ABIRONE
Abiraterone Acetate Tablets 250 mg

ABIRONE (Abiraterone Acetate Tablets 250 mg)
Each uncoated tablet contains: Abiraterone Acetate 250 mg

DRUG DESCRIPTION

Abiraterone acetate is a prodrug that is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17-α-hydroxylase/C17, 20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

Abiraterone acetate is a white to off-white or cream color powder. It is Practically insoluble in water. Abiraterone acetate Tablets 250 mg contain the following inactive ingredients: Microcrystalline Cellulose (Avicel pH 101), Lactose monohydrate (Fast flo 316), Croscarmellose sodium (Ac-Di-Sol), Povidone (Plasdone K 29/32), Sodium Lauryl Sulfate (Sipacid WA 100), Microcrystalline Cellulose (Avicel pH 102), Colloidal silicon dioxide (Aerosil 200), Magnesium Stearate, Purified Water.

THERAPEUTIC INDICATIONS

Abiraterone Acetate tablets 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 indicated and in adult men who have progressed on or after docetaxel therapy;
- 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 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 to maintain their integrity.

Medical castration with LHRH analogue should be continued during treatment in patients not surgically castrated.

Dosage of prednisone or prednisolone

For metastatic hormone sensitive prostate cancer (mHSPC), Abiraterone is used with 5 mg prednisone or prednisone daily.

For metastatic castration-resistant prostate cancer (mCRPC), Abiraterone is used with 5 mg prednisone or prednisone daily.

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 who are starting Abiraterone or those that have resumed dosing after interruption of Abiraterone, consider maintaining the patient's prednisone level at ≥ 10 mg daily.

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 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, 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 when administered to patients with moderate pre-existing hepatic impairment, Child-Pugh Class B or C. No dose adjustment can be predicted. Abiraterone 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 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 and hepatic function should be monitored (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 (one 500 mg tablet or two 250 mg tablets) daily. If ALT or AST increases to more than five times the upper limit of normal during treatment, serum transaminases should be monitored at a minimum of every two weeks 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.

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 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 primary 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 other bisphosphonates or to any of the excipients listed in section 6.1.
- 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 may cause hypertension, hypokalemia and fluid retention (see Adverse Reactions) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Pharmacologic Properties – Mechanism of action). Co-administration of a corticosteroid (prednisone or prednisolone) suppresses ACTH drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions could be adversely affected by changes in mineralocorticoid activity, for example, patients with severe cardiac failure, unstable angina pectoris, post-myocardial infarction sclerosis, severe renal impairment, or patients who are being treated with medicinal products which may cause hypokalemia.

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The phase 3 studies conducted with Abiraterone excluded patients with uncontrolled hypertension, clinically significant heart disease or evidence for myocardial infarction or arterial thrombosis within 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) (see Pharmacodynamic Properties – Clinical studies). In the Phase 3 clinical studies, patients received Safety: prednisone 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 Study 302) were 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. Monitor patients treated with Abiraterone combined with glucocorticoids for cardiac failure to 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 complaints 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 treatment if there is a clinically significant decrease in cardiac function (see Dosage and Administration).

Hepatotoxicity and hepatic impairment

Marked increases in liver function tests (hepatotoxicity) to treatment discontinuation or dose modification occurred in controlled clinical studies (see Adverse Reactions). Liver function tests (bilirubin, ALT and AST) should be measured prior to commencing 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 in the absence of bone metastases and 10 times the upper limit of normal in the presence of bone metastases, treatment should be withheld 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 in this population.

There are no data on the clinical safety and efficacy of multiple doses of Abiraterone when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. Abiraterone 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 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 post-marketing reports of acute liver failure and hepatic failure leading to death, 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 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 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 with cytotoxic chemotherapy has not been established (see Pharmacological Properties – Clinical studies).

Use in combination with radium 223 dichloride

In a randomised 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 plus prednisone/prednisolone showed an increase in mortality and an increased rate of fractures. Radium 223 dichloride is not recommended for use in combination with Abiraterone 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 23.2 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.

Interactions

Effect of food on Abiraterone

Administration with food significantly increases the absorption of Abiraterone. The efficacy and safety of Abiraterone given with food have not been established. Abiraterone 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 exposure

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 1,000 mg, the mean plasma AUC∞ of abiraterone was decreased by 61%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with Abiraterone 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 to affect exposure of 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 (also prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.8 fold. The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 32%.

Caution is advised when Abiraterone 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 should be considered to obtain maximum effect. Examples of narrow therapeutic index drugs include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, nortriptyline, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three metabolites of 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 (also 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. Although these results indicate that no clinically meaningful increases in exposure are expected when Abiraterone 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. Examples of medicinal products metabolised by CYP2C8 include paclitaxel and repaglinide.

Pregnancy, Breast feeding and Fertility

Pregnancy

Abiraterone is not for use in women.

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

There are no data on the use of Abiraterone in pregnancy and Abiraterone 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 Data – Reproductive Toxicity).

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

To avoid exposure to spermatozoa, women who are pregnant or women who may be pregnant should not handle Abiraterone without protection, e.g., gloves.

Breast-feeding

Abiraterone is not for use in women.

It is not known if either Abiraterone or its metabolites are excreted in 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 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 based on the comprehensive assessment of the available adverse event information. A causal relationship with Abiraterone 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, adverse reactions that were observed in ≥ 10% of patients were hypertension, peripheral oedema, hypokalemia, urinary tract infection, and upper respiratory tract infection (see Adverse Reactions and Clinical studies).

