ABIRATERONE-TEVA FC TABLET 250 MG

DOSAGE FORMS AND STRENGTHS
250 mg film coated Tablets: Each tablet contains 250 mg of abiraterone acetate.

White modified oval shaped film coated tablet, debossed with "TEVA" on one side and "1125" on the other side.
For excipients, see Pharmaceutical Information - List of Excipients.

CLINICAL INFORMATION
Indications
ABIRATERONE-TEVA FC TABLET is indicated with prednisone or prednisolone for:
- The treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (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 (four 250 mg tablets) as a single daily dose that must not be taken with food. Abiraterone-Teva FC Tablet 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.

Dosage of prednisone or prednisolone
For metastatic hormone sensitive prostate cancer (mHSPC), Abiraterone-Teva FC Tablet is used with 5 mg prednisone or prednisolone daily.

For metastatic castration-resistant prostate cancer (mCRPC), Abiraterone-Teva FC Tablet is used with 10 mg prednisone or prednisolone 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 with pre-existing hypokalemia or those that develop hypokalemia whilst being treated with Abiraterone Tablet, 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 Tablet 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-TEVA FC TABLET, 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 Tablet 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 Tablet 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 (one 500 mg tablet or 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 Tablet.

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 Tablet 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 Tablet.

Abiraterone Tablet should be used with caution in patients with a history of cardiovascular disease. The phase 3 studies conducted with Abiraterone Tablet 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 Tablet, 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 Tablet 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 Tablet 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 Tablet 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 Tablet 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 Tablet 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 Tablet 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.

Hypoglycemia
Isolated cases of hypoglycemia have been reported when Abiraterone plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see Interactions - Interactions with other drugs - Potential for Abiraterone to affect exposures to other drugs). Blood glucose should be monitored in patients with diabetes.

Use with chemotherapy
The safety and efficacy of concomitant use of Abiraterone Tablet 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 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 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 26 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 Tablet.

Interactions
Effect of food on abiraterone acetate
Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of Abiraterone Tablet given with food have not been established. Abiraterone Tablet 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 Tablet 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 Tablet 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 AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when Abiraterone Tablet 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, flecainide, 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. 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 pioglitazone and repaglinide (see Warnings and Precautions - Hypoglycemia).

Pregnancy, Breast-feeding and Fertility
Pregnancy
Abiraterone Tablet is not for use in women.
Abiraterone Tablet is contraindicated in women who are or may potentially be pregnant (see *Contraindications*).

There are no human data on the use of Abiraterone Tablet in pregnancy and Abiraterone Tablet 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.

Breast-feeding
Abiraterone Tablet 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 Tablet 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 Tablet, 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 Tablet 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 Tablet 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 Tablet, 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 mineralocorticoid excess*).

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

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

	Abiraterone Tablet 1000 mg daily with prednisone or prednisolone n=2659[b]		
System Organ Class Adverse Reaction	All grade%	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 failuree	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 Tablet 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 Tablet 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 Tablet. 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 Tablet, 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 Tablet. Ten patients who received Abiraterone Tablet 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 Tablet 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 Tablet, 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 Tablet. 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 Tablet). 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 Tablet 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 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 Tablet 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 acetatedecreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects
Abiraterone acetatedecreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists (or 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 3 clinical study of patients who failed prior chemotherapy with taxanes, 38% of patients treated with Abiraterone acetate, 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 acetate were not allowed to use spironolactone as spironolactone binds to the androgen receptor and may increase PSA levels.

Clinical studies
The efficacy of Abiraterone acetate was established in three randomised 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) mHNPC 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 (excluding lymph node disease) metastasis. In the active arm, Abiraterone acetate was administered at a dose of 1000 mg daily in combination with low dose prednisone or prednisolone 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 placebos for both Abiraterone acetate and prednisone.

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

Because changes in PSA serum concentration do not always predict clinical benefit in all studies patients were maintained on Abiraterone acetate 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=1199) the median age of enrolled patients was 67 years. The ECOG performance status was 0 or 1 for 97% of patients. Patients with uncontrolled hypertension, significant heart disease, or NYHA Class II or worse heart failure were excluded. Co- primary efficacy endpoints were overall survival (OS) 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 3011 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 by bone scan (according to modified PCWG2) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1).

