PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

ZYTIGA® 250 mg tablets

ZYTIGA® 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYTIGA® 250 mg tablets

Each tablet contains 250 mg of abiraterone acetate.

Excipients with known effect

Each tablet contains 198,7 mg of lactose and 6,8 mg of sodium.

ZYTIGA® 500 mg tablets

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

Excipients with known effect

Each film-coated tablet contains 253,2 mg of lactose and 13,5 mg of sodium.

Contains sugar (lactose monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZYTIGA® 250 mg tablets:

ZYTIGA® 250 mg uncoated tablets are white to off white, oval tablets 16 mm long, debossed with AA250 on one side.

ZYTIGA 500 mg film-coated tablets:

ZYTIGA® 500 mg tablets are 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 low-dose corticosteroids (prednisone or prednisolone) in adult males for the treatment of:

- high-risk metastatic hormone treatment naïve prostate cancer (mHNPC) or newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (LHRH agonist or surgical castration).

  High-risk is defined as having at least 2 of the following 3 risk factors:

  (1) Gleason score of ≥ 8,

  (2) presence of 3 or more bone lesions,

  (3) presence of measurable visceral (excluding lymph node disease) metastasis.
- metastatic castration resistant prostate cancer with bone metastases who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

- metastatic advanced prostate cancer (castration resistant prostate cancer) who have received prior chemotherapy containing docetaxel.

4.2 Posology and method of administration

This medicine should be prescribed by an appropriate healthcare professional.

Posology

The recommended dose of ZYTIGA is 1 g (two 500 mg tablets or four 250 mg tablets) as a single daily dose that **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 (see *Method of administration* below). Taking ZYTIGA with food increases systemic exposure to abiraterone (see sections 4.5 and 5.2).

Patients should be maintained on ZYTIGA until radiographic progression and symptomatic/clinical progression and until PSA progression (confirmed 25 % increase over the patient's baseline/nadir).

Dosage of prednisone or prednisolone

For metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate cancer (mHSPC), ZYTIGA is used with 5 mg prednisone or prednisolone once daily.

For metastatic castration-resistant prostate cancer (mCRPC), ZYTIGA is used with 10 mg prednisone or prednisolone daily.

Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see section 4.4).

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.

Hepatic impairment:

No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh class A. There are no data on the clinical safety and efficacy of multiple doses of ZYTIGA when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

For patients who develop hepatotoxicity during treatment with ZYTIGA (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases above 5 times the upper limit of normal or bilirubin increases above 3 times the upper limit of normal), treatment should be withheld immediately until liver function tests normalise (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 once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, treatment should be discontinued. Reduced doses should not be taken with food (see previous).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, ZYTIGA should be discontinued and patients should not be re-treated with ZYTIGA.

Renal impairment:

No dose adjustment is necessary for patients with renal impairment (see section 5.2).

Paediatric population:

There is no relevant use of ZYTIGA in paediatric patients, as prostate cancer is not present in the paediatric population.

Method of administration

ZYTIGA is for oral use.

ZYTIGA must be taken on an empty stomach, at least one hour before or at least two hours after a meal. The tablets should be swallowed whole with water.

Precautions to be taken before handling or administering ZYTIGA.

Based on its mechanism of action, ZYTIGA may harm a developing foetus; therefore, women (including healthcare professionals), who are pregnant or women who may be pregnant should not handle ZYTIGA 250 mg tablets without protection, e.g., gloves (see section 4.6 and 6.6).

For concomitant use with prednisolone, the Professional Information for prednisolone should be consulted.

4.3 Contraindications

ZYTIGA is contraindicated in:

- Patients with hypersensitivity to abiraterone acetate or to any of the excipients listed in section 6.1.
- Pregnancy and Lactation (see section 4.6).
- Moderate (Child-Pugh B) to severe (Child- Pugh C) hepatic impairment (see sections 4.2, 4.4 and 5.2).
- Women should not use ZYTIGA.
- Concomitant administration with rifampicin (see section 4.5).
- 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 dysrhythmia 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 ZYTIGA discontinuation or dose modification occurred in controlled clinical studies (see section 4.8). Serum transaminase and bilirubin levels should be measured prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with ZYTIGA should be interrupted immediately and liver function closely monitored.

Re-treatment with ZYTIGA 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 upper limit of normal) anytime while on therapy, ZYTIGA should be permanently discontinued and patients should not be re-treated with ZYTIGA.

There are no data on the clinical safety and efficacy of multiple doses of ZYTIGA when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). ZYTIGA should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

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

Interactions with other medicines

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)

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients need to be withdrawn from prednisone or prednisolone. If ZYTIGA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see previous).

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage 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.

Use with chemotherapy

The safety and efficacy of concomitant use of ZYTIGA with cytotoxic chemotherapy has not been established.

Use in combination with radