ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 250 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of abiraterone acetate equivalent to 223 mg of abiraterone.

Excipients with known effect
Each tablet contains 198.65 mg of lactose monohydrate and 6.8 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White to off-white oval tablets (15.9 mm long x 9.5 mm wide), debossed with AA250 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYTIGA 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) (see section 5.1)
- 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 section 5.1)
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

4.2 Posology and method of administration

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology
The recommended dose is 1 000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food (see "Method of administration" below). Taking the tablets with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Dosage of prednisone or prednisolone
For mHSPC, ZYTIGA is used with 5 mg prednisone or prednisolone daily.

For mCRPC, ZYTIGA is used with 10 mg prednisone or prednisolone daily.

Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

Recommended monitoring
Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure

should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see section 4.4).

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

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with ZYTIGA 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 ZYTIGA, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatotoxicity
For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately (see section 4.4). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two 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.

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

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

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 section 5.2). 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. The use of ZYTIGA should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). ZYTIGA should not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see section 4.4).

Paediatric population
There is no relevant use of ZYTIGA in the paediatric population.

Method of administration
ZYTIGA is for oral use.
The tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. ZYTIGA tablets must be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may potentially be pregnant (see section 4.6).

- Severe hepatic impairment [Child-Pugh Class C (see sections 4.2, 4.4 and 5.2)].
- ZYTIGA with prednisone or prednisolone is contraindicated in combination with Ra-223.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess
ZYTIGA may cause hypertension, hypokalaemia and fluid retention (see section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see section 5.1). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

ZYTIGA should be used with caution in patients with a history of cardiovascular disease. The Phase 3 studies conducted with ZYTIGA 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 Class (NYHA) 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%. In studies 3011 and 302, patients with atrial fibrillation, or other cardiac arrhythmia requiring medical therapy were excluded. Safety in patients with left ventricular ejection fraction (LVEF) < 50% or NYHA Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in studies 3011 and 302) was not established (see sections 4.8 and 5.1).

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 ZYTIGA, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with ZYTIGA treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function (see section 4.2).

Hepatotoxicity and hepatic impairment
Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the ULN, treatment should be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see section 4.2).

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

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

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The use of ZYTIGA should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). ZYTIGA should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see section 4.8).

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 ZYTIGA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

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

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

Hypoglycaemia
Cases of hypoglycaemia have been reported when ZYTIGA plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be monitored in patients with diabetes.

Use with chemotherapy
The safety and efficacy of concomitant use of ZYTIGA with cytotoxic chemotherapy has not been established (see section 5.1).

Intolerance to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine. This medicinal product contains 27.2 mg (1.18 mmol) sodium per dose of four tablets, equivalent to 1.36% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

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

Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223
Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased

mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of food on abiraterone
Administration with food significantly increases the absorption of abiraterone. The efficacy and safety when given with food have not been established therefore this medicinal product must not be taken with food (see sections 4.2 and 5.2).

Interactions with other medicinal products
Potential for other medicinal products to affect abiraterone exposures
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 1 000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

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

Potential to affect exposures to other medicinal products
Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.
In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised 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 medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and 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 1 000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (see section 4.4).

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Use with products known to prolong QT interval
Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ZYTIGA with medicinal products known to prolong the QT interval or medicinal

products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ZYTIGA is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of ZYTIGA in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females
It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
ZYTIGA is not for use in women and is contraindicated in women who are or may potentially be pregnant (see section 4.3 and 5.3).

Breast-feeding
ZYTIGA is not for use in women.

Fertility
Abiraterone acetate affected fertility in male and female rats, but these effects were fully reversible (see section 5.3).

4.7 Effects on ability to drive and use machines

ZYTIGA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

ZYTIGA may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo: hypokalaemia 18% vs. 8%, hypertension 22% vs. 16% and fluid retention (peripheral oedema) 23% vs. 17%, respectively. In patients treated with abiraterone acetate versus patients treated with placebo: CTCAE (version 4.0) Grades 3 and 4 hypokalaemia were observed in 6% versus 1%, CTCAE (version 4.0) Grades 3 and 4 hypertension were observed in 7% versus 5%, and fluid retention (peripheral oedema) Grades 3 and 4 were observed in 1% versus 1% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

Tabulated list of adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1 000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (frequency cannot be estimated from the available data).

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

Table 1: Adverse reactions identified in clinical studies and post-marketing

System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Immune system disorders	not known: anaphylactic reactions
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased[b] rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash
Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

** Fractures includes osteoporosis and all fractures with the exception of pathological fractures

[a] Spontaneous reports from post-marketing experience

[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

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

A higher incidence of hypertension and hypokalaemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8% and 20.2% in studies 301 and 302, respectively. Hypokalaemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2% and 14.9% in 301 and 302, respectively).

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

Description of selected adverse reactions

Cardiovascular reactions

The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2.6% vs. 2.0%, tachycardia 1.9% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with ZYTIGA. Ten patients who received ZYTIGA were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 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 section 4.2). 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of overdose with ZYTIGA is limited.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action
Abiraterone acetate (ZYTIGA) 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 section 4.4).

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 ZYTIGA decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects
ZYTIGA 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. 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.

Clinical efficacy and safety
Efficacy was established in three randomised placebo-controlled multicentre Phase 3 clinical studies (studies 3011, 302 and 301) of patients with mHSPC and mCRPC. Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomisation) 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 (excluding lymph node disease) metastasis. In the active arm, ZYTIGA was administered at a dose of 1 000 mg daily in combination with low dose 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 placebos for both ZYTIGA and prednisone. Study 302 enrolled docetaxel naïve 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, ZYTIGA 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.

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in all studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

In all studies spironolactone use was not allowed as spironolactone binds to the androgen receptor and may increase PSA levels.

Study 3011 (patients with newly diagnosed high risk mHSPC)
In Study 3011, (n=1199) the median age of enrolled patients was 67 years. The number of patients treated with ZYTIGA by racial group was Caucasian 832 (69.4%), Asian 246 (20.5%), Black or African American 25 (2.1%), other 80 (6.7%), unknown/not reported 13 (1.1%), and American Indian or Alaska Native 3 (0.3%). The ECOG performance status was 0 or 1 for 97% of patients. Patients with known brain metastasis, uncontrolled hypertension, significant heart disease, or NYHA Class II-IV heart failure were excluded. Patients that were treated with prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer were excluded with the exception of up to 3 months of ADT or 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease. 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. 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 randomisation 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).

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)

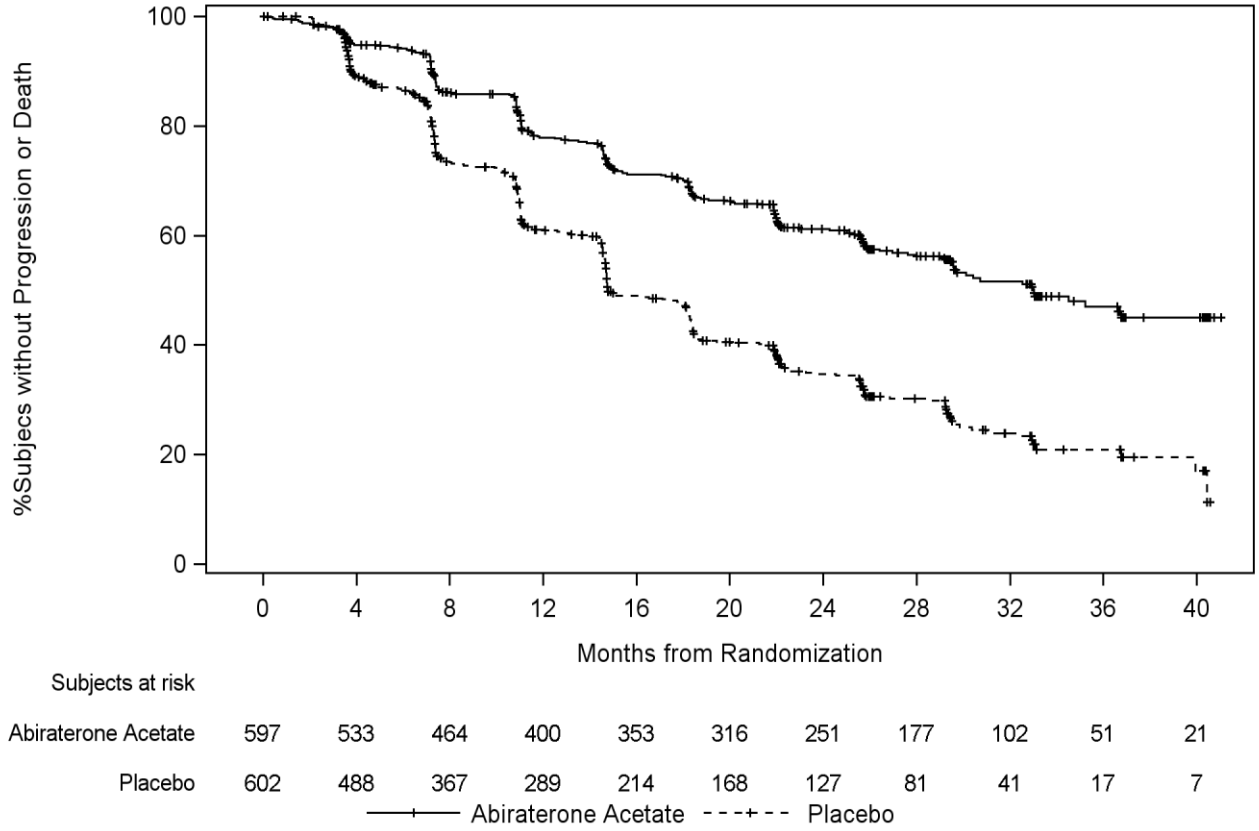
	AA-P	**Placebo**
Subjects randomised	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

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 lesion (absent or present).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours AA-P.

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



A statistically significant improvement in OS in favour of AA-P plus ADT was observed with a 34% reduction in the risk of death compared to Placebo plus ADT (HR=0.66; 95% CI: 0.56, 0.78; p<0.0001), (see Table 3 and Figure 2).

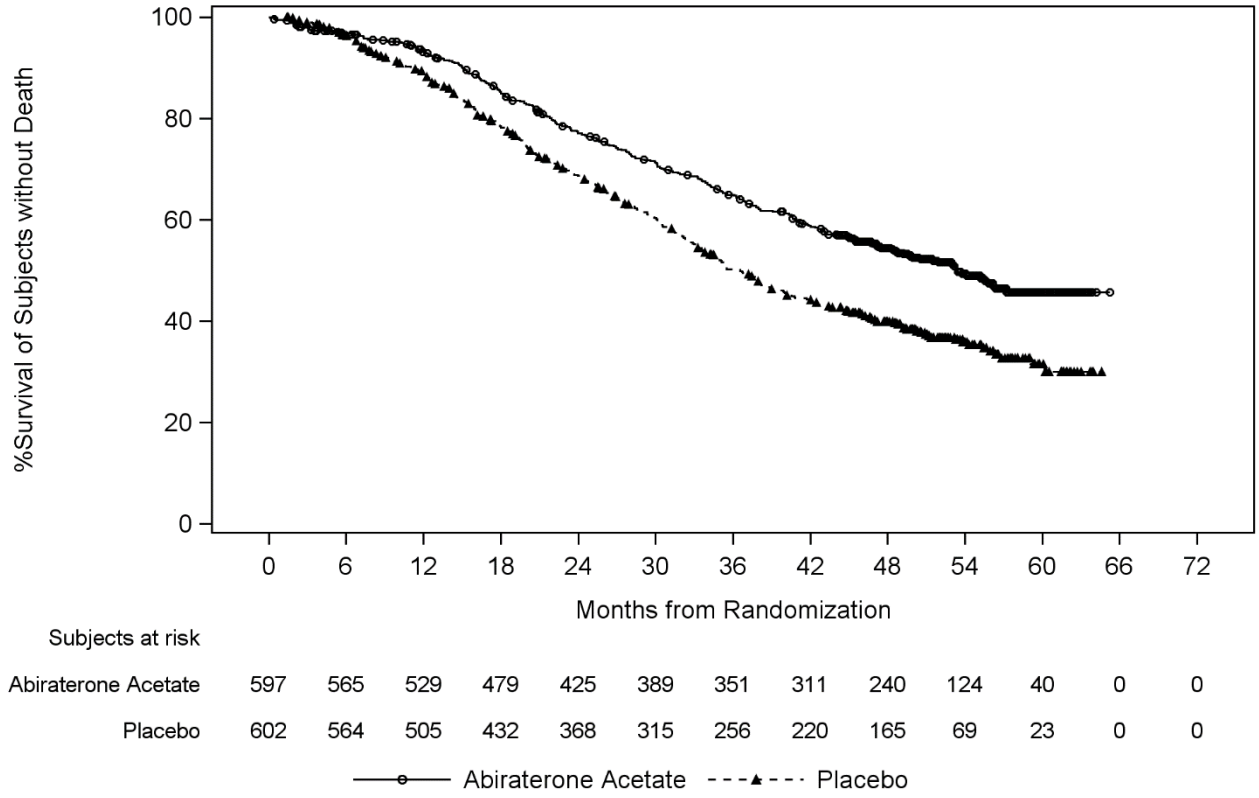
Table 3: Overall Survival of Patients Treated with Either ZYTIGA or Placebos in Study PCR3011 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA with Prednisone (N=597)	Placebos (N=602)
Deaths (%)	275 (46%)	343 (57%)
Median survival (months)	53.3	36.5
(95% CI)	(48.2, NE)	(33.5, 40.0)
Hazard ratio (95% CI)[1]	0.66 (0.56, 0.78)	

NE=Not estimable

[1] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favours ZYTIGA with prednisone.

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in Study PCR3011 Analysis



Subgroup analyses consistently favour treatment with ZYTIGA. The treatment effect of AA-P on rPFS and OS across the pre-specified subgroups was favourable and consistent with the overall study population, except for the subgroup of ECOG score of 2 where no trend towards benefit was observed, however the small sample size (n=40) limits drawing any meaningful conclusion.

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for ZYTIGA vs. placebo treatment in all prospectively-defined secondary endpoints.

Study 302 (chemotherapy naïve patients)
This study enrolled chemotherapy naïve 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 = 1 088) the median age of enrolled patients was 71 years for patients treated with ZYTIGA plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The number of patients treated with ZYTIGA by racial group was Caucasian 520 (95.4%), Black 15 (2.8%), Asian 4 (0.7%) and other 6 (1.1%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. 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). 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 (rPFS) was assessed with the use of sequential imaging studies as defined by PCWG2 criteria (for bone lesions) and modified Response Evaluation Criteria In Solid

Tumours (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilised centrally-reviewed radiographic assessment of progression.

At the planned rPFS analysis there were 401 events, 150 (28%) 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 4 and Figure 3).

Table 4: Study 302: Radiographic progression-free survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

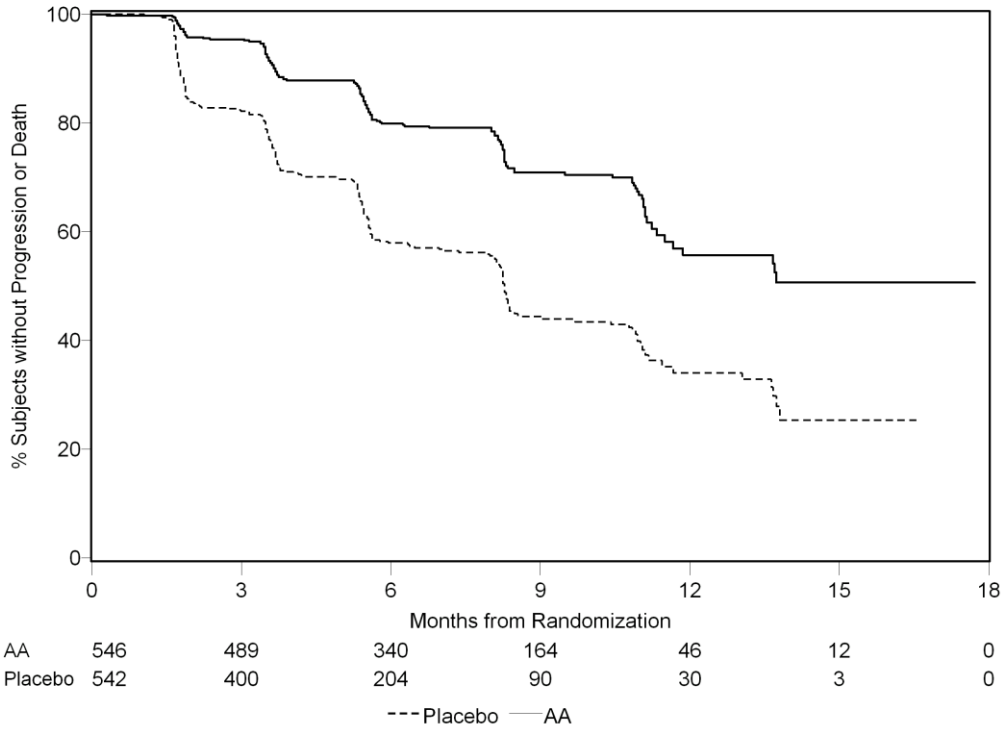
	ZYTIGA (N = 546)	**Placebo (N = 542)**
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66; NE)	8.3 (8.12; 8.54)
p-value*	< 0.0001	
Hazard ratio** (95% CI)	0.425 (0.347; 0.522)	

NE = Not estimated

* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)

** Hazard ratio < 1 favours ZYTIGA

Figure 3: Kaplan Meier curves of radiographic progression-free survival in patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = ZYTIGA

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 5 and Figure 4.

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

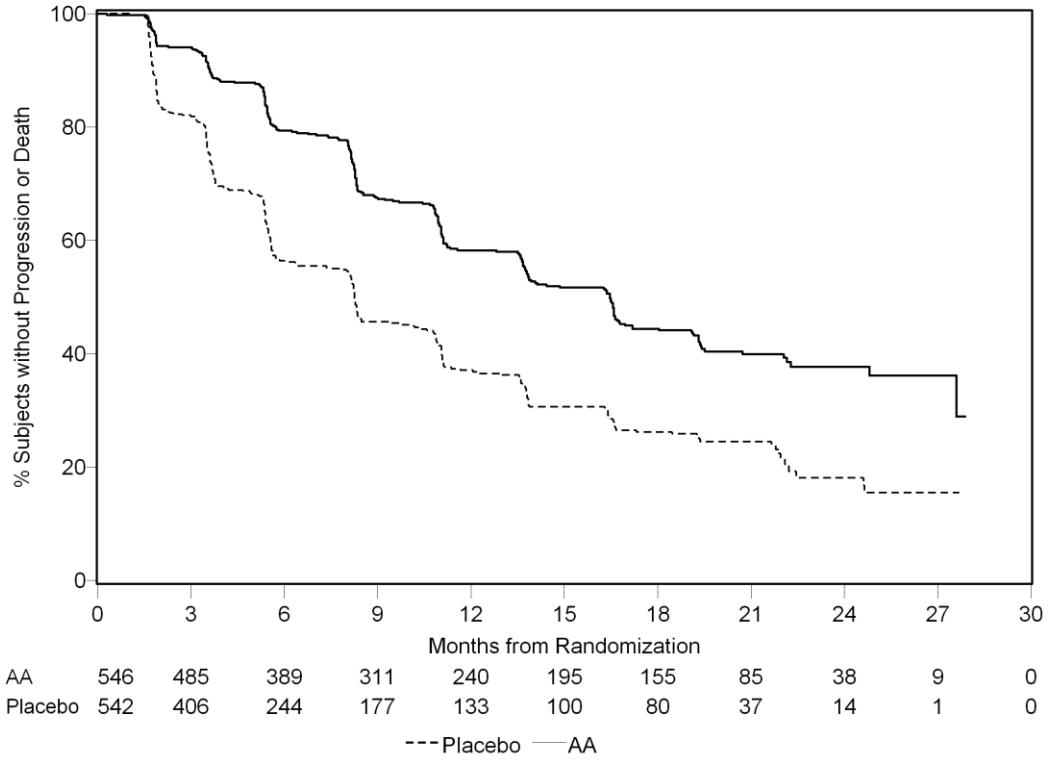
decreased the risk of radiographic progression or death by 47% compared with placebo (HR = 0.530; 95% CI: [0.451; 0.623], p < 0.0001). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

Table 5: Study 302: Radiographic progression-free survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	ZYTIGA (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 ZYTIGA

Figure 4: Kaplan Meier curves of radiographic progression-free survival in patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)



AA = ZYTIGA

A planned interim analysis (IA) for OS 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 ZYTIGA. Overall survival was longer for ZYTIGA 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 4). 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 ZYTIGA, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favour of the ZYTIGA-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 (ZYTIGA 34.7 months, placebo 30.3 months) (see Table 6 and Figure 5). This improvement was demonstrated even though 44% of patients in the placebo arm received ZYTIGA as subsequent therapy.