Abiraterone may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid excess mostly occurred in patients who were concomitantly treated with prednisone. Hypertension was observed in 19% of hypokalemia 10% across 8%, hypertension 22% versus 10% and fluid retention (peripheral oedema) 22% versus 17%, respectively. In patients treated with Abiraterone, CTCAE (version 3.0) Grade 3 and 4 hypokalemia were observed in 2.6% and 0.2% of patients, CTCAE (version 3.0) Grade 3 and 4 hypertension were observed in 8% and 0.1% of patients, and grades 3 and 4 fluid retention adverse were observed in 1% and 1% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Discontinuation of Abiraterone treatment for adverse events of these types occurred in 2% of patients (see Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess).

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, Abiraterone was 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 ≥ 5% (all grades) are shown in Table 1.

Table 1. Adverse Reactions in ≥ 1% of Patients in Clinical Studies

System Organ Class Adverse Reaction	Abiraterone 1000 mg daily with prednisone or prednisolone n = 2035b All grades %	 Grade 3 %	 Grade 4 %
General Disorders and Administration Site Conditions			
Oedema peripheral	20	< 1	0
Metabolism and Nutrition Disorders			
Hypokalemia	20	5	< 1
Hypertriglyceridemia	2	< 1	0
Infections and Infestations			
Urinary tract infection	10	2	< 1
Reproductive Disorders			
ALT increased and/or AST increased[a]	13	4	< 1
Vascular Disorders			
Hypertension	21	6	0
Injury, poisoning and procedural complications			
Fractures[c]	7	2	< 1
Cardiac Disorders			
Cardiac failure[e]	3	< 1	< 1
Angina pectoris	2	< 1	0
Arrhythmia	5	2	0
Atrial fibrillation	3	1	< 1
Tachycardia	2	< 1	0
Renal and urinary disorders			
Hematuria	2	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 include 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 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 or evidence of 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 302) and 2003 or cardiac ejection fraction measurement < 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 have 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 versus patients taking placebo were: cardiac disorders 14% versus 12%, atrial fibrillation 2.6% versus 0.8%, cardiacfailure 2.0% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2% and arrhythmia 5.2% vs. 0.3%.

Hepatotoxicity

Unexplained transaminitis, with elevated ALT, AST and total bilirubin levels both reported in patients treated with Abiraterone. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 × ULN or bilirubin increases > 1.5 × ULN) were reported in approximately 6% of patients who received Abiraterone, typically during the first six months of treatment. Hepatotoxicity was reversible in most patients with available data. Grade 3 or 4 hepatotoxicity was observed in 4.2% of patients treated with Abiraterone. These patients with normal baseline liver function, experienced ALT or AST elevations sufficient to interrupt treatment, followed by a return to baseline liver function after treatment discontinuation. Hepatotoxicity resulting in permanent discontinuation of treatment occurred in 0.8% of patients treated with Abiraterone. Hepatotoxicity resulting in permanent dose reductions occurred in 0.4% of patients treated with Abiraterone. Abiraterone liver abnormalities resolved in all but 2 patients (2 with new multiple liver metastases and 1 with ALT elevation approximately 3 weeks after the last dose of Abiraterone). In Phase 3 clinical studies, treatment discontinuation due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with Abiraterone and 0.0% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was elevated in a subpopulation of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 2011 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 were excluded. Bilirubin elevations 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 > 5 x ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were rigorously managed by ongoing treatment interruption and permitting on treatment only after return of liver function tests to the patient's baseline (see Dosage and Administration and Warnings and Precautions). 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 risk/benefit for hepatotoxicity is not understood.

Post-marketing experience

Adverse reactions identified during the post-marketing experience based on spontaneous reports with Abiraterone 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).

System Organ Class: Immune System Disorders – Hypersensitivity
Very rare: Anaphylactic reaction (severe allergic reactions that include, but are not limited to difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash/urticaria).

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, 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 catalyzes 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 adrenal gland (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 analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with Abiraterone decreases serum testosterone in castrated men (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a Phase 2 clinical study of patients who failed prior chemotherapy with taxanes, 28% of patients treated with Abiraterone, versus 10% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Use of Spironolactone

Patients in pivotal clinical trials with Abiraterone were not allowed to use spironolactone as spironolactone binds to the androgen receptor and may increase PSA levels.

Clinical studies

The efficacy of Abiraterone was established in three randomized placebo-controlled multicenter phase 3 clinical studies (Studies 3011, 302, and 301) of patients with hormone sensitive metastatic prostate cancer and metastatic castration resistant prostate cancer.

Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomization) mHSPC who had high-risk prognostic factors. High-risk prognosis was defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥ 8; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (including lymph node disease metastasis). The patients in the Abiraterone arm were administered a dose of 1000 mg daily in combination with low dose prednisone or prednisone 5 mg once daily. In addition to ADT (LHRH agonist or orchiectomy), which was the standard of care treatment. Patients in the control arm received ADT and placebo for both Abiraterone and prednisone.

Study 302 enrolled docetaxel-naive patients, whereas Study 301 enrolled patients who had received prior docetaxel. Patients were using an LHRH analogue or were previously treated with orchiectomy. In the active treatment arm, Abiraterone was administered at a dose of 1,000 mg daily in combination with low dose prednisone or prednisone 5 mg twice daily. Control patients received placebo and low dose prednisone or prednisone 5 mg twice daily.

