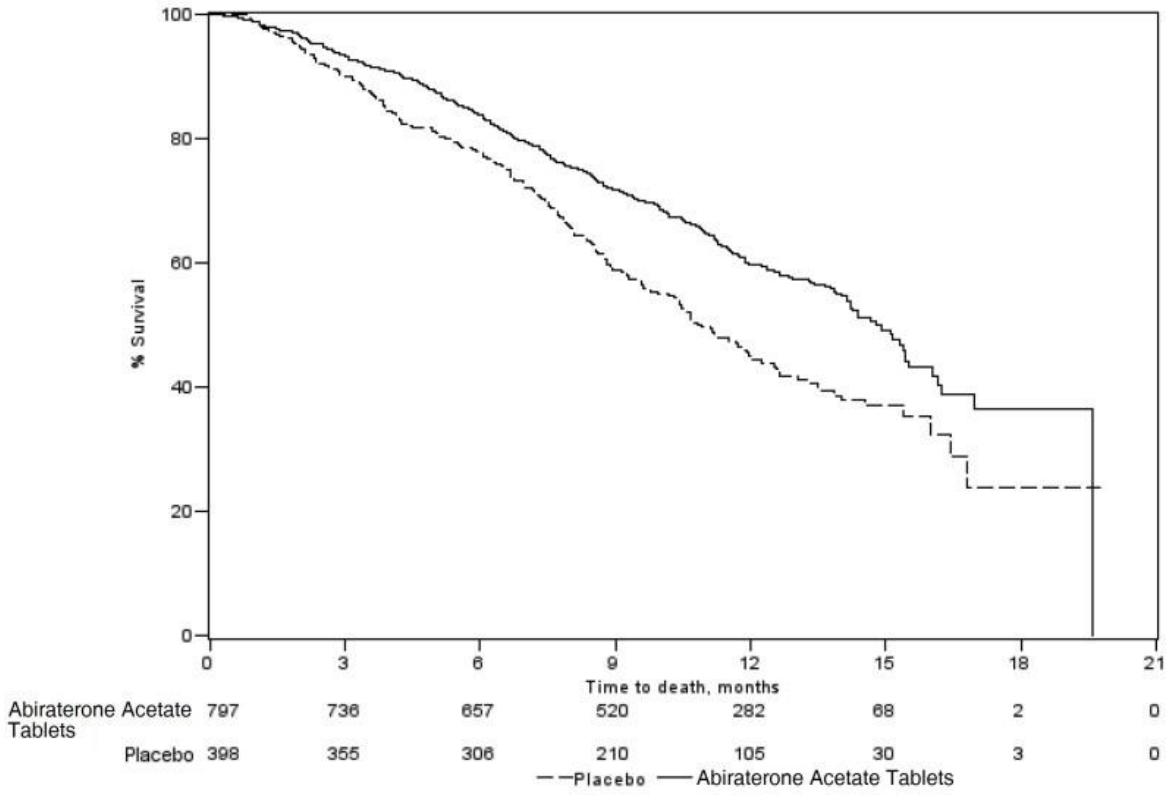
Table 5: Overall Survival of Patients Treated with Either Abiraterone Acetate Tablets or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)

	Abiraterone Acetate Tablets (N=797)		**Placebo (N=398)**
Primary Survival Analysis			
Deaths (%)	333 (42%)		219 (55%)
Median survival (months) (95% CI)	14.8 (141.1, 15.4)		10.9 (10.2, 12)
p-value[1]		<0.0001	
Hazard ratio (95% CI)[2]		0.646 (0.543, 0.768)	
Updated Survival Analysis			
Deaths (%)	501 (63%)		274 (69%)
Median survival (months)	15.8 (14.8, 17)		11. (10.4, 13.1)

(95% CI)	
Hazard ratio (95% CI)[2]	0.740 (0.638, 0.859)

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 to 1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate tablets.

Figure 1: Kaplan-Meier Overall Survival Curves in Study 1 (Intent-to-Treat Analysis)



Study 2
Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy
In Study 2, 1088 patients were randomized 1:1 to receive either abiraterone acetate tablets at a dose of 1,000 mg once daily (N=546) or Placebo once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with abiraterone acetate tablets was 95.4% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0 to 1 (asymptomatic) in 66% of patients and 2 to 3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

The planned final analysis for OS, conducted after 741 deaths (median follow up of 49 months) demonstrated a statistically significant OS improvement in patients treated with abiraterone acetate tablets compared to those treated with placebo (Table 6 and Figure 2). Sixty-five percent of patients on the abiraterone acetate tablets arm and 78% of patients on the placebo arm used subsequent therapies that may prolong OS in metastatic CRPC.