Table 6: Study 302: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

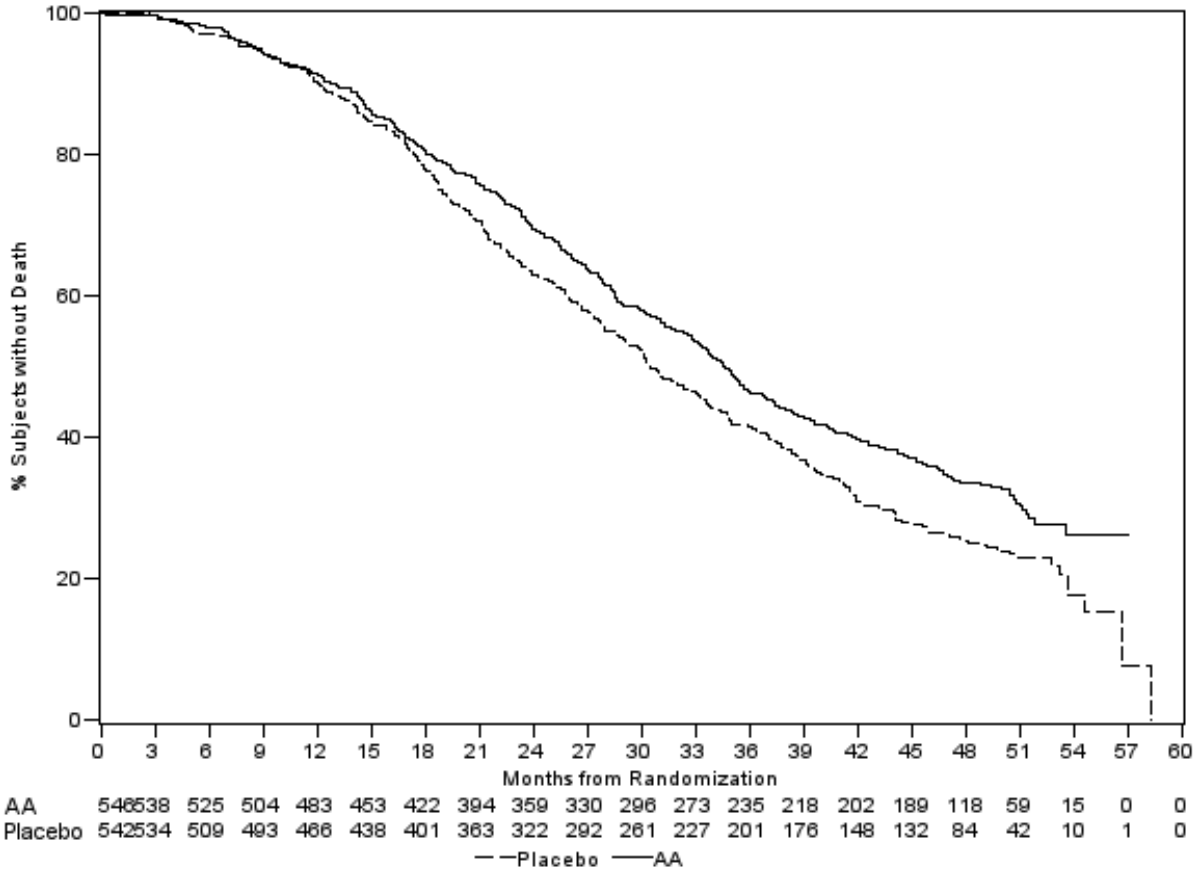
	ZYTIGA (N = 546)	**Placebo (N = 542)**
Interim survival analysis		
Deaths (%)	147 (27%)	186 (34%)
Median survival (months) (95% CI)	Not reached (NE; NE)	27.2 (25.95; NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606; 0.934)	
Final survival analysis		
Deaths	354 (65%)	387 (71%)
Median overall 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 ZYTIGA

Figure 5: Kaplan Meier survival curves of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy, final analysis



AA = ZYTIGA

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for ZYTIGA vs. placebo treatment in all 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 ZYTIGA 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 ZYTIGA treatment (HR = 0.488). The proportion of subjects with a confirmed PSA response was greater in the ZYTIGA group than in the placebo group (62% vs. 24%; $p < 0.0001$). In subjects with measurable soft tissue disease, significantly increased numbers of complete and partial tumour responses were seen with ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 favour of ZYTIGA 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 ZYTIGA group and 16% in the placebo group ($p < 0.0001$).

Pain: Treatment with ZYTIGA 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 ZYTIGA group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score): Treatment with ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 ZYTIGA.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with ZYTIGA 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 ZYTIGA (see Table 7).

Table 7: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

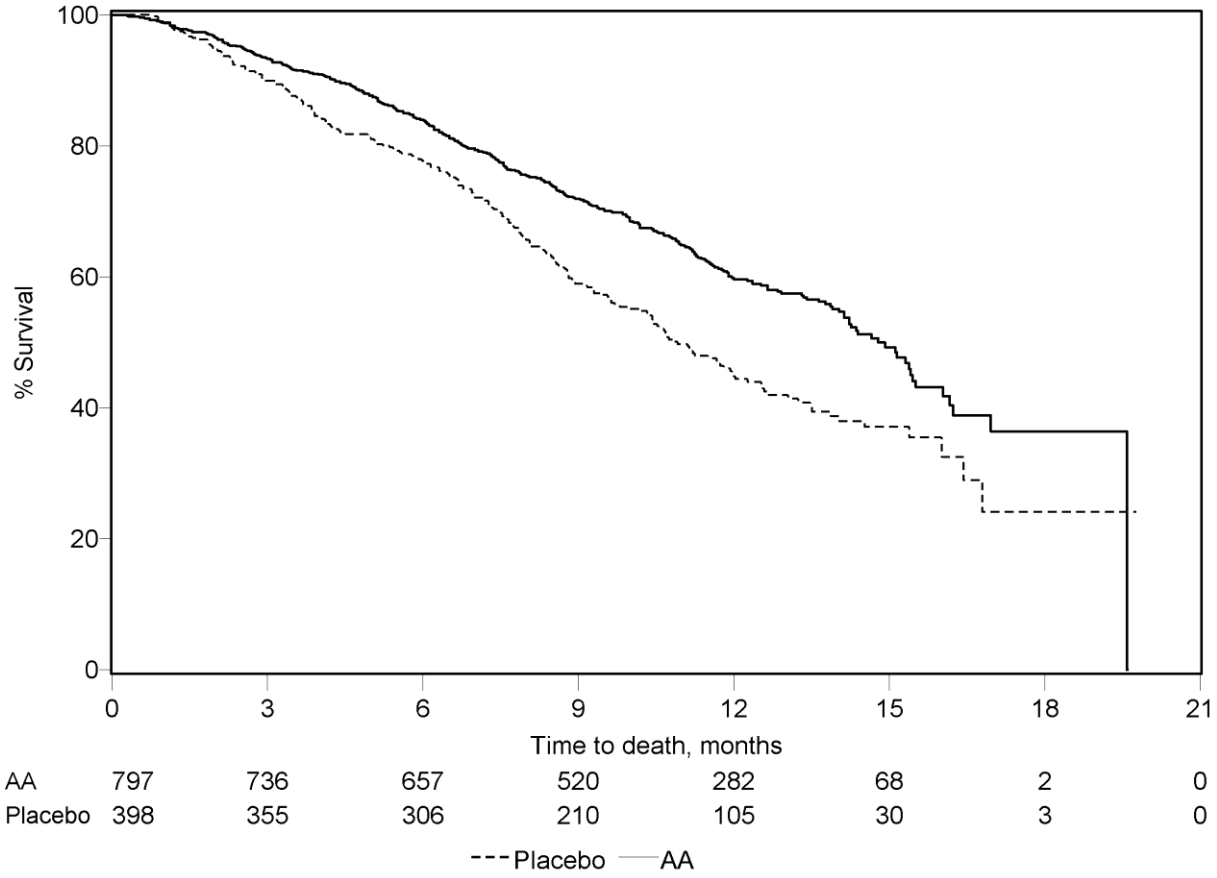
	ZYTIGA (N = 797)	**Placebo (N = 398)**
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1; 15.4)	10.9 (10.2; 12.0)
p-value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.646 (0.543; 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median 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 ZYTIGA

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with ZYTIGA remained alive, compared with the proportion of patients treated with placebo (see Figure 6).

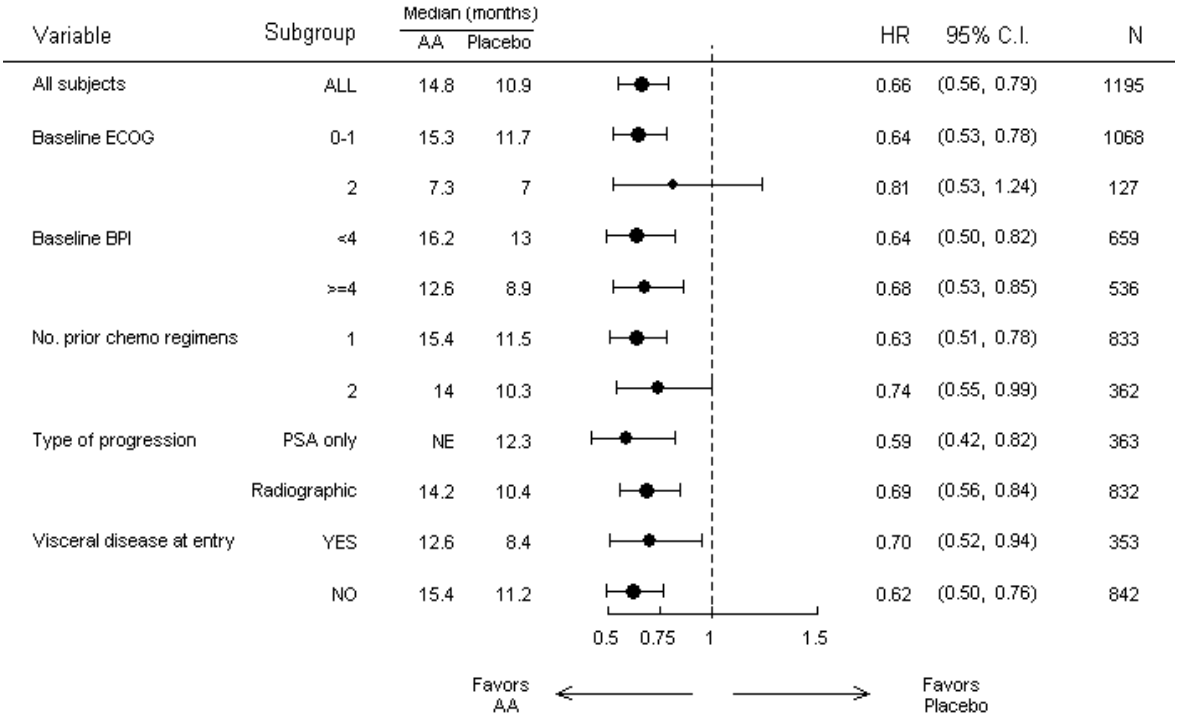
Figure 6: Kaplan Meier survival curves of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = ZYTIGA

Subgroup survival analyses showed a consistent survival benefit for treatment with ZYTIGA (see Figure 7).

Figure 7: Overall survival by subgroup: hazard ratio and 95% confidence interval



AA = ZYTIGA; 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 ZYTIGA and were statistically significant after adjusting for multiple testing as follows:

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

The median time to PSA progression was 10.2 months for patients treated with ZYTIGA 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 ZYTIGA 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 ZYTIGA group than in the placebo group (44% vs. 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 ZYTIGA had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 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 ZYTIGA group, versus 4.7 months in the placebo group.

Skeletal-related events
A lower proportion of patients in the ZYTIGA group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs. 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the ZYTIGA 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with ZYTIGA in all subsets of the paediatric population in advanced prostate cancer. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone has 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 section 5.1).

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 ZYTIGA with meals has the potential to result in highly variable exposures. Therefore, ZYTIGA must not be taken with food. ZYTIGA tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. The tablets must be swallowed whole with water (see section 4.2).

Distribution
The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5 630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation
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).

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.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n = 8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The AUC to abiraterone increased by approximately 600% and the fraction of free drug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment. The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 4.4). abiraterone acetate should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 4.4).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see sections 4.2 and 4.4).

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 section 4.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

5.3 Preclinical safety data

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.

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 foetal 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.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. 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.

Environmental risk assessment (ERA)
The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Povidone (K29/K32)
Colloidal anhydrous silica
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Round white HDPE bottles fitted with a polypropylene child-resistant closure containing 120 tablets. Each pack contains one bottle.

6.6 Special precautions for disposal and other handling

Based on its mechanism of action, this medicinal product may harm a developing foetus; therefore, women who are pregnant or may be pregnant should not handle it without protection, e.g., gloves.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment (see section 5.3).