Because changes in PSA serum concentration do not always predict clinical benefit in all studies patients were maintained on Abiraterone until discontinuation criteria were met as specified below for each study.

Study 3011 (patients with newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC)

In Study 3011, n= 1189 the median age of enrolled patients was 67 years. The ECOG performance status was 0 or 1 for 87% of patients. Patients with uncontrolled hypertension, significant heart disease, or NYHA Class II or worse heart failure were excluded. Cardiac ejection fraction measurement was not required. ECG and radiographic progression-free survival (rPFS). The median baseline pain score, as measured by the Brief Pain Inventory Short Form (BPI-SF) was 2.0 in both the treatment and placebo groups. In addition to the co primary endpoint measures, Benefit was also assessed using time to skeletal-related event (SRE), time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, time to pain progression and time to PSA progression.

In the 2011 study, treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death.

Radiographic progression-free survival was defined as the time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression included progression to bone scan (according to modified PCWG2) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1).

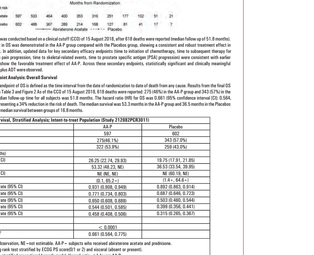
At the planned rPFS analysis there were 583 events; 238 (40.0%) of patients treated with Abiraterone and 354 (58.4%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 2 and Figure 1).

Table 2: Radiographic Progression Free Survival - Stratified Analysis, Intent-to-treat Population (Study PCR3011)

	AA P	Placebo
Subjects randomized	597	602
Event	238 (40.0%)	354 (58.8%)
Censored	359 (60.0%)	248 (41.2%)
Time to Event (months)		
25th percentile (95% CI)	14.93 (11.47, 15.15)	7.43 (7.29, 10.58)
Median (95% CI)	33.10 (29.57, NE)	14.78 (14.68, 16.56)
75th percentile (95% CI)	NE (NE, NE)	30.38 (29.24, 39.99)
Range	(0.0+, 41.1+)	(0.0+, 46.9+)
6-month event-free rate (95% CI)	0.841 (0.818, 0.863)	0.667 (0.630, 0.693)
12-month event-free rate (95% CI)	0.728 (0.742, 0.813)	0.611 (0.567, 0.652)
18-month event-free rate (95% CI)	0.702 (0.681, 0.739)	0.478 (0.431, 0.520)
24-month event-free rate (95% CI)	0.611 (0.588, 0.663)	0.347 (0.303, 0.391)
30-month event-free rate (95% CI)	0.532 (0.483, 0.579)	0.250 (0.206, 0.296)
36-month event-free rate (95% CI)	0.471 (0.414, 0.526)	0.208 (0.162, 0.260)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

Note: + = censored observation, NE = not estimable. The radiographic progression and death are considered in defining the rPFS event.
AA P - subjects who received abiraterone acetate and prednisone.
a p value is from a log-rank test stratified by ECOG PS score(0 or 2) and visceral (absent or present).
b Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors AA P.

Figure 1: Kaplan-Meier Plot of Radiographic Progression-Free Survival, Intent to treat Population (Study PCR3011)



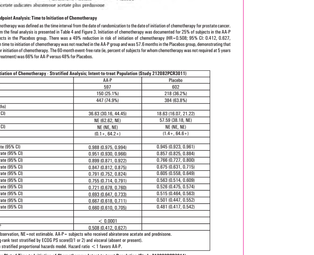
This final analysis of OS was conducted based on a clinical cutoff (CCO) of 15 August 2018, after 618 deaths were reported (median follow-up of 55.8 months). Abiraterone treatment in OS was demonstrated in the AA P group compared with the Placebo group. There was a 19% reduction in the risk of death (HR=0.808; 95% CI: 0.612, 0.827; p < 0.0001). The median time to initiation of chemotherapy was not reached in the AA P group and was 57.4 months in the Placebo group, demonstrating that AA P delayed the need for initiation of chemotherapy. The 60-month event-free rate (ie, percent of subjects for whom chemotherapy was not required at 5 years after initiation of study treatment was 60% in the AA P group and 37% in the Placebo group.

Table 3: Overall Survival, Stratified Analysis, Intent-to-treat Population (Study 3011)(PCR3011)

	AA P	Placebo
Subjects randomized	597	602
Event	225(68.1%)	340 (57.5%)
Censored	372 (31.9%)	252 (42.5%)
Overall Survival (months)		
25th percentile (95% CI)	36.8 (32.18, 44.49)	18.83 (16.87, 21.23)
Median (95% CI)	NE (62.62, NE)	57.39 (51.18, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1+, 66.2+)	(1.4+, 64.8+)
6-month event free rate (95% CI)	0.884 (0.855, 0.909)	0.816 (0.783, 0.847)
12-month event free rate (95% CI)	0.815 (0.784, 0.843)	0.695 (0.659, 0.729)
18-month event free rate (95% CI)	0.749 (0.715, 0.781)	0.597 (0.559, 0.634)
24-month event free rate (95% CI)	0.664 (0.631, 0.695)	0.509 (0.466, 0.551)
30-month event free rate (95% CI)	0.581 (0.547, 0.614)	0.420 (0.378, 0.461)
36-month event free rate (95% CI)	0.516 (0.479, 0.552)	0.353 (0.313, 0.393)
42-month event free rate (95% CI)	0.451 (0.412, 0.489)	0.298 (0.261, 0.336)
48-month event free rate (95% CI)	0.394 (0.357, 0.431)	0.253 (0.218, 0.289)
54-month event free rate (95% CI)	0.342 (0.305, 0.378)	0.207 (0.175, 0.241)
60-month event free rate (95% CI)	0.298 (0.264, 0.331)	0.169 (0.141, 0.202)
p value[a]	0.0010	
Hazard ratio (95% CI)[b]	0.808 (0.691, 0.950)	