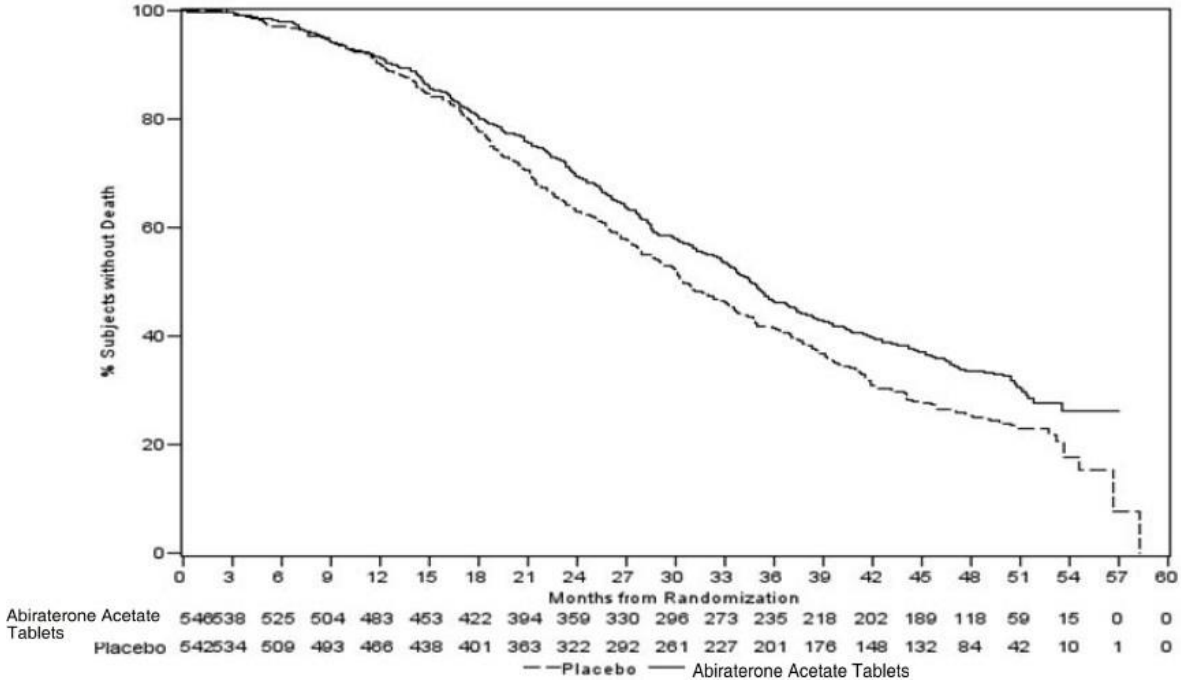
Abiraterone acetate tablets were used as a subsequent therapy in 13% of patients on the abiraterone acetate tablets arm and 44% of patients on the placebo arm.

Table 6: Overall Survival of Patients Treated with Either Abiraterone Acetate Tablets or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Overall Survival	Abiraterone Acetate Tablets (N=546)	Placebo (N=542)
Deaths	354 (65%)	387 (71%)
Median survival (months) (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
p-value[1]	0.0033	
Hazard ratio[2] (95% CI)	0.81 (0.70, 0.93)	

[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate tablets

Figure 2: Kaplan Meier Overall Survival Curves in Study 2



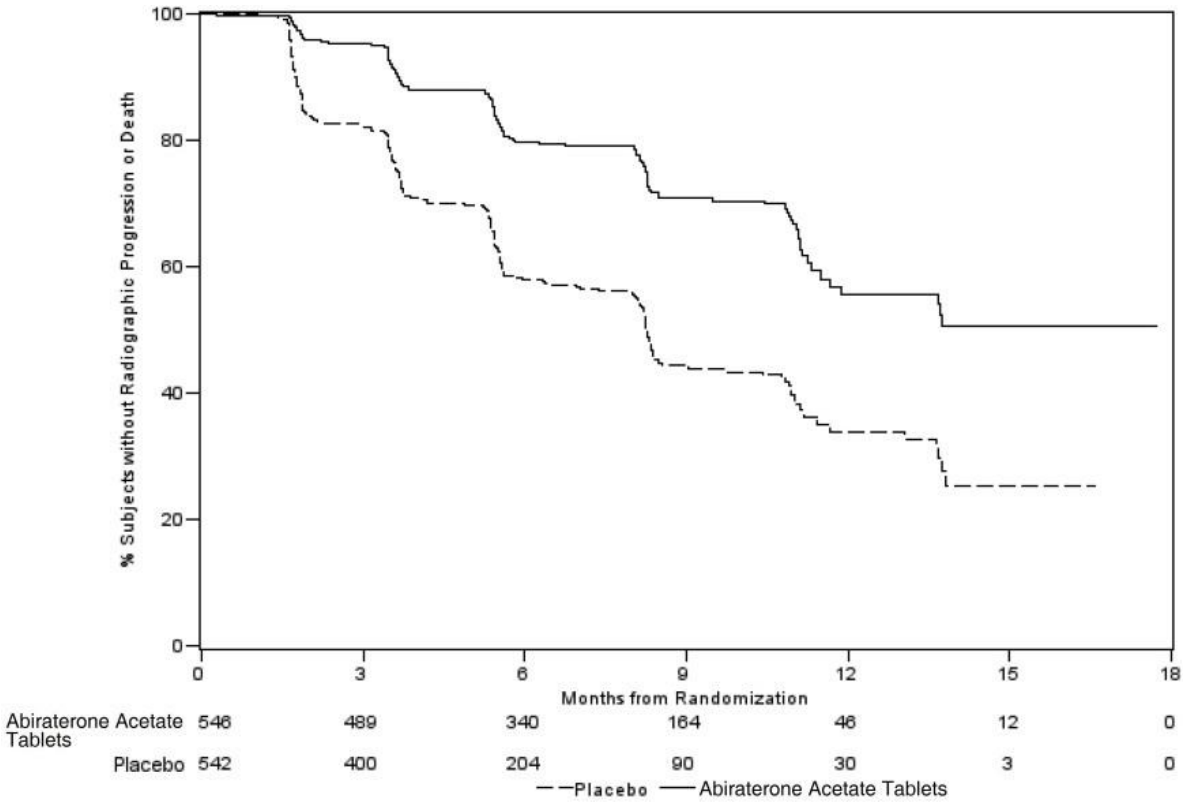
At the pre-specified rPFS analysis, 150 (28%) patients treated with abiraterone acetate tablets and 251 (46%) patients treated with placebo had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 7 and Figure 3).

Table 7: Radiographic Progression-free Survival of Patients T reated with Either Abiraterone Acetate Tablets or Placebo in Combination with Prednisolone in Study 2 (Intent-to-Treat Analysis)

Radiographic Progression-free Survival	Abiraterone Acetate Tablets (N=546)	Placebo (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value[1]	<0.0001	
Hazard ratio[2] (95% CI)	0.425 (0.347, 0.522)	

NR=Not reached
[1] p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[2] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors abiraterone acetate tablets

Figure 3: Kaplan Meier Curves of Radiographic Progression-free Survival in Study 2 (Intent-to-Treat Analysis)



The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving abiraterone acetate tablets and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], $p < 0.0001$).

The median time to opiate use for prostate cancer pain was not reached for patients receiving abiraterone acetate tablets and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the abiraterone acetate tablets arm.

Pharmacokinetic Properties

General introduction

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have 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 (see *Pharmacological Properties – Mechanism of action*).

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 10-fold (AUC) and up to a 17-fold (Cmax) 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 must be taken on an empty stomach, at least one hour before or at least two hours after a meal. The tablets should be swallowed whole with water (see *Dosage and Administration*).

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 hydrolysed 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 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 (approximately 55% and 22% of the administered dose, respectively).

Special Populations
Renal impairment
The pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis.

Administration in patients with renal impairment, including severe renal impairment, does not require dose reduction (see *Dosage and Administration – Renal impairment*). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

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 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 (see *Dosage and Administration – Hepatic impairment* and *Warnings and Precautions – Hepatotoxicity and Hepatic impairment*). Abiraterone acetate should not be used in patients with severe hepatic impairment. For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see *Dosage and Administration – Hepatic impairment*, *Contraindications* and *Warnings and Precautions – Hepatoxicity and Hepatic impairment*).

NON-CLINICAL INFORMATION
Carcinogenicity and Mutagenicity
Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not carcinogenic in female rats.

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay.

Reproductive Toxicology
In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced fetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Abiraterone acetate is contraindicated in pregnancy (see *Contraindications* and *Pregnancy, Breast- feeding and Fertility – Pregnancy*).

Animal Toxicology
In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

PHARMACEUTICAL INFORMATION

List of Excipients
Inter-granular Portion
Microcrystalline Cellulose
Lactose Monohydrate
Povidone
Sodium Lauryl Sulfate
Croscarmellose Sodium (Part-1)
Purified water

Extra-granular Portion
Croscarmellose Sodium (Part-2)
Microcrystalline Cellulose (Part-2)
Colloidal Silicon Dioxide
Magnesium Stearate

Shelf Life
24 months

In-Use Shelf Life
30 days

Storage Conditions
Store below 30°C. Protect from light.
Keep out of reach of children.

Nature and Contents of Container

Abiraterone acetate tablets 250 mg are white to off-white, oval-shaped tablets debossed with A on one side and 250 on other side. Abiraterone acetate tablets 250 mg are available in high-density polyethylene bottles.

Bottles of 120 tablets

NAME AND ADDRESS OF PRODUCT REGISTRANT
Accord Healthcare Private Limited
6 Shenton Way, OUE Downtown #38-01
Singapore, 068809

DATE OF REVISION OF PACKAGE INSERT
July 2020