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 2011

Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of abiraterone acetate equivalent to 446 mg of abiraterone.

Excipients with known effect
Each film-coated tablet contains 253.2 mg of lactose monohydrate and 13.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Purple, oval-shaped, film-coated tablets (20 mm long by 10 mm wide), debossed with "AA" on one side and "500" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYTIGA 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) (see section 5.1)
- 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 section 5.1)
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

4.2 Posology and method of administration

This medicinal product should be prescribed by an appropriate healthcare professional.

Posology
The recommended dose is 1 000 mg (two 500 mg tablets) as a single daily dose that must not be taken with food (see "Method of administration" below). Taking the tablets with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Dosage of prednisone or prednisolone
For mHSPC, ZYTIGA is used with 5 mg prednisone or prednisolone daily.

For mCRPC, ZYTIGA is used with 10 mg prednisone or prednisolone daily.

Medical castration with luteinising hormone releasing hormone (LHRH) analogue should be continued during treatment in patients not surgically castrated.

Recommended monitoring
Serum transaminases should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly. However, patients with a significant risk for congestive heart failure

should be monitored every 2 weeks for the first three months of treatment and monthly thereafter (see section 4.4).

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

For patients who develop Grade ≥ 3 toxicities including hypertension, hypokalaemia, oedema and other non-mineralocorticoid toxicities, treatment should be withheld and appropriate medical management should be instituted. Treatment with ZYTIGA 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 ZYTIGA, prednisone or prednisolone, treatment should be resumed the following day with the usual daily dose.

Hepatotoxicity
For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]), treatment should be withheld immediately (see section 4.4). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (one tablet) 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.

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

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

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 section 5.2). 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. The use of ZYTIGA should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). ZYTIGA should not be used in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with renal impairment (see section 5.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (see section 4.4).

Paediatric population
There is no relevant use of ZYTIGA in the paediatric population.

Method of administration
ZYTIGA is for oral use.
The tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. ZYTIGA tablets must be swallowed whole with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are or may potentially be pregnant (see section 4.6).

- Severe hepatic impairment [Child-Pugh Class C (see sections 4.2, 4.4 and 5.2)].
- ZYTIGA with prednisone or prednisolone is contraindicated in combination with Ra-223.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess
ZYTIGA may cause hypertension, hypokalaemia and fluid retention (see section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see section 5.1). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment).

ZYTIGA should be used with caution in patients with a history of cardiovascular disease. The Phase 3 studies conducted with ZYTIGA 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 Class (NYHA) 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%. In studies 3011 and 302, patients with atrial fibrillation, or other cardiac arrhythmia requiring medical therapy were excluded. Safety in patients with left ventricular ejection fraction (LVEF) < 50% or NYHA Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in studies 3011 and 302) was not established (see sections 4.8 and 5.1).

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 ZYTIGA, cardiac failure should be treated and cardiac function optimised. Hypertension, hypokalaemia and fluid retention should be corrected and controlled. During treatment, blood pressure, serum potassium, fluid retention (weight gain, peripheral oedema), and other signs and symptoms of congestive heart failure should be monitored every 2 weeks for 3 months, then monthly thereafter and abnormalities corrected. QT prolongation has been observed in patients experiencing hypokalaemia in association with ZYTIGA treatment. Assess cardiac function as clinically indicated, institute appropriate management and consider discontinuation of this treatment if there is a clinically significant decrease in cardiac function (see section 4.2).

Hepatotoxicity and hepatic impairment
Marked increases in liver enzymes leading to treatment discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the ULN, treatment should be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (see section 4.2).

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

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

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). The use of ZYTIGA should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). ZYTIGA should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see section 4.8).

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 ZYTIGA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see information above).

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

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

Hypoglycaemia
Cases of hypoglycaemia have been reported when ZYTIGA plus prednisone/prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see section 4.5); therefore, blood sugar should be monitored in patients with diabetes.

Use with chemotherapy
The safety and efficacy of concomitant use of ZYTIGA with cytotoxic chemotherapy has not been established (see section 5.1).

Intolerance to excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
This medicinal product contains 27 mg (1.17 mmol) sodium per dose of two tablets, equivalent to 1.35% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

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

Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure to abiraterone (see section 4.5).

Combination of abiraterone and prednisone/prednisolone with Ra-223
Treatment with abiraterone and prednisone/prednisolone in combination with Ra-223 is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased

mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical trials.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of food on abiraterone
Administration with food significantly increases the absorption of abiraterone. The efficacy and safety when given with food have not been established therefore this medicinal product must not be taken with food (see sections 4.2 and 5.2).

Interactions with other medicinal products
Potential for other medicinal products to affect abiraterone exposures
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 1 000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [*Hypericum perforatum*]) during treatment are to be avoided, unless there is no therapeutic alternative.

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

Potential to affect exposures to other medicinal products
Abiraterone is an inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8.
In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when administering with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised 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 medicinal products requiring CYP2D6 to form their active analgesic metabolites).

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and 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 1 000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (see section 4.4).

In vitro, the major metabolites abiraterone sulphate and N-oxide abiraterone sulphate were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of medicinal products eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Use with products known to prolong QT interval
Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering ZYTIGA with medicinal products known to prolong the QT interval or medicinal

products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with Spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with ZYTIGA is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of ZYTIGA in pregnancy and this medicinal product is not for use in women of childbearing potential.

Contraception in males and females
It is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
ZYTIGA is not for use in women and is contraindicated in women who are or may potentially be pregnant (see section 4.3 and 5.3).

Breast-feeding
ZYTIGA is not for use in women.

Fertility
Abiraterone acetate affected fertility in male and female rats, but these effects were fully reversible (see section 5.3).

4.7 Effects on ability to drive and use machines

ZYTIGA has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

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

ZYTIGA may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies, anticipated mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate than in patients treated with placebo: hypokalaemia 18% vs. 8%, hypertension 22% vs. 16% and fluid retention (peripheral oedema) 23% vs. 17%, respectively. In patients treated with abiraterone acetate versus patients treated with placebo: CTCAE (version 4.0) Grades 3 and 4 hypokalaemia were observed in 6% versus 1%, CTCAE (version 4.0) Grades 3 and 4 hypertension were observed in 7% versus 5%, and fluid retention (peripheral oedema) Grades 3 and 4 were observed in 1% versus 1% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see section 4.4).

Tabulated list of adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using an LHRH analogue, or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1 000 mg daily in combination with low dose prednisone or prednisolone (either 5 or 10 mg daily depending on the indication).

Adverse reactions observed during clinical studies and post-marketing experience are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000) and not known (frequency cannot be estimated from the available data).

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

Table 1: Adverse reactions identified in clinical studies and post-marketing

System Organ Class	Adverse reaction and frequency
Infections and infestations	very common: urinary tract infection common: sepsis
Immune system disorders	not known: anaphylactic reactions
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, atrial fibrillation, tachycardia uncommon: other arrhythmias not known: myocardial infarction, QT prolongation (see sections 4.4 and 4.5)
Vascular disorders	very common: hypertension
Respiratory, thoracic and mediastinal disorders	rare: allergic alveolitis[a]
Gastrointestinal disorders	very common: diarrhoea common: dyspepsia
Hepatobiliary disorders	very common: alanine aminotransferase increased and/or aspartate aminotransferase increased[b] rare: hepatitis fulminant, acute hepatic failure
Skin and subcutaneous tissue disorders	common: rash
Musculoskeletal and connective tissue disorders	uncommon: myopathy, rhabdomyolysis
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

** Fractures includes osteoporosis and all fractures with the exception of pathological fractures

[a] Spontaneous reports from post-marketing experience

[b] Alanine aminotransferase increased and/or aspartate aminotransferase increased includes ALT increased, AST increased, and hepatic function abnormal.

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

A higher incidence of hypertension and hypokalaemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8% and 20.2% in studies 301 and 302, respectively. Hypokalaemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2% and 14.9% in 301 and 302, respectively).

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

Description of selected adverse reactions

Cardiovascular reactions

The three Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of < 50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH analogues, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking abiraterone acetate versus patients taking placebo were as follows: atrial fibrillation 2.6% vs. 2.0%, tachycardia 1.9% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2%, and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone acetate. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g., ALT or AST increases of > 5 x ULN or bilirubin increases > 1.5 x ULN) were reported in approximately 6% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with ZYTIGA. Ten patients who received ZYTIGA were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the Phase 3 clinical studies, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 x ULN, or elevations in bilirubin > 3 x ULN were observed, abiraterone acetate was withheld or discontinued. In two instances marked increases in liver function tests occurred (see section 4.4). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 x ULN and bilirubin elevations 2 to 6 x ULN. Upon discontinuation of treatment, both patients had normalisation of their liver function tests and one patient was re-treated without recurrence of the elevations. In study 302, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with abiraterone acetate. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of abiraterone acetate). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with abiraterone acetate and 0.6% of patients treated with placebo; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 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 section 4.2). 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Human experience of overdose with ZYTIGA is limited.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

Mechanism of action
Abiraterone acetate (ZYTIGA) 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 section 4.4).

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 ZYTIGA decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects
ZYTIGA 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. 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.

Clinical efficacy and safety
Efficacy was established in three randomised placebo-controlled multicentre Phase 3 clinical studies (studies 3011, 302 and 301) of patients with mHSPC and mCRPC. Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomisation) 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 (excluding lymph node disease) metastasis. In the active arm, ZYTIGA was administered at a dose of 1 000 mg daily in combination with low dose 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 placebos for both ZYTIGA and prednisone. Study 302 enrolled docetaxel naïve 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, ZYTIGA 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.

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in all studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

In all studies spironolactone use was not allowed as spironolactone binds to the androgen receptor and may increase PSA levels.

Study 3011 (patients with newly diagnosed high risk mHSPC)
In Study 3011, (n=1199) the median age of enrolled patients was 67 years. The number of patients treated with ZYTIGA by racial group was Caucasian 832 (69.4%), Asian 246 (20.5%), Black or African American 25 (2.1%), other 80 (6.7%), unknown/not reported 13 (1.1%), and American Indian or Alaska Native 3 (0.3%). The ECOG performance status was 0 or 1 for 97% of patients. Patients with known brain metastasis, uncontrolled hypertension, significant heart disease, or NYHA Class II-IV heart failure were excluded. Patients that were treated with prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer were excluded with the exception of up to 3 months of ADT or 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease. 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. 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 randomisation 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).