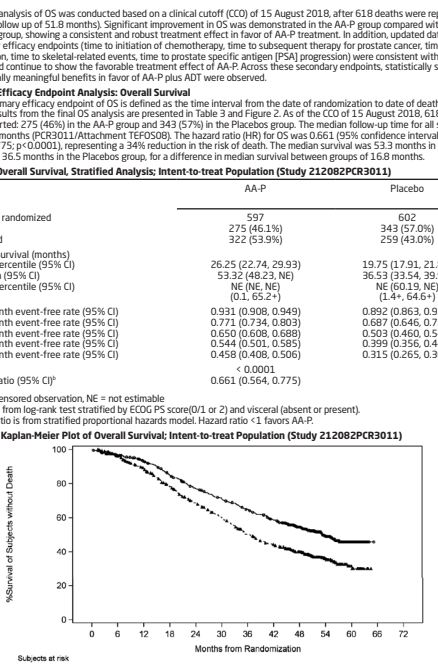
At the planned rPFS analysis there were 593 events; 239 (40.0%) of patients treated with Abiraterone acetate and 354 (58.8%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 2 and Figure 1).

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

	AA-P	Placebo
Subjects randomized	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
25th percentile (95% CI)	14.59 (11.47, 15.61)	7.43 (7.29, 10.58)
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
75th percentile (95% CI)	NE (NE, NE)	30.36 (29.24, 39.95)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
6-month event-free rate (95% CI)	0.941 (0.918, 0.957)	0.867 (0.836, 0.892)
12-month event-free rate (95% CI)	0.779 (0.742, 0.812)	0.611 (0.567, 0.652)
18-month event-free rate (95% CI)	0.702 (0.661, 0.739)	0.476 (0.431, 0.520)
24-month event-free rate (95% CI)	0.611 (0.565, 0.652)	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)	0.209 (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 (0/1 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 51.8 months). Significant improvement in OS was demonstrated in the AA-P group compared with the Placebos group, showing a consistent and robust treatment effect in favor of AA-P treatment. In addition, updated data for key secondary efficacy endpoints (time to initiation of chemotherapy, time to subsequent therapy for prostate cancer, time to pain progression, time to skeletal-related events, time to prostate specific antigen [PSA] progression) were consistent with earlier results and continue to show the favorable treatment effect of AA-P. Across these secondary endpoints, statistically significant and clinically meaningful benefits in favor of AA-P plus ADT were observed.

Primary Efficacy Endpoint Analysis: Overall Survival
The co-primary efficacy endpoint of OS is defined as the time interval from the date of randomization to date of death from any cause. Results from the final OS analysis are presented in Table 3 and Figure 2. As of the CCO of 15 August 2018, 618 deaths were reported: 275 (46%) in the AA-P group and 343 (57%) in the Placebos group. The median follow-up time for all subjects was 51.8 months (PCR3011/Attachment TEFOS08). The hazard ratio (HR) for OS was 0.661 (95% confidence interval [CI]: 0.564, 0.775; p<0.0001), representing a 34% reduction in the risk of death. The median survival was 53.3 months in the AA-P group and 36.5 months in the Placebos group, for a difference in median survival between groups of 16.8 months.

Table 3: Overall Survival, Stratified Analysis; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	275 (46.1%)	343 (57.0%)
Censored	322 (53.9%)	259 (43.0%)
Overall Survival (months)		
25th percentile (95% CI)	26.25 (22.74, 29.93)	19.75 (17.91, 21.85)
Median (95% CI)	53.32 (48.23, NE)	36.53 (33.54, 39.95)
75th percentile (95% CI)	NE (NE, NE)	NE (60.19, NE)
Range	(0.1, 65.2+)	(1.4+, 64.6+)
12-month event-free rate (95% CI)	0.931 (0.908, 0.949)	0.892 (0.863, 0.914)
24-month event-free rate (95% CI)	0.771 (0.734, 0.803)	0.687 (0.646, 0.723)
36-month event-free rate (95% CI)	0.650 (0.608, 0.688)	0.503 (0.460, 0.544)
48-month event-free rate (95% CI)	0.544 (0.501, 0.585)	0.399 (0.356, 0.441)
60-month event-free rate (95% CI)	0.458 (0.408, 0.506)	0.315 (0.265, 0.367)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.661 (0.564, 0.775)	

Note:+= censored observation, NE = not estimable
[a]p value is from 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 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study 212082PCR3011)

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 (ie, docetaxel, cabazitaxel, abiraterone acetate, enzalutamide, sipuleucel-T, and radium-223) is summarized for the final analysis in Table 5 and Figure 4. There were 29% of subjects in the AA-P group and 45% of subjects in the Placebos 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 29.6 months in the Placebos 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 60- month event-free rate was 60% for AA-P and 37% for Placebos.