Note: + = censored observation, NE = not estimable.
a p value is from a log-rank test stratified by ECOG PS score(0 or 2) and visceral (absent or present).
b hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors AA P.

Figure 2: Kaplan-Meier Plot of Overall Survival, Intent to treat Population (Study 3011)(PCR3011)



Note Abiraterone acetate indicates abiraterone acetate plus prednisone

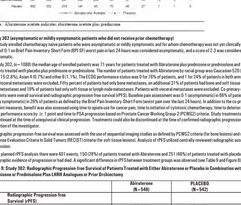
Secondary Efficacy Endpoint Analysis: Time to Initiation of Chemotherapy

Time to initiation of chemotherapy was defined as the time interval from the date of randomization to the date of initiation of chemotherapy for prostate cancer. Updated information from the final analysis is presented in Table 4 and Figure 3. Initiation of chemotherapy was documented for 25% of subjects in the AA P group and 36% of subjects in the Placebo group. There was a 40% reduction in risk of initiation of chemotherapy (HR=0.598; 95% CI: 0.412, 0.821; p < 0.0001). The median time to initiation of chemotherapy was not reached in the AA P group and was 57.4 months in the Placebo group, demonstrating that AA P delayed the need for initiation of chemotherapy. The 60-month event-free rate (ie, percent of subjects for whom chemotherapy was not required at 5 years after initiation of study treatment was 60% in the AA P group and 37% in the Placebo group.

Table 4: Time to Initiation of Chemotherapy - Stratified Analysis; Intent-to treat Population (Study 3011)(PCR3011)

	AA P	Placebo
Subjects randomized	597	602
Event	150 (25.1%)	218 (36.2%)
Censored	447 (74.9%)	384 (63.8%)
Overall Survival (months)		
25th percentile (95% CI)	36.83 (32.18, 44.49)	18.83 (16.87, 21.23)
Median (95% CI)	NE (62.62, NE)	57.39 (51.18, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1+, 66.2+)	(1.4+, 64.8+)
6-month event free rate (95% CI)	0.934 (0.915, 0.951)	0.849 (0.815, 0.881)
12-month event free rate (95% CI)	0.861 (0.835, 0.886)	0.757 (0.725, 0.784)
18-month event free rate (95% CI)	0.809 (0.781, 0.837)	0.700 (0.667, 0.731)
24-month event free rate (95% CI)	0.747 (0.717, 0.776)	0.675 (0.637, 0.711)
30-month event free rate (95% CI)	0.701 (0.672, 0.729)	0.600 (0.558, 0.640)
36-month event free rate (95% CI)	0.656 (0.624, 0.687)	0.563 (0.519, 0.605)
42-month event free rate (95% CI)	0.621 (0.589, 0.652)	0.526 (0.479, 0.574)
48-month event free rate (95% CI)	0.603 (0.567, 0.638)	0.515 (0.464, 0.563)
54-month event free rate (95% CI)

Figure 5: Kaplan-Meier Plot of PSA Progression; Intent-to-treat Population (Study 2120BCPCR3011)



Note: Abiraterone acetate indicates abiraterone acetate plus prednisone

Time to Life Extending Subsequent Therapy for Prostate Cancer

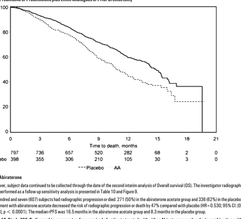
Time to life extending subsequent therapy for prostate cancer (ketoconazol, cabiscatinat, abiraterone acetate, enzalutamide, sipuleucel T, and radium-223) is summarized for the final analysis in Table 7 and Figure 6. There were 29% of subjects in the AA-P group and 45% of subjects in the Placebo group who received life extending subsequent therapy. The median time to life extending subsequent therapy was not reached in the AA-P group and was 26.0 months in the Placebo group, demonstrating that AA-P delayed the need for initiation of life extending subsequent therapy (HR=0.431; 95% CI: 0.356, 0.522; p < 0.0001). The 95-month event free rate was 60% for AA-P and 27% for Placebo.

Table 7: Time to life extending Subsequent Therapy for Prostate Cancer: Stratified Analysis; Intentto treat Population (Study 2120BCPCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	170 (28.5%)	273 (45.3%)
Censored	427 (71.5%)	329 (54.7%)
Time to Event (months)		
25th percentile (95% CI)	30.62 (26.61, 34.88)	14.85 (13.21, 16.68)
Median (95% CI)	NE (60.78, NE)	26.62 (25.86, 34.99)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(13.1+, 58.2+)	(1.4+, 63.8+)
6-month event free rate (95% CI)	0.888 (0.870, 0.904)	0.938 (0.915, 0.955)
12-month event free rate (95% CI)	0.840 (0.824, 0.862)	0.872 (0.787, 0.925)
18-month event free rate (95% CI)	0.800 (0.774, 0.824)	0.805 (0.663, 0.724)
24-month event free rate (95% CI)	0.618 (0.782, 0.646)	0.577 (0.531, 0.620)
30-month event free rate (95% CI)	0.754 (0.713, 0.790)	0.494 (0.446, 0.540)
36-month event free rate (95% CI)	0.708 (0.665, 0.745)	0.439 (0.390, 0.486)
42-month event free rate (95% CI)	0.671 (0.625, 0.713)	0.408 (0.360, 0.457)
48-month event free rate (95% CI)	0.651 (0.604, 0.693)	0.388 (0.338, 0.437)
54-month event free rate (95% CI)	0.621 (0.572, 0.666)	0.388 (0.338, 0.437)
60-month event free rate (95% CI)	0.598 (0.546, 0.646)	0.367 (0.305, 0.429)
p value[a]	< 0.0001	
Hazard ratio (95% CI)b	0.431 (0.356, 0.522)	

Note: ++ censored observation, NE=not estimable.
[a] p-value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or Present)
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio: < 1 favors AA-P.

Figure 6: Kaplan-Meier Plot of Time to Life-extending Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study 2120BCPCR3011)



Life-extending therapies include Docetaxel, Cabiscatinat, Abiraterone acetate plus prednisone, Enzalutamide, Sipuleucel T, and Radium-223 Note: Abiraterone acetate indicates abiraterone plus prednisone

Time to Pain Progression

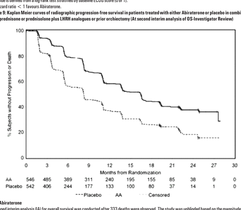
Time to pain progression was defined as the time interval from randomization to the first date a subject experienced ≥ 30% increase from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive visits(at least 2-4 weeks apart. Updated data for time to pain progression from the final analysis is presented in Table 8 and Figure 7. Pain progression was documented for 41% of subjects in the AA-P group and 40% of subjects in the Placebo group. There was a 23% reduction in risk of pain progression (HR=0.771; 95% CI: 0.651, 0.912; p = 0.0003). The median time to pain progression was 41.4 months in the AA-P group and 16.6 months in the Placebo group. The 60-month event free rate was 50% for AA-P and 30% for the Placebo group.

Table 8: Time to Pain Progression (BPI2): Stratified Analysis; Intent-to-treat Population (Study 2120BCPCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	245 (41.0%)	292 (48.5%)
Censored	352 (58.9%)	310 (51.5%)
Time to Event (months)		
25th percentile (95% CI)	4.67 (2.85, 6.47)	2.79 (2.73, 3.71)
Median (95% CI)	47.41 (33.15, NE)	16.62 (11.61, 23.95)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.2+, 66.7+)	(0.5+, 55.8+)
6-month event free rate (95% CI)	0.723 (0.685, 0.758)	0.635 (0.594, 0.673)
12-month event free rate (95% CI)	0.630 (0.588, 0.669)	0.534 (0.490, 0.576)
18-month event free rate (95% CI)	0.603 (0.560, 0.645)	0.498 (0.451, 0.540)
24-month event free rate (95% CI)	0.577 (0.533, 0.618)	0.448 (0.400, 0.495)
30-month event free rate (95% CI)	0.558 (0.515, 0.598)	0.417 (0.367, 0.467)
36-month event free rate (95% CI)	0.541 (0.498, 0.585)	0.410 (0.358, 0.461)
42-month event free rate (95% CI)	0.526 (0.478, 0.573)	0.410 (0.358, 0.461)
48-month event free rate (95% CI)	0.498 (0.439, 0.557)	0.388 (0.324, 0.451)
54-month event free rate (95% CI)	0.498 (0.439, 0.557)	0.388 (0.324, 0.451)
60-month event free rate (95% CI)	0.498 (0.439, 0.557)	NE (NE, NE)
p value[a]	0.0002	
Hazard ratio (95% CI)[b]	0.771 (0.651, 0.912)	

Note: ++ censored observation, NE=not estimable.
[a] p-value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or Present)
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio: < 1 favors AA-P.

Figure 7: Kaplan-Meier Plot of Time to Pain Progression (BPI2); Intent-to-treat Population (Study 2120BCPCR3011)



Note: Abiraterone acetate indicates abiraterone acetate plus prednisone

Study 2120 Secondary endpoints on time to symptomatic progression with or without prior chemotherapy

Time to pain progression was defined as the time interval from randomization to the first date a subject experienced ≥ 30% increase from baseline in the BPI-SF worst pain intensity (item 3) observed at 2 consecutive visits(at least 2-4 weeks apart. Updated data for time to pain progression from the final analysis is presented in Table 8 and Figure 7. Pain progression was documented for 41% of subjects in the AA-P group and 40% of subjects in the Placebo group. There was a 23% reduction in risk of pain progression (HR=0.771; 95% CI: 0.651, 0.912; p = 0.0003). The median time to pain progression was 47.4 months in the AA-P group and 16.6 months in the Placebo group. The 60-month event free rate was 50% for AA-P and 30% for the Placebo group.

Radiographic progression-free survival was assessed with the use of sequential imaging studies (as defined by PCWG2 criteria for bone lesions) and modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

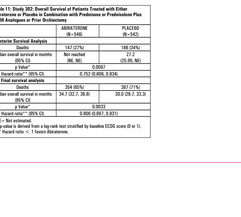
At the planned rPFS analysis there were 401 events; 150 (25%) of patients treated with Zytiga and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 9 and Figure 8).

Table 9: Study 302: Radiographic Progression-Free Survival of Patients Treated with Ether Abiraterone or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Analogues or Prior Orchiectomy

	Abiraterone (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median (95% CI) in months	NE (NE,NE)	16.5 (14.8, 19.4)
(95% CI)	(11.66, NE)	(8.12, 9.44)
p value[a]	< 0.0001	
Hazard ratio[b] (95% CI)	0.425 (0.347, 0.522)	

NE = Not Estimated
[a] p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
[b] Hazard ratio: < 1 favors Abiraterone.

Figure 8: Kaplan-Meier Curves of Radiographic Progression-free Survival in Patients Treated with Ether Abiraterone or Placebo in Combination with Prednisone or Prednisolone plus LHRH Analogues or Prior Orchiectomy



AA + Abiraterone

However, subjects declined to be collected through the date of the second interim analysis of Overall survival (OS). The investigator radiographic review of rPFS performed as a follow-up sensitivity analysis is presented in Table 10 and Figure 9.

Six hundred and seven (607) subjects had radiographic progression or died: 271 (50%) in the abiraterone acetate group and 336 (62%) in the placebo group. Radiographic progression-free survival was significantly longer in the abiraterone acetate plus prednisone group (HR=0.533; 95% CI: 0.451, 0.631); p < 0.0001). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

Table 10: Study 302: Radiographic progression-free survival of patients treated with ether Abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS Investigator Review)

	Abiraterone (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50%)	336 (62%)
Median (rPFS in months)	16.5	8.3
(95% CI)	(13.80, 18.79)	(8.05, 9.43)
p value[a]	< 0.0001	
Hazard ratio[b] (95% CI)	0.530 (0.451, 0.623)	

[a] p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
[b] Hazard ratio: < 1 favors Abiraterone.

Figure 9: Kaplan-Meier curves of radiographic progression-free survival in patients treated with either Abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS Investigator Review)

AA + Abiraterone

A planned interim analysis (IA) for overall survival was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed for Abiraterone acetate plus prednisone/prednisolone compared to placebo plus prednisone/prednisolone. At the time of this analysis, 25% reduction in risk of death (HR = 0.752; 95% CI: 0.606, 0.934); p = 0.0051), but OS was not mature and immune-mediated adverse events were the pre-specified stopping boundary for statistical significance (see Table 8). Survival continued to be followed after this IA.

The planned final analysis for OS was conducted after 741 deaths were observed (median follow-up of 49 months). Sixty-five percent (254 of 546) of patients treated with Abiraterone, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favor of the Abiraterone treated group was demonstrated with a 19.4% reduction in risk of death (HR = 0.806; 95% CI: [0.697, 0.931]; p = 0.0033) and an improvement in median OS of 4.4 months (Abiraterone 34.7 months, placebo 30.3 months) (see Table 8 and Figure 8). This improvement was demonstrated despite subsequent therapies being common, irrespective of whether patients initially received abiraterone acetate or placebo. Subsequent therapies in the abiraterone acetate and placebo patient groups included abiraterone acetate, 68 (13%) and 238 (44%); docetaxel, 311 (57%) and 321 (61%); Cabazitaxel, 100 (18%) and 105 (19%); and enzalutamide 81 (15%) and 54 (10%) patients respectively.

Table 11: Study 302: Overall Survival of Patients Treated with Ether Abiraterone or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Analogues or Prior Orchiectomy

	ABIRATERONE (N=546)	PLACEBO (N=542)
Interim Survival Analysis		
Deaths	147 (27%)	186 (34%)
Median overall survival in months (95% CI)	Not reached (NE, NE)	27.2 (25.99, NE)
p value[a]	0.0051	
Hazard ratio[b] (95% CI)	0.752 (0.606, 0.934)	
Final survival analysis		
Deaths	254 (65%)	387 (71%)
Median overall survival in months (95% CI)	34.7 (32.7, 38.8)	30.0 (28.7, 33.3)
p Value[a]	0.0033	
Hazard ratio[b] (95% CI)	0.806 (0.697, 0.931)	

NE = Not estimated
[a] p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
[b] Hazard ratio: < 1 favors Abiraterone.

Figure 10: Kaplan-Meier Survival Curves of Patients Treated with Ether Abiraterone or Placebo in Combination with Prednisone or Prednisolone plus LHRH Analogues or Prior Orchiectomy, Final analysis

AA + Abiraterone

Subgroup analyses consistently favor treatment with Abiraterone (see Figure 11)

Figure 11: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval

Variable	Subgroup	Median (months) AA	Placebo	HR	95% C.I.	Subjects AA	Placebo
All subjects	ALL	34.7	30.3	0.81	(0.70, 0.93)	354/546	387/542
Baseline ECOG	0	38.4	32.0	0.79	(0.66, 0.94)	203/316	230/314
	1	27.9	26.4	0.87	(0.66, 1.16)	93/130	95/128
Baseline BPI	0-1	38.1	33.4	0.77	(0.64, 0.93)	223/370	233/346
	2-3	26.4	27.4	0.87	(0.76, 1.27)	130/129	120/147
Bone Metastasis Only At Entry	YES	36.9	34.1	0.79	(0.62, 0.97)	147/238	162/241
	NO	31.6	29.0	0.83	(0.69, 1.00)	207/308	225/301
Age	<65	34.5	30.2	0.79	(0.59, 1.03)	89/138	111/105
	>=65	34.7	30.8	0.81	(0.69, 0.96)	265/411	276/397
	<=75	35.3	29.9	0.79	(0.61, 1.01)	129/180	120/180
	>75	25.8	25.9	0.86	(0.71, 1.04)	209/282	209/282
Baseline PSA stratum median	NO	43.1	34.4	0.72	(0.58, 0.90)	140/264	161/262
	YES	31.2	24.9	0.74	(0.61, 0.96)	192/273	203/269
Baseline LDH stratum median	NO	36.3	30.8	0.85	(0.68, 1.05)	162/266	164/283
	YES	28.6	26.8	0.92	(0.76, 1.11)	211/279	201/256
Baseline ALK-P stratum median	NO	44.5	33.2	0.66	(0.55, 0.80)	143/267	186/266
	YES	27.0	31.2	0.74	(0.61, 0.91)	164/267	195/275
Region	NA	37.0	31.2	0.90	(0.73, 1.11)	172/240	189/267
	Other	33.2	30.1				

AA = Abiraterone; ALK-P = alkaline phosphatase; BPI = Brief Pain Inventory; C.I. = confidence interval; ECOG = Eastern Cooperative Oncology Group performance score; HR = Hazard ratio; LDH = lactic dehydrogenase; N = North America; NE = not estimable

In addition to the observed improvement in overall survival and rPFS, benefit was demonstrated for Abiraterone vs. placebo treatment in all prospectively defined secondary endpoint analyses as follows:

Time to Pain Progression (Worst Pain) as measured by PCWG2 criteria

The median time to PSA progression was 11.1 months for patients receiving Abiraterone and 5.6 months for patients receiving placebo (HR = 0.488; 95% CI: [0.429, 0.549]; p < 0.0001). The time to PSA progression was approximately doubled with Abiraterone treatment (HR = 0.488). The proportion of subjects with a confirmed PSA response was greater in the Abiraterone group (from the placebo group: 62% versus 24%; p < 0.0001). In subjects with measurable soft tissue disease, significantly increased numbers of complete and partial tumor responses were seen with Abiraterone treatment.

Time to opiate use for cancer pain

The median time to opiate use for prostate cancer pain at the time of final analysis was 33.4 months for patients receiving Abiraterone and was 23.4 months for patients receiving placebo (HR = 0.721; 95% CI: [0.614, 0.846]; p < 0.0001).

Time to initiation of cytotoxic chemotherapy

The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving Abiraterone and 18.8 months for patients receiving placebo (HR = 0.580; 95% CI: [0.487, 0.691]; p < 0.0001).

Time to deterioration of ECOG performance status by ≥ 1 point

The median time to deterioration of ECOG performance status by ≥ 1 point was 12.3 months for patients receiving Abiraterone and 10.0 months for patients receiving placebo (HR = 0.821; 95% CI: [0.714, 0.943]; p = 0.0053).

The following study endpoints demonstrated a statistically significant advantage in favor of Abiraterone treatment:

Objective response

Objective response was defined as the proportion of subjects with measurable disease achieving a complete or partial response according to RECIST criteria Baseline lymph node size was required to be ≥ 2 cm to be considered a target lesion. The proportion of subjects with measurable disease at baseline who had an objective response was 38% in the Abiraterone group and 16% in the placebo group (p < 0.0001).

Pain

Treatment with Abiraterone significantly reduced the risk of average pain intensity progression by 18% compared with placebo (p = 0.0400). The median time to progression was 26.7 months in the Abiraterone group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score)

Treatment with Abiraterone decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (p = 0.0020). The median time to degradation in FACT-P (Total Score) was 12.7 months in the Abiraterone group and 8.3 months in the placebo group.

Study 301 patients who had received prior chemotherapy

Study 301 enrolled 797 patients who had received docetaxel. Patients were not required to show disease progression on docetaxel, as toxicity from this chemotherapy may have led to discontinuation.

Patients were maintained on study treatments until there was PSA progression (confirmed 25% increase over the patient's baseline/nadir) together with protocol defined radiographic progression and symptomatic or clinical progression. Patients with prior ketoconazole treatment were excluded from this study. The primary efficacy endpoint was overall survival.

The median age of the patients was 68 years (range 40-95). The number of patients treated with Abiraterone by racial group was Caucasian 737 (93.2%), Black 28 (3.5%), Asian 11 (1.4%) and other 14 (1.8%). Eleven percent of patients enrolled had an ECOG performance score of 2. 70% had radiographic evidence of disease progression with or without PSA progression. 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with Abiraterone.

In a planned analysis conducted after 552 deaths were observed, 42% (232 of 797) of patients treated with Abiraterone compared with 55% (218 of 388) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients treated with Abiraterone (see Table 12 and Figure 12). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for the final analysis) were observed.

Results from this updated survival analysis were consistent with those in the primary survival analysis (see Table 12).

Table 12: Study 301: Overall survival of patients treated with either Abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

	Abiraterone (N=797)	PLACEBO (N=398)
Primary Survival Analysis		
Deaths	333 (42%)	218 (55%)
Median overall survival in months (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value[a]	< 0.0001	
Hazard ratio[b] (95% CI)	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths	501 (63%)	274 (69%)
Median overall survival in months (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 12.1)
Hazard ratio[b] (95% CI)	0.745 (0.638, 0.870)	

[a] p Value is derived from a log rank test stratified by ECOG performance status score (0 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).
[b] Hazard ratio: < 1 favors Abiraterone; Hazard ratio is estimated using Cox proportional hazards model.

A sustained survival benefit of 12 months or more for treatment, a higher proportion of patients treated with Abiraterone remained alive, compared with the proportion of patients treated with placebo (see Figure 13).

Figure 12: Kaplan-Meier survival curves of patients treated with either Abiraterone or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA + Abiraterone

Subgroup survival analyses showed a consistent survival benefit for treatment with Abiraterone (see Figure 13).

Figure 13: Overall survival by subgroup: hazard ratio and 95% confidence interval

Variable	Subgroup	Median (months) AA	Placebo	HR	95% C.I.	N
All subjects	ALL	14.8	10.9	0.66	(0.66, 0.78)	1196
Baseline ECOG	0-1	15.3	11.7	0.64	(0.53, 0.76)	1068
	2	7.3	7	0.69	(0.53, 1.24)	127
Disease SH	<4	16.3	13	0.64	(0.56, 0.82)	659
	>=4	12.6	8.9	0.68	(0.53, 0.88)	536
No. prior chemo regimens	1	15.4	11.5	0.63	(0.51, 0.78)	833
	2	14	10.3	0.74	(0.55, 0.99)	362
Type of progression	PSA only	NE	12.3	0.59	(0.42, 0.82)	363
	Radiographic	14.2	10.4	0.69	(0.56, 0.84)	832
Visceral disease at entry	YES	12.6	8.4	0.70	(0.52, 0.94)	251
	NO	15.4	11.2	0.62	(0.56, 0.76)	942



AA = Abiraterone; BPI = Brief Pain Inventory; C.I. = confidence interval; ECOG = Eastern Cooperative Oncology Group performance score; HR = hazard ratio; NE = not evaluable

In addition to the observed improvement in overall survival, all secondary study endpoints favoured Abiraterone and were statistically significant after adjusting for multiple testing as follows:

Patients receiving Abiraterone demonstrated a significantly higher total PSA response rate (defined as ≥ 50% reduction from baseline), compared with patients receiving placebo, 38% versus 10%, p < 0.0001.

Patients treated with Abiraterone had a longer time to PSA progression (6.6 months versus 4.0 months for patients treated with placebo (HR = 0.580; 95% CI: [0.462, 0.728]; p < 0.0001).

The median radiographic progression-free survival was 5.6 months for patients treated with Abiraterone and 3.9 months for patients who received placebo (HR = 0.673; 95% CI: [0.585, 0.774]; p < 0.0001).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the Abiraterone group than in the placebo group (44% versus 27%, p = 0.0002). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the BPI-SF worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline pain score of ≥ 4 and at least one post baseline pain score were analyzed (N = 537) for pain palliation.

A lower proportion of patients treated with Abiraterone had disease progression compared to patients taking placebo at 0.22% versus 28%; 12.00% versus 38%; and 18 months (26% versus 46%). Pain progression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the last 24 hours without a decrease in analgesic usage score observed at two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two consecutive visits. The time to pain progression at the 25th percentile was 7.4 months in the Abiraterone group, versus 4.7 months in the placebo group.

Skeletal-related events.

A lower proportion of patients in the Abiraterone group had skeletal events compared with the placebo group (8 months (18% versus 28%), 12 months (30% versus 43%), and 18 months (50% versus 62%). The time to first skeletal-related event at the 25th percentile in the Abiraterone group was twice that of the control group at 9.8 months versus 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

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 a by 10-fold (AUC) and by a 7-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 with meals has the potential to result in highly variable exposures. Therefore, Abiraterone must be taken without food. Abiraterone 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 14C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation

Following oral administration of 14C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulfation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 20 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 42% 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 14C-abiraterone acetate (1,000mg), approximately 89% 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 50% 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 pre-existing moderate hepatic impairment (see Dosage and Administration - Hepatic impairment). Abiraterone 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 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 - Hepatotoxicity and Hepatic impairment).

NON CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic TgrasH2 mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell proliferations in the testes. This finding is considered related to the pharmacological action of abiraterone and not indicative of a carcinogenic potential in humans (see Pharmacology).

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 10 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, Breastfeeding 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

HOW SUPPLIED

ABIRONE (Abiraterone Acetate tablets 250 mg)

Off white to cream colored, oval shaped, biconvex tablets debossed with 'A1' on one side and 'AI' on the other side.

List of Excipients

Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Povidone, Sodium Lauryl Sulfate, Colloidal silicon dioxide and Magnesium Stearate.

Incompatibilities

Not applicable.

STORAGE:

Store below 30°C and protect from moisture.

Shelf Life

18 Months

Shelf life after first opening (bottle): 1 month (store at or below 30°C).

Pack Size

120's Count HDPE Container Pack

Product Owner:
HETERO LABS LIMITED
7-2-A-2, Hetero Corporate,
Industrial Estates, Sanath nagar,
Hyderabad - 500 018, INDIA.

2xxxxxx

Manufactured by:
HETERO LABS LIMITED
Unit V, TSIIC Formulation SEZ,
Jadcherla Mandal, Mahabboobnagar Dist.,
Telangana, India.