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)

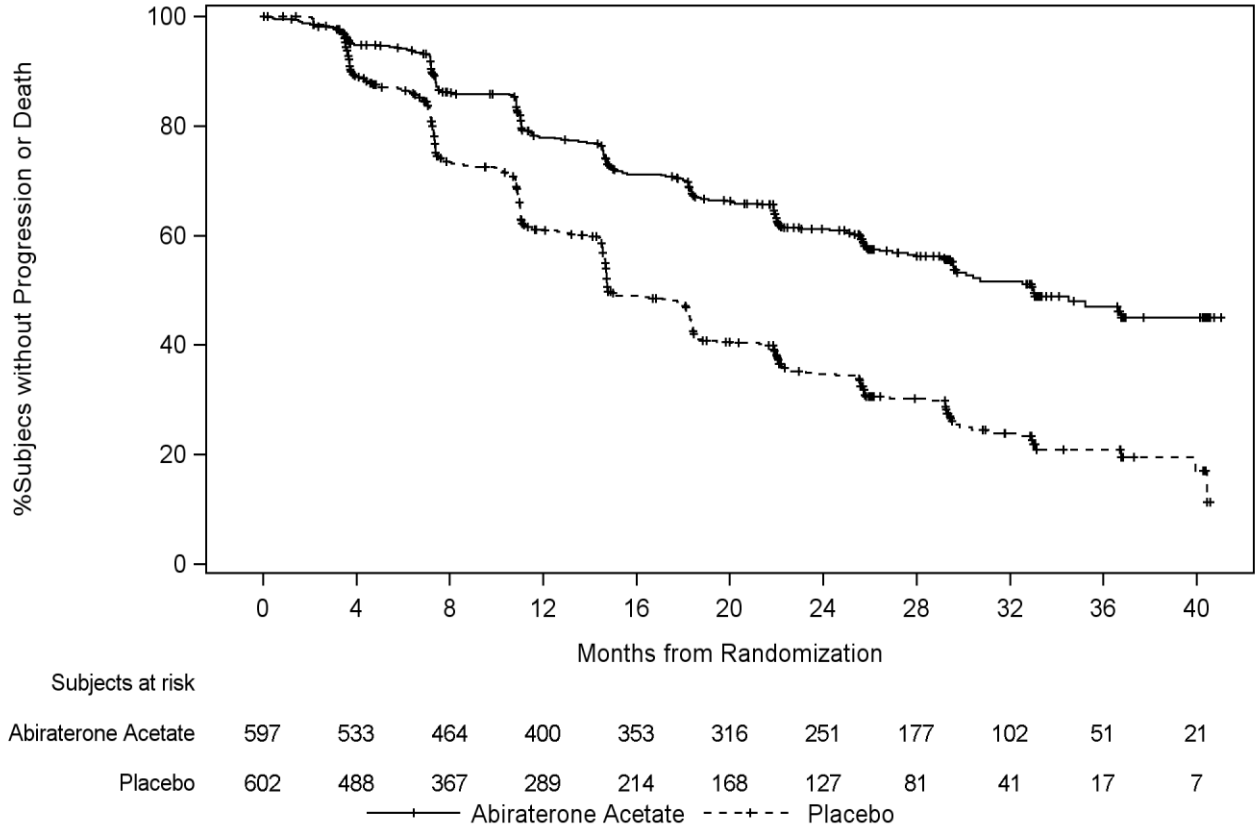
	AA-P	**Placebo**
Subjects randomised	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

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 lesion (absent or present).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours AA-P.

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



A statistically significant improvement in OS in favour of AA-P plus ADT was observed with a 34% reduction in the risk of death compared to Placebo plus ADT (HR=0.66; 95% CI: 0.56, 0.78; p<0.0001), (see Table 3 and Figure 2).

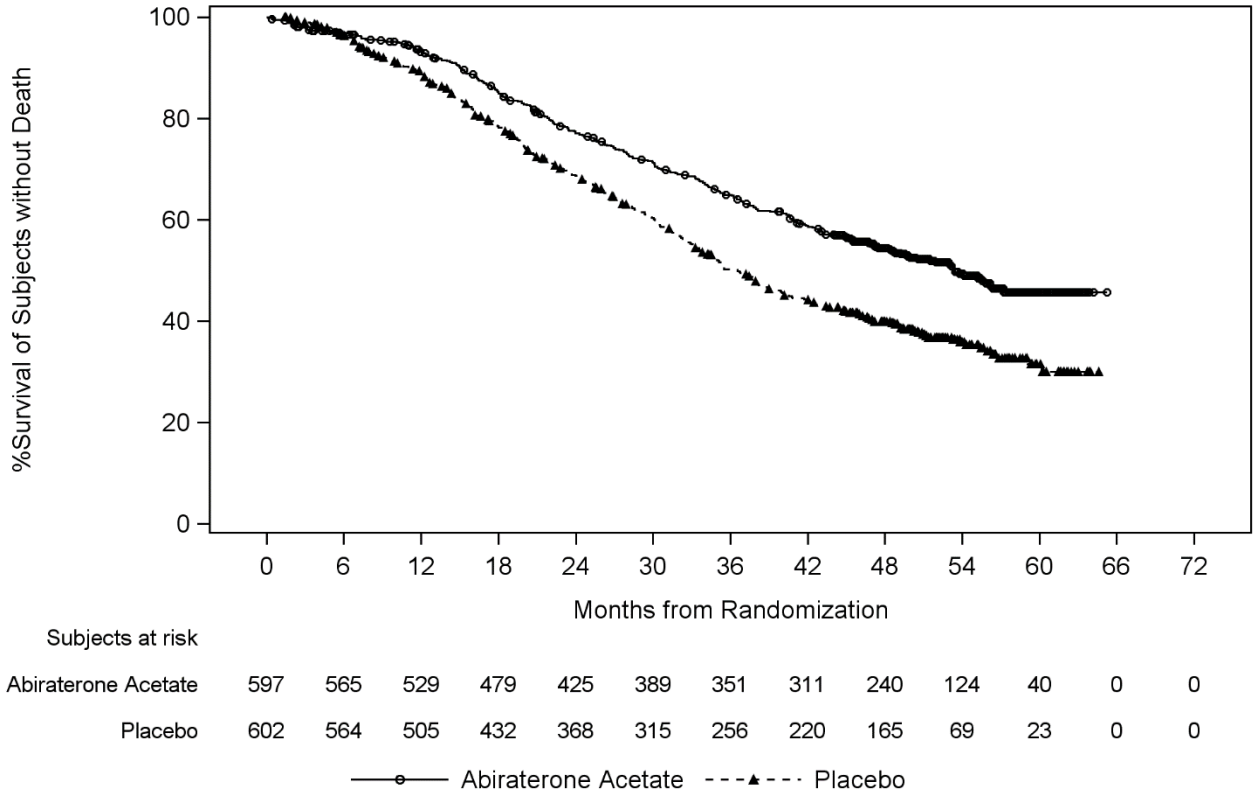
Table 3: Overall Survival of Patients Treated with Either ZYTIGA or Placebos in Study PCR3011 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA with Prednisone (N=597)	Placebos (N=602)
Deaths (%)	275 (46%)	343 (57%)
Median survival (months)	53.3	36.5
(95% CI)	(48.2, NE)	(33.5, 40.0)
Hazard ratio (95% CI)[1]	0.66 (0.56, 0.78)	

NE=Not estimable

[1] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favours ZYTIGA with prednisone.

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population in Study PCR3011 Analysis



Subgroup analyses consistently favour treatment with ZYTIGA. The treatment effect of AA-P on rPFS and OS across the pre-specified subgroups was favourable and consistent with the overall study population, except for the subgroup of ECOG score of 2 where no trend towards benefit was observed, however the small sample size (n=40) limits drawing any meaningful conclusion.

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for ZYTIGA vs. placebo treatment in all prospectively-defined secondary endpoints.

Study 302 (chemotherapy naïve patients)
This study enrolled chemotherapy naïve 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 = 1 088) the median age of enrolled patients was 71 years for patients treated with ZYTIGA plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The number of patients treated with ZYTIGA by racial group was Caucasian 520 (95.4%), Black 15 (2.8%), Asian 4 (0.7%) and other 6 (1.1%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. 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). 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 (rPFS) was assessed with the use of sequential imaging studies as defined by PCWG2 criteria (for bone lesions) and modified Response Evaluation Criteria In Solid

Tumours (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilised centrally-reviewed radiographic assessment of progression.

At the planned rPFS analysis there were 401 events, 150 (28%) 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 4 and Figure 3).

Table 4: Study 302: Radiographic progression-free survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

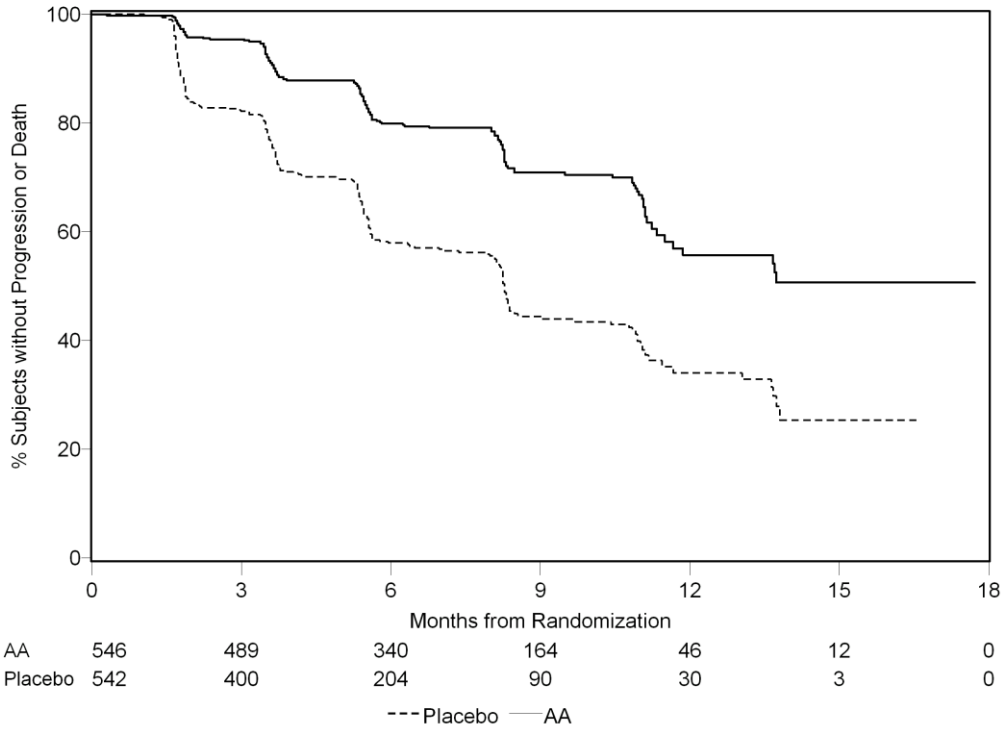
	ZYTIGA (N = 546)	**Placebo (N = 542)**
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66; NE)	8.3 (8.12; 8.54)
p-value*	< 0.0001	
Hazard ratio** (95% CI)	0.425 (0.347; 0.522)	

NE = Not estimated

* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)

** Hazard ratio < 1 favours ZYTIGA

Figure 3: Kaplan Meier curves of radiographic progression-free survival in patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = ZYTIGA

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 5 and Figure 4.