Table 5: Time to life-extending Subsequent Therapy for Prostate Cancer-Stratified Analysis; Intent- to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	176 (29.5%)	273 (45.3%)
Censored	421 (70.5%)	329 (54.7%)
Time to Event (months)		
25th percentile (95% CI)	30.62 (26.61, 34.99)	14.85 (13.21, 16.66)
Median (95% CI)	NE (60.78, NE)	29.63 (25.86, 34.99)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1+, 64.2+)	(1.4+, 63.8+)
6-month event-free rate (95% CI)	0.988 (0.975, 0.994)	0.938 (0.915, 0.955)
12-month event-free rate (95% CI)	0.946 (0.924, 0.962)	0.822 (0.787, 0.852)
18-month event-free rate (95% CI)	0.888 (0.858, 0.912)

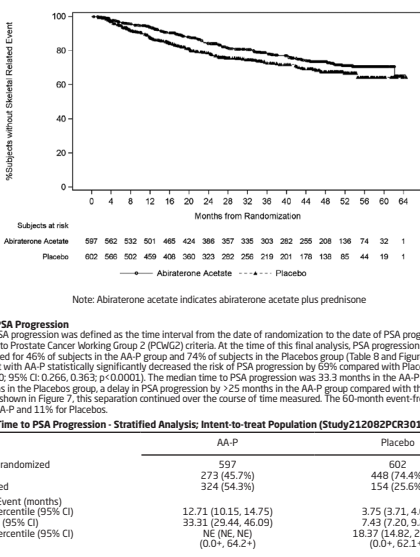
Time to Skeletal-related Event
Time to skeletal-related event was defined as the earliest of the following: clinical or pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. Updated information from the final analysis is presented for time to skeletal-related event in Table 7 and Figure 6. Skeletal-related events were reported for 22% of subjects in the AA-P group and 25% of subjects in the Placebos group. There was a 24% reduction in the risk of skeletal-related event (HR=0.759; 95% CI: 0.601, 0.960; p=0.0208). The 25th percentile time to skeletal-related event was 43.0 months for the AA-P group and 31.3 months for Placebos. The 60-month event-free rate was 71% for AA-P and 64% for Placebos.

Table 7: Time to Skeletal-Related Event - Stratified Analysis; Intent-to-treat Population (Study212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	133 (22.3%)	150 (24.9%)
Censored	464 (77.7%)	452 (75.1%)
Time to Event (months)		
25th percentile (95% CI)	43.04 (34.56, 53.52)	31.34 (23.29, 41.92)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1, 64.2+)	(0.8, 64.6+)
6-month event-free rate (95% CI)	0.965 (0.947, 0.977)	0.945 (0.924, 0.961)
12-month event-free rate (95% CI)	0.935 (0.911, 0.952)	0.877 (0.847, 0.902)
18-month event-free rate (95% CI)	0.892 (0.863, 0.915)	0.827 (0.792, 0.856)
24-month event-free rate (95% CI)	0.841 (0.807, 0.870)	0.786 (0.748, 0.819)
30-month event-free rate (95% CI)	0.807 (0.770, 0.839)	0.753 (0.712, 0.789)
36-month event-free rate (95% CI)	0.783 (0.743, 0.817)	0.728 (0.685, 0.767)
42-month event-free rate (95% CI)	0.753 (0.711, 0.790)	0.707 (0.662, 0.748)
48-month event-free rate (95% CI)	0.736 (0.692, 0.774)	0.674 (0.625, 0.718)
54-month event-free rate (95% CI)	0.706 (0.658, 0.748)	0.667 (0.616, 0.713)
60-month event-free rate (95% CI)	0.706 (0.658, 0.748)	0.643 (0.584, 0.697)
p value[a]	0.0208	
Hazard ratio (95% CI)[b]	0.759 (0.601, 0.960)	

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 Skeletal-related event; Intent-to-treat Population (Study212082PCR3011)



Note: Abiraterone acetate indicates abiraterone acetate plus prednisone

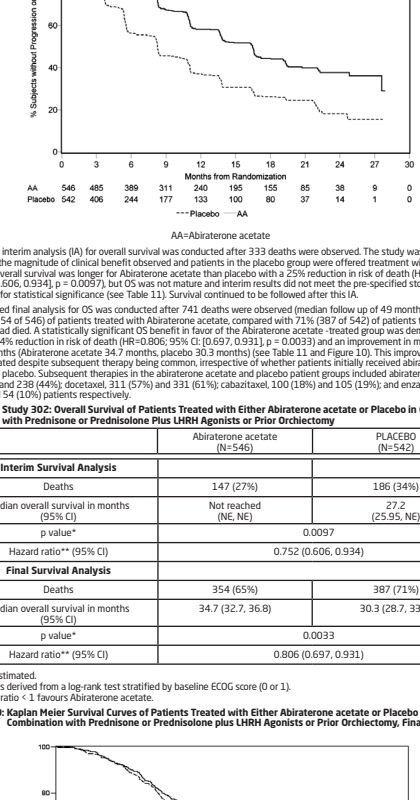
Time to PSA Progression
Time to PSA progression was defined as the time interval from the date of randomization to the date of PSA progression, according to Prostate Cancer Working Group 2 (PCWG2) criteria. At the time of this final analysis, PSA progression was documented for 46% of subjects in the AA-P group and 74% of subjects in the Placebos group (Table 8 and Figure 7). Treatment with AA-P statistically significantly decreased the risk of PSA progression by 69% compared with Placebos (HR=0.310; 95% CI: 0.266, 0.363; p<0.0001). The median time to PSA progression was 33.3 months in the AA-P group and 7.4 months in the Placebos group, a delay in PSA progression by >25 months in the AA-P group compared with the Placebos group. As shown in Figure 7, this separation continued over the course of time measured. The 60-month event-free rate was 42% for AA-P and 11% for Placebos.

Table 8: Time to PSA Progression - Stratified Analysis; Intent-to-treat Population (Study212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	273 (45.7%)	448 (74.4%)
Censored	324 (54.3%)	154 (25.6%)
Time to Event (months)		
25th percentile (95% CI)	12.71 (10.15, 14.75)	3.75 (3.71, 4.63)
Median (95% CI)	33.31 (29.44, 46.09)	7.43 (7.20, 9.20)
75th percentile (95% CI)	NE (NE, NE)	18.37 (14.82, 20.30)
Range	(0.0+, 64.2+)	(0.0+, 62.1+)
6-month event-free rate (95% CI)	0.885 (0.856, 0.909)	0.616 (0.574, 0.656)
12-month event-free rate (95% CI)	0.751 (0.712, 0.785)	0.356 (0.315, 0.397)
18-month event-free rate (95% CI)	0.665 (0.623, 0.704)	0.254 (0.217, 0.293)
24-month event-free rate (95% CI)	0.577 (0.532, 0.618)	0.184 (0.151, 0.220)
30-month event-free rate (95% CI)	0.527 (0.481, 0.570)	0.140 (0.110, 0.174)
36-month event-free rate (95% CI)	0.489 (0.443, 0.534)	0.121 (0.092, 0.153)
42-month event-free rate (95% CI)	0.468 (0.422, 0.513)	0.112 (0.084, 0.144)
48-month event-free rate (95% CI)	0.453 (0.406, 0.498)	0.109 (0.081, 0.141)
54-month event-free rate (95% CI)	0.430 (0.382, 0.478)	0.109 (0.081, 0.141)
60-month event-free rate (95% CI)	0.423 (0.373, 0.472)	0.109 (0.081, 0.141)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.310 (0.266, 0.363)	

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 PSA Progression; Intent-to-treat Population (Study 212082PCR3011)



Note: Abiraterone acetate indicates abiraterone acetate plus prednisone

Study 302 (asymptomatic or mildly symptomatic patients who did not receive prior chemotherapy)
This study enrolled chemotherapy naive patients who were asymptomatic or mildly symptomatic and for whom chemotherapy was not yet clinically indicated. A score of 0-1 on Brief Pain Inventory-Short Form (BPI-SF) worst pain in last 24 hours was considered asymptomatic, and a score of 2-3 was considered mildly symptomatic.

In Study 302, (n=1088) the median age of enrolled patients was 71 years for patients treated with Abiraterone acetate plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The number of patients treated with Abiraterone acetate by racial group was Caucasian 520 (95.4%), Black 15 (2.8%), Asian 4 (0.7%) and other 6 (1.1%). The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. Patients with visceral metastases were excluded. Fifty percent of patients had only bone metastases, an additional 31% of patients had bone and soft tissue or lymph node metastases and 19% of patients had only soft tissue or lymph node metastases. Patients with visceral metastases were excluded. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours). In addition to the co-primary endpoint measures, benefit was also assessed using time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥ 1 point and time to PSA progression based on Prostate Cancer Working Group-2 (PCWG2) criteria. Study treatments were discontinued at the time of unequivocal clinical progression. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

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 (28%) of patients treated with Abiraterone acetate 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 Either Abiraterone acetate or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Agonists or Prior Orchiectomy

	Abiraterone acetate (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66, NE)	8.3 (8.12, 8.54)
p value*	<0.0001	
Hazard ratio** (95% CI)	0.425 (0.347, 0.522)	

NE=Not Estimated.
* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
** Hazard ratio (HR) < 1 favours Abiraterone acetate.

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

AA=Abiraterone acetate

However, subject data continued 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. Treatment with abiraterone acetate decreased the risk of radiographic progression or death by 47% compared with placebo (HR=0.530; 95% CI: [0.451, 0.623], 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 either Abiraterone acetate or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	Abiraterone acetate (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50%)	336 (62%)
Median rPFS in months (95% CI)	16.5 (13.80, 16.79)	8.3 (8.05, 9.43)
p-value*	< 0.0001	
Hazard ratio** (95% CI)	0.530 (0.451, 0.623)	

* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
** Hazard ratio < 1 favours Abiraterone acetate.

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

AA=Abiraterone acetate

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 and patients in the placebo group were offered treatment with Abiraterone acetate. Overall survival was longer for Abiraterone acetate than placebo with a 25% reduction in risk of death (HR = 0.752; 95% CI: [0.606, 0.934], p = 0.0097), but OS was not mature and interim results did not meet the pre-specified stopping boundary for statistical significance (see Table 11). 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 (354 of 546) of patients treated with Abiraterone acetate, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favor of the Abiraterone acetate -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 acetate 34.7 months, placebo 30.3 months) (see Table 11 and Figure 10). This improvement was demonstrated despite subsequent therapy 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, 69 (13%) and 238 (44%); docetaxel, 311 (57%) and 331 (61%); cabazitaxel, 100 (18%) and 105 (19%); and enzalutamide 87 (16%) and 54 (10%) patients respectively.

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

	Abiraterone acetate (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 (25.95, NE)
p value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606, 0.934)	
Final Survival Analysis		
Deaths	354 (65%)	387 (71%)
Median overall survival in months (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
p value*	0.0033	
Hazard ratio** (95% CI)	0.806 (0.697, 0.931)	

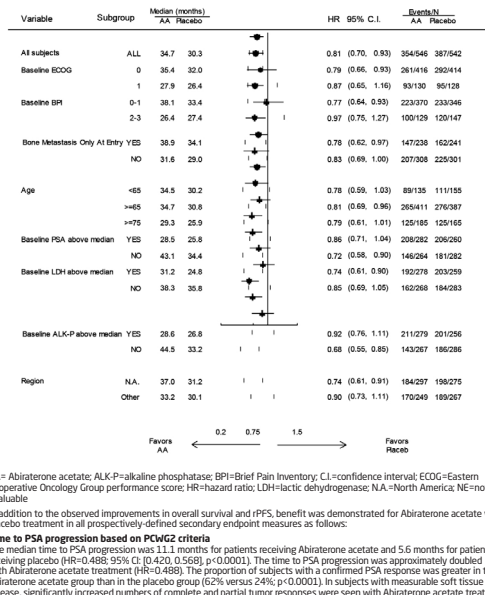
NE=Not Estimated.
* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
** Hazard ratio < 1 favours Abiraterone acetate.

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

AA= Abiraterone acetate

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

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



AA= Abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; CI.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

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

Time to PSA progression based on PCWG2 criteria
The median time to PSA progression was 11.1 months for patients receiving Abiraterone acetate and 5.6 months for patients receiving placebo (HR=0.488; 95% CI: [0.420, 0.568], p<0.0001). The time to PSA progression was approximately doubled with Abiraterone acetate treatment (HR=0.488). The proportion of subjects with a confirmed PSA response was greater in the Abiraterone acetate group than in 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 acetate 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 acetate 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 acetate and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], p<0.0001).

Time to deterioration in ECOG performance score by ≥ 1 point
The median time to deterioration in ECOG performance score by ≥ 1 point was 12.3 months for patients receiving Abiraterone acetate and 10.9 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 acetate 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 36% in the Abiraterone acetate group and 16% in the placebo group (p<0.0001).

Pain
Treatment with Abiraterone acetate significantly reduced the risk of average pain intensity progression by 18% compared with placebo (p=0.0490). The median time to progression was 26.7 months in the Abiraterone acetate group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score)
Treatment with Abiraterone acetate decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (p=0.0028). The median time to degradation in FACT-P (Total Score) was 12.7 months in the Abiraterone acetate group and 8.3 months in the placebo group.

Study 301 (patients who had received prior chemotherapy)
Study 301 enrolled patients who had received prior 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 for prostate cancer were excluded from this study. The primary efficacy endpoint was overall survival.

The median age of enrolled patients was 69 years (range 39-95). The number of patients treated with Abiraterone acetate 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 acetate.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with Abiraterone acetate compared with 55% (219 of 398) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients treated with Abiraterone acetate (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 3).

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

	Abiraterone acetate (N=797)	PLACEBO (N=398)
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value a	<0.0001	
Hazard ratio (95% CI) b	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) b	0.740 (0.638, 0.859)	

[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 is derived from a stratified proportional hazards model. Hazard ratio < 1 favours Abiraterone acetate

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with Abiraterone acetate remained alive, compared with the proportion of patients treated with placebo (see Figure 12).

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

AA= Abiraterone acetate

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

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

AA= Abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; CI.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

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

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

The median time to PSA progression was 10.2 months for patients treated with Abiraterone acetate and 6.6 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 acetate and 3.6 months for patients who received placebo (HR=0.673; 95% CI: [0.585; 0.776], p < 0.0001).

Pain
The proportion of patients with pain palliation was statistically significantly higher in the Abiraterone acetate 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 analysed (N=512) for pain palliation.

A lower proportion of patients treated with Abiraterone acetate had pain progression compared to patients taking placebo at 6 (22% versus 28%), 12 (30% versus 38%) and 18 months (35% versus 46%). Pain progression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the previous 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 acetate group, versus 4.7 months in the placebo group.

Skeletal-related events
A lower proportion of patients in the Abiraterone acetate group had skeletal-related events compared with the placebo group at 6 months (18% versus 28%), 12 months (30% versus 40%), and 18 months (35% versus 40%). The time to first skeletal-related event at the 25th percentile in the Abiraterone acetate group was twice that of the control group at 9.9 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 up to a 10-fold (AUC) and up to a 17-fold (C_{max}) 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 Tablet with meals has the potential to result in highly variable exposures. Therefore, Abiraterone Tablet must not be taken with food. Abiraterone Tablet 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 Tablet 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 Tablet 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 (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 Tablet 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
ABIRATERONE-TEVA FC tablet 250 mg contain the following excipients:

Tablet core:
Microcrystalline Cellulose, Croscarmellose Sodium, Lactose Monohydrate, Povidone, Sodium Lauryl Sulfate, Colloidal Silicon Dioxide, Magnesium Stearate.

Film coat:
Opadry II 85F18378 White: Polyvinyl Alcohol (part hydrolyzed), Titanium Dioxide, Polyethylene Glycol 3350, Talc.

Incompatibilities
Not applicable.

Shelf Life
Observe expiry date on the outer pack.

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

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

Nature and Contents of Container
ABIRATERONE-TEVA FC tablet 250 mg are available in round white HDPE bottles fitted with a polypropylene cap containing 120 tablets with oxygen absorbers (PharmaKeep Oxygen). Each pack contains one bottle.

Instructions for Use and Handling and Disposal
Any unused product or waste material should be disposed of in accordance with local requirements.

MANUFACTURED BY
TEVA Pharmaceutical Industries Ltd.
18 Eli Hurvitz Street
Industrial Zone, Kfar-Saba
ISRAEL

DATE OF REVISION OF TEXT
June 2021