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

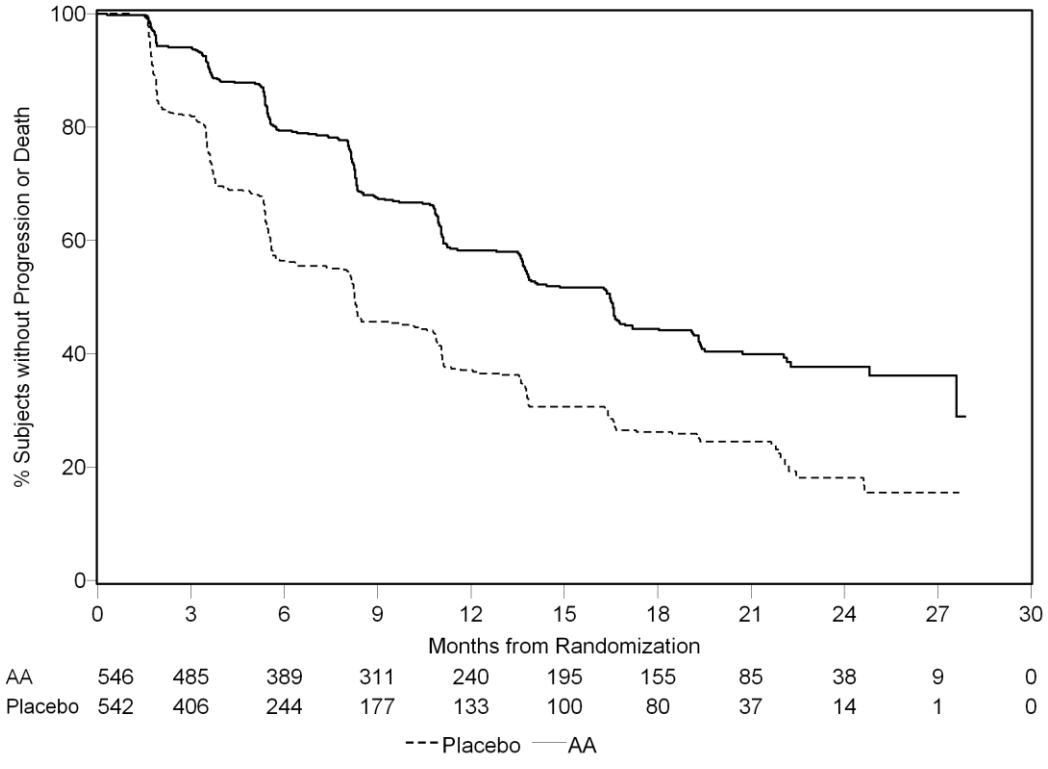
decreased the risk of radiographic progression or death by 47% compared with placebo (HR = 0.530; 95% CI: [0.451; 0.623], p < 0.0001). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

Table 5: Study 302: Radiographic progression-free survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	ZYTIGA (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 ZYTIGA

Figure 4: Kaplan Meier curves of radiographic progression-free survival in patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)



AA = ZYTIGA

A planned interim analysis (IA) for OS 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 ZYTIGA. Overall survival was longer for ZYTIGA 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 4). 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 ZYTIGA, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favour of the ZYTIGA-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 (ZYTIGA 34.7 months, placebo 30.3 months) (see Table 6 and Figure 5). This improvement was demonstrated even though 44% of patients in the placebo arm received ZYTIGA as subsequent therapy.

Table 6: Study 302: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

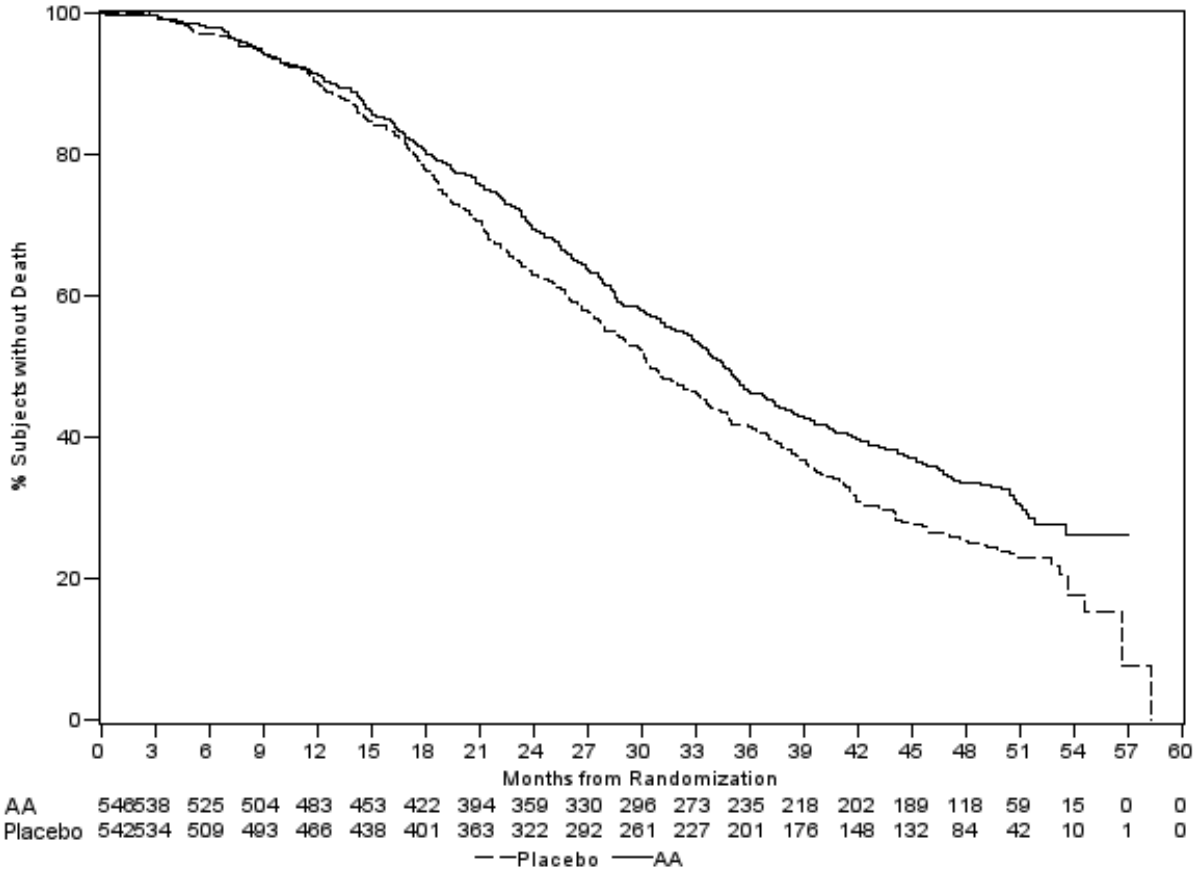
	ZYTIGA (N = 546)	**Placebo (N = 542)**
Interim survival analysis		
Deaths (%)	147 (27%)	186 (34%)
Median survival (months) (95% CI)	Not reached (NE; NE)	27.2 (25.95; NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606; 0.934)	
Final survival analysis		
Deaths	354 (65%)	387 (71%)
Median overall 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 ZYTIGA

Figure 5: Kaplan Meier survival curves of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy, final analysis



AA = ZYTIGA

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for ZYTIGA vs. placebo treatment in all 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 ZYTIGA 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 ZYTIGA treatment (HR = 0.488). The proportion of subjects with a confirmed PSA response was greater in the ZYTIGA group than in the placebo group (62% vs. 24%; $p < 0.0001$). In subjects with measurable soft tissue disease, significantly increased numbers of complete and partial tumour responses were seen with ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 favour of ZYTIGA 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 ZYTIGA group and 16% in the placebo group ($p < 0.0001$).

Pain: Treatment with ZYTIGA 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 ZYTIGA group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score): Treatment with ZYTIGA 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 ZYTIGA 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 ZYTIGA 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 ZYTIGA.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with ZYTIGA 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 ZYTIGA (see Table 7).

Table 7: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

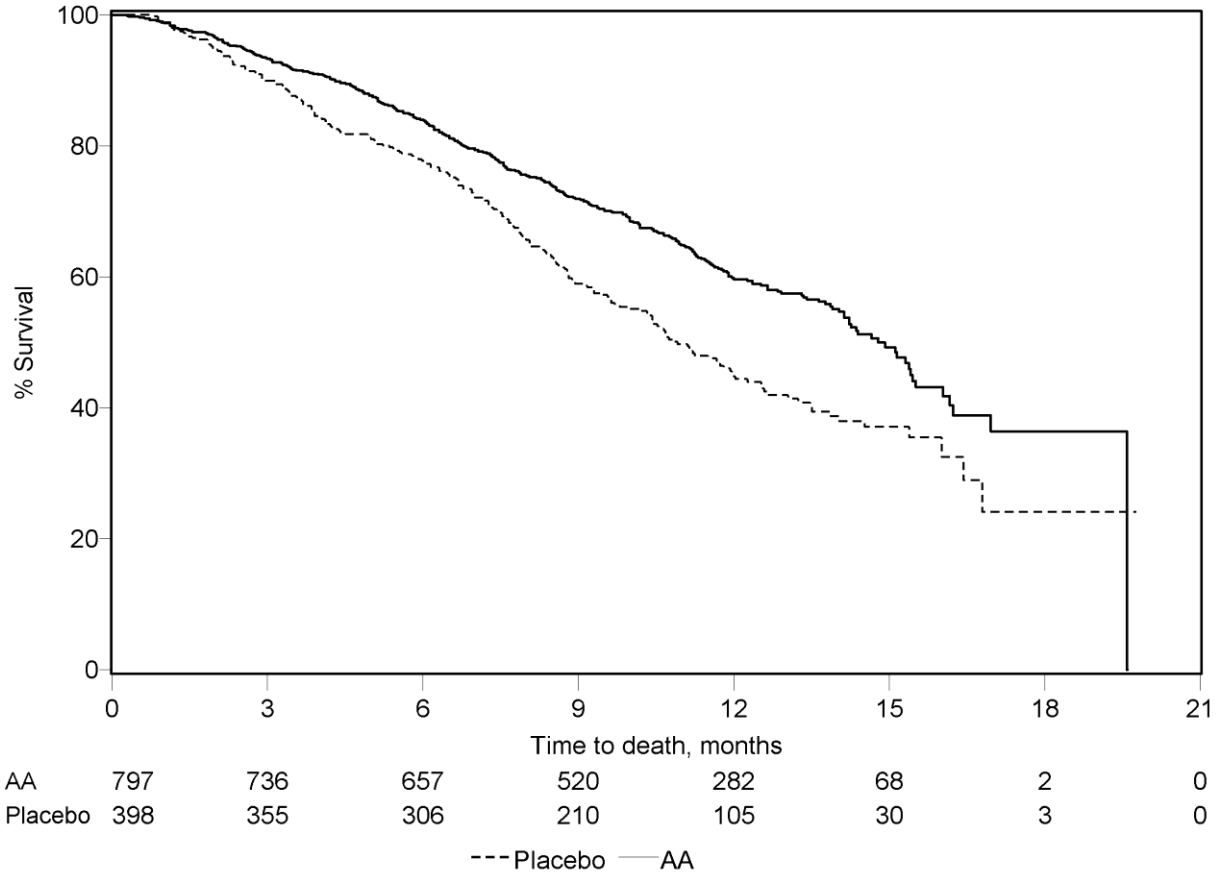
	ZYTIGA (N = 797)	**Placebo (N = 398)**
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1; 15.4)	10.9 (10.2; 12.0)
p-value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.646 (0.543; 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median 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 ZYTIGA

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with ZYTIGA remained alive, compared with the proportion of patients treated with placebo (see Figure 6).

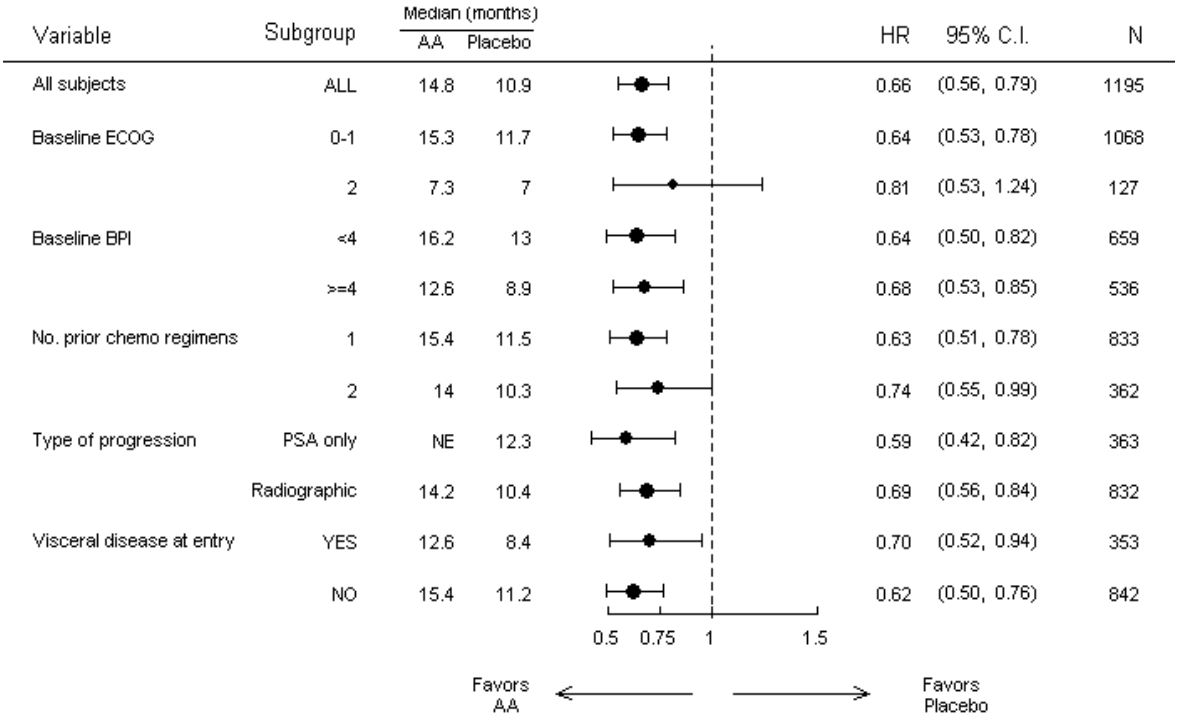
Figure 6: Kaplan Meier survival curves of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



AA = ZYTIGA

Subgroup survival analyses showed a consistent survival benefit for treatment with ZYTIGA (see Figure 7).

Figure 7: Overall survival by subgroup: hazard ratio and 95% confidence interval



AA = ZYTIGA; 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 ZYTIGA and were statistically significant after adjusting for multiple testing as follows:

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

The median time to PSA progression was 10.2 months for patients treated with ZYTIGA 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 ZYTIGA 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 ZYTIGA group than in the placebo group (44% vs. 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 ZYTIGA had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 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 ZYTIGA group, versus 4.7 months in the placebo group.

Skeletal-related events
A lower proportion of patients in the ZYTIGA group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs. 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the ZYTIGA 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with ZYTIGA in all subsets of the paediatric population in advanced prostate cancer. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone has 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 section 5.1).

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 ZYTIGA with meals has the potential to result in highly variable exposures. Therefore, ZYTIGA must not be taken with food. ZYTIGA tablets must be taken as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. The tablets must be swallowed whole with water (see section 4.2).

Distribution
The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5 630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Biotransformation
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).

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.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n = 8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The AUC to abiraterone increased by approximately 600% and the fraction of free drug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment. The use of abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 4.4). abiraterone acetate should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 4.4).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see sections 4.2 and 4.4).

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 section 4.2). However, there is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients.

5.3 Preclinical safety data

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.

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 foetal 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.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. 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.

Environmental risk assessment (ERA)
The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (silicified)
Croscarmellose sodium
Hypromellose 2910 (15 mPa.S)
Lactose monohydrate
Magnesium stearate
Colloidal anhydrous silica
Sodium laurilsulfate

Film-coat
Iron oxide black (E172)
Iron oxide red (E172)
Macrogol 3350
Polyvinyl alcohol
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVdC/PE/PVC/aluminium blister of 14 film-coated tablets in a cardboard wallet. Each carton contains (56 film-coated tablets) 4 wallets.
PVdC/PE/PVC/aluminium blister of 12 film-coated tablets in a cardboard wallet. Each carton contains (60 film-coated tablets) 5 wallets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment (see section 5.3).

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/002 - 56 film-coated tablets (4 wallet packs of 14)
EU/1/11/714/003 - 60 film-coated tablets (5 wallet packs of 12)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 September 2011

Date of latest renewal: 26 May 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGIVAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA
Via C. Janssen
IT-04100 Borgo San Michele
Latina
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 250 mg

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 250 mg tablets
abiraterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 250 mg abiraterone acetate.

3. LIST OF EXCIPIENTS

Contains lactose and sodium.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

120 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take ZYTIGA at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Women who are or may be pregnant should not handle ZYTIGA without gloves.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYTIGA 250 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 250 mg

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 250 mg tablets
abiraterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 250 mg abiraterone acetate.

3. LIST OF EXCIPIENTS

Contains lactose and sodium.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

120 tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take ZYTIGA at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Women who are or may be pregnant should not handle ZYTIGA without gloves.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/001

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 500 mg

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 500 mg film-coated tablets
abiraterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg abiraterone acetate.

3. LIST OF EXCIPIENTS

Contains lactose and sodium.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
60 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Take ZYTIGA at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA.
Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/002 (56 film-coated tablets)
EU/1/11/714/003 (60 film-coated tablets)

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYTIGA 500 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 500 mg (30 days)

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 500 mg film-coated tablets
abiraterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg abiraterone acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Fill in your weekdays

Start date:

Day

Read the package leaflet before use.
Take ZYTIGA at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA.
Swallow the tablets whole with water.
Do not break the tablets.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/003

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYTIGA 500 mg

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

WALLET 500 mg (28 days)

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 500 mg film-coated tablets
abiraterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 500 mg abiraterone acetate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Take ZYTIGA at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA.
Swallow the tablets whole with water.

Do not break the tablets.

Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused contents appropriately in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/714/002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYTIGA 500 mg

PARTICULARS TO APPEAR ON BLISTERS or STRIPS

BLISTER 500 mg

1. NAME OF THE MEDICINAL PRODUCT

ZYTIGA 500 mg film-coated tablets
abiraterone acetate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ZYTIGA 250 mg tablets
abiraterone acetate

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

What is in this leaflet:

1. What ZYTIGA is and what it is used for

ZYTIGA contains a medicine called abiraterone acetate. It is used to treat prostate cancer in adult men that has spread to other parts of the body. ZYTIGA stops your body from making testosterone; this can slow the growth of prostate cancer.

When ZYTIGA is prescribed for the early stage of disease where it is still responding to hormone therapy, it is used with a treatment that lowers testosterone (androgen deprivation therapy).

When you take this medicine your doctor will also prescribe another medicine called prednisone or prednisolone. This is to lower your chances of getting high blood pressure, having too much water in your body (fluid retention), or having reduced levels of a chemical known as potassium in your blood.

2. What you need to know before you take ZYTIGA

Do not take ZYTIGA
- if you are allergic to abiraterone acetate or any of the other ingredients of this medicine (listed in section 6).
- if you are a woman, especially if pregnant. ZYTIGA is for use in male patients only.
- if you have severe liver damage.
- in combination with Ra-223 (which is used to treat prostate cancer).

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine:
- if you have liver problems
- if you have been told you have high blood pressure or heart failure or low blood potassium (low blood potassium may increase the risk of heart rhythm problems)
- if you have had other heart or blood vessel problems
- if you have an irregular or rapid heart rate

- if you have shortness of breath
- if you have gained weight rapidly
- if you have swelling in the feet, ankles, or legs
- if you have taken a medicine known as ketoconazole in the past for prostate cancer
- about the need to take this medicine with prednisone or prednisolone
- about possible effects on your bones
- if you have high blood sugar.

Tell your doctor if you have been told you have any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions.

Tell your doctor if you have yellowing of the skin or eyes, darkening of the urine, or severe nausea or vomiting, as these could be signs or symptoms of liver problems. Rarely, failure of the liver to function (called acute liver failure) may occur, which can lead to death.

Decrease in red blood cells, reduced sex drive (libido), muscle weakness and/or muscle pain may occur.

ZYTIGA must not be given in combination with Ra-223 due to a possible increase in the risk of bone fracture or death.

If you plan to take Ra-223 following treatment with ZYTIGA and prednisone/prednisolone, you must wait 5 days before starting treatment with Ra-223.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Blood monitoring
ZYTIGA may affect your liver, and you may not have any symptoms. When you are taking this medicine, your doctor will check your blood periodically to look for any effects on your liver.

Children and adolescents
This medicine is not for use in children and adolescents. If ZYTIGA is accidentally ingested by a child or adolescent, go to the hospital immediately and take the package leaflet with you to show to the emergency doctor.

Other medicines and ZYTIGA
Ask your doctor or pharmacist for advice before taking any medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because ZYTIGA may increase the effects of a number of medicines including heart medicines, tranquilisers, some medicines for diabetes, herbal medicines (e.g., St John's wort) and others. Your doctor may want to change the dose of these medicines. Also, some medicines may increase or decrease the effects of ZYTIGA. This may lead to side effects or to ZYTIGA not working as well as it should.

Androgen deprivation treatment may increase the risk of heart rhythm problems. Tell your doctor if you are receiving medicine
- used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol);
- known to increase the risk of heart rhythm problems [e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics (used for serious mental illnesses)].

Tell your doctor if you are taking any of the medicines listed above.

ZYTIGA with food
- This medicine must not be taken with food (see section 3, "Taking this medicine").

- Taking ZYTIGA with food may cause side effects.

Pregnancy and breast-feeding
ZYTIGA is not for use in women.
- **This medicine may cause harm to the unborn child if it is taken by women who are pregnant.**
- **Women who are pregnant or who may be pregnant should wear gloves if they need to touch or handle ZYTIGA.**
- **If you are having sex with a woman who can become pregnant, use a condom and another effective birth control method.**
- **If you are having sex with a pregnant woman, use a condom to protect the unborn child.**

Driving and using machines
This medicine is not likely to affect your being able to drive and use any tools or machines.

ZYTIGA contains lactose and sodium
- ZYTIGA contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
- This medicine contains 27.2 mg sodium (main component of cooking/table salt) in a four tablet daily dose. This is equivalent to 1.36% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take ZYTIGA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is 1 000 mg (four tablets) once a day.

Taking this medicine
- Take this medicine by mouth.
- **Do not take ZYTIGA with food**. Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- Take ZYTIGA tablets as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. (see section 2, “ZYTIGA with food”).
- Swallow the tablets whole with water.
- Do not break the tablets.
- ZYTIGA is taken with a medicine called prednisone or prednisolone. Take the prednisone or prednisolone exactly as your doctor has told you.
- You need to take prednisone or prednisolone every day while you are taking ZYTIGA.
- The amount of prednisone or prednisolone you take may need to change if you have a medical emergency. Your doctor will tell you if you need to change the amount of prednisone or prednisolone you take. Do not stop taking prednisone or prednisolone unless your doctor tells you to.

Your doctor may also prescribe other medicines while you are taking ZYTIGA and prednisone or prednisolone.

If you take more ZYTIGA than you should
If you take more than you should, talk to your doctor or go to a hospital immediately.

If you forget to take ZYTIGA
- If you forget to take ZYTIGA or prednisone or prednisolone, take your usual dose the following day.

- If you forget to take ZYTIGA or prednisone or prednisolone for more than one day, talk to your doctor without delay.

If you stop taking ZYTIGA
Do not stop taking ZYTIGA or prednisone or prednisolone unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking ZYTIGA and see a doctor immediately if you notice any of the following:
- Muscle weakness, muscle twitches or a pounding heart beat (palpitations). These may be signs that the level of potassium in your blood is low.

Other side effects include:
Very common (may affect more than 1 in 10 people):
Fluid in your legs or feet, low blood potassium, liver function test increases, high blood pressure, urinary tract infection, diarrhoea.
Common (may affect up to 1 in 10 people):
High fat levels in your blood, chest pain, irregular heart beat (atrial fibrillation), heart failure, rapid heart rate, severe infections called sepsis, bone fractures, indigestion, blood in urine, rash.
Uncommon (may affect up to 1 in 100 people):
Adrenal gland problems (related to salt and water problems), abnormal heart rhythm (arrhythmia), muscle weakness and/or muscle pain.
Rare (may affect up to 1 in 1 000 people):
Lung irritation (also called allergic alveolitis).
Failure of the liver to function (also called acute liver failure).
Not known (frequency cannot be estimated from the available data):
Heart attack, changes in ECG - electrocardiogram (QT prolongation), and serious allergic reactions with difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash.

Bone loss may occur in men treated for prostate cancer. ZYTIGA in combination with prednisone or prednisolone may increase bone loss.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ZYTIGA

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the bottle label. The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What ZYTIGA contains
- The active substance is abiraterone acetate. Each tablet contains 250 mg abiraterone acetate.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone (K29/K32), colloidal anhydrous silica, and sodium laurilsulfate (see section 2, "ZYTIGA contains lactose and sodium").

What ZYTIGA looks like and contents of the pack
- ZYTIGA tablets are white to off-white, oval shaped (15.9 mm long x 9.5 mm wide), with "AA250" written on one side.
- The tablets are provided in a plastic bottle with a child-resistant closure. Each bottle contains 120 tablets. Each carton contains one bottle.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen-Cilag SpA
Via C. Janssen
Borgo San Michele
I-04100 Latina, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

България
„Джонсън & Джонсън България" ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel. +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf: +45 45 94 82 82
jacdk@its.jnj.com

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955
jancil@its.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111
janssen@jacnl.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: +353 1 800 709 122

Ísland
Janssen-Cilag AB
c/o Vistor hf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.+48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
Janssen_safety_slo@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the user

ZYTIGA 500 mg film-coated tablets
abiraterone acetate

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

What is in this leaflet:

1. What ZYTIGA is and what it is used for

ZYTIGA contains a medicine called abiraterone acetate. It is used to treat prostate cancer in adult men that has spread to other parts of the body. ZYTIGA stops your body from making testosterone; this can slow the growth of prostate cancer.

When ZYTIGA is prescribed for the early stage of disease where it is still responding to hormone therapy, it is used with a treatment that lowers testosterone (androgen deprivation therapy).

When you take this medicine your doctor will also prescribe another medicine called prednisone or prednisolone. This is to lower your chances of getting high blood pressure, having too much water in your body (fluid retention), or having reduced levels of a chemical known as potassium in your blood.

2. What you need to know before you take ZYTIGA

Do not take ZYTIGA
- if you are allergic to abiraterone acetate or any of the other ingredients of this medicine (listed in section 6).
- if you are a woman, especially if pregnant. ZYTIGA is for use in male patients only.
- if you have severe liver damage.
- in combination with Ra-223 (which is used to treat prostate cancer).

Do not take this medicine if any of the above apply to you. If you are not sure, talk to your doctor or pharmacist before taking this medicine.

Warnings and precautions
Talk to your doctor or pharmacist before taking this medicine:
- if you have liver problems
- if you have been told you have high blood pressure or heart failure or low blood potassium (low blood potassium may increase the risk of heart rhythm problems)
- if you have had other heart or blood vessel problems
- if you have an irregular or rapid heart rate

- if you have shortness of breath
- if you have gained weight rapidly
- if you have swelling in the feet, ankles, or legs
- if you have taken a medicine known as ketoconazole in the past for prostate cancer
- about the need to take this medicine with prednisone or prednisolone
- about possible effects on your bones
- if you have high blood sugar.

Tell your doctor if you have been told you have any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions.

Tell your doctor if you have yellowing of the skin or eyes, darkening of the urine, or severe nausea or vomiting, as these could be signs or symptoms of liver problems. Rarely, failure of the liver to function (called acute liver failure) may occur, which can lead to death.

Decrease in red blood cells, reduced sex drive (libido), muscle weakness and/or muscle pain may occur.

ZYTIGA must not be given in combination with Ra-223 due to a possible increase in the risk of bone fracture or death.

If you plan to take Ra-223 following treatment with ZYTIGA and prednisone/prednisolone, you must wait 5 days before starting treatment with Ra-223.

If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before taking this medicine.

Blood monitoring
ZYTIGA may affect your liver, and you may not have any symptoms. When you are taking this medicine, your doctor will check your blood periodically to look for any effects on your liver.

Children and adolescents
This medicine is not for use in children and adolescents. If ZYTIGA is accidentally ingested by a child or adolescent, go to the hospital immediately and take the package leaflet with you to show to the emergency doctor.

Other medicines and ZYTIGA
Ask your doctor or pharmacist for advice before taking any medicine.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is important because ZYTIGA may increase the effects of a number of medicines including heart medicines, tranquilisers, some medicines for diabetes, herbal medicines (e.g., St John's wort) and others. Your doctor may want to change the dose of these medicines. Also, some medicines may increase or decrease the effects of ZYTIGA. This may lead to side effects or to ZYTIGA not working as well as it should.

Androgen deprivation treatment may increase the risk of heart rhythm problems. Tell your doctor if you are receiving medicine
- used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol);
- known to increase the risk of heart rhythm problems [e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics (used for serious mental illnesses)].

Tell your doctor if you are taking any of the medicines listed above.

ZYTIGA with food
- This medicine must not be taken with food (see section 3, "Taking this medicine").

- Taking ZYTIGA with food may cause side effects.

Pregnancy and breast-feeding
ZYTIGA is not for use in women.
- **This medicine may cause harm to the unborn child if it is taken by women who are pregnant.**
- **If you are having sex with a woman who can become pregnant, use a condom and another effective birth control method.**
- **If you are having sex with a pregnant woman, use a condom to protect the unborn child.**

Driving and using machines
This medicine is not likely to affect your being able to drive and use any tools or machines.

ZYTIGA contains lactose and sodium
- ZYTIGA contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.
- This medicine contains 27 mg sodium (main component of cooking/table salt) in a two tablet daily dose. This is equivalent to 1.35% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to take ZYTIGA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is 1 000 mg (two tablets) once a day.

Taking this medicine
- Take this medicine by mouth.
- **Do not take ZYTIGA with food**. Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- Take ZYTIGA tablets as a single dose once daily on an empty stomach. ZYTIGA must be taken at least two hours after eating and food must not be eaten for at least one hour after taking ZYTIGA. (see section 2, “ZYTIGA with food”).
- Swallow the tablets whole with water.
- Do not break the tablets.
- ZYTIGA is taken with a medicine called prednisone or prednisolone. Take the prednisone or prednisolone exactly as your doctor has told you.
- You need to take prednisone or prednisolone every day while you are taking ZYTIGA.
- The amount of prednisone or prednisolone you take may need to change if you have a medical emergency. Your doctor will tell you if you need to change the amount of prednisone or prednisolone you take. Do not stop taking prednisone or prednisolone unless your doctor tells you to.

Your doctor may also prescribe other medicines while you are taking ZYTIGA and prednisone or prednisolone.

If you take more ZYTIGA than you should
If you take more than you should, talk to your doctor or go to a hospital immediately.

If you forget to take ZYTIGA
- If you forget to take ZYTIGA or prednisone or prednisolone, take your usual dose the following day.
- If you forget to take ZYTIGA or prednisone or prednisolone for more than one day, talk to your doctor without delay.

If you stop taking ZYTIGA
Do not stop taking ZYTIGA or prednisone or prednisolone unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Stop taking ZYTIGA and see a doctor immediately if you notice any of the following:
- Muscle weakness, muscle twitches or a pounding heart beat (palpitations). These may be signs that the level of potassium in your blood is low.

Other side effects include:
Very common (may affect more than 1 in 10 people):
Fluid in your legs or feet, low blood potassium, liver function test increases, high blood pressure, urinary tract infection, diarrhoea.
Common (may affect up to 1 in 10 people):
High fat levels in your blood, chest pain, irregular heart beat (atrial fibrillation), heart failure, rapid heart rate, severe infections called sepsis, bone fractures, indigestion, blood in urine, rash.
Uncommon (may affect up to 1 in 100 people):
Adrenal gland problems (related to salt and water problems), abnormal heart rhythm (arrhythmia), muscle weakness and/or muscle pain.
Rare (may affect up to 1 in 1 000 people):
Lung irritation (also called allergic alveolitis).
Failure of the liver to function (also called acute liver failure).
Not known (frequency cannot be estimated from the available data):
Heart attack, changes in ECG - electrocardiogram (QT prolongation), and serious allergic reactions with difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash.

Bone loss may occur in men treated for prostate cancer. ZYTIGA in combination with prednisone or prednisolone may increase bone loss.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ZYTIGA

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton, cardboard wallet, and the blister. The expiry date refers to the last day of that month.
- This medicinal product does not require any special storage conditions.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What ZYTIGA contains
- The active substance is abiraterone acetate. Each film-coated tablet contains 500 mg abiraterone acetate.
- The other ingredients are microcrystalline cellulose (silicified); croscarmellose sodium; hypromellose 2910 (15 mPa.S); lactose monohydrate; magnesium stearate; colloidal anhydrous silica; and sodium laurilsulfate (see section 2, "ZYTIGA contains lactose and sodium") The film-coating contains iron oxide black (E172); iron oxide red (E172); macrogol 3350; polyvinyl alcohol; talc; and titanium dioxide.

What ZYTIGA looks like and contents of the pack
- ZYTIGA tablets are purple, oval-shaped, film-coated (20 mm long by 10 mm wide) with "AA" written on one side and "500" on the other side.
  Each 28 day carton contains 56 film-coated tablets in 4 cardboard wallets of 14 film-coated tablets each.
  Each 30 day carton contains 60 film-coated tablets in 5 cardboard wallets of 12 film-coated tablets each.
- Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen-Cilag SpA
Via C. Janssen
Borgo San Michele
I-04100 Latina, Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

България
„Джонсън & Джонсън България" ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel. +420 227 012 227

Danmark
Janssen-Cilag A/S
Tlf: +45 45 94 82 82
jacdk@its.jnj.com

Lietuva
UAB "JOHNSON & JOHNSON"
Tel: +370 5 278 68 88
lt@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955
jancil@its.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: +353 1 800 709 122

Ísland
Janssen-Cilag AB
c/o Vistor hf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111
janssen@jacnl.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.+48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
Janssen_safety_slo@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

This leaflet was last revised in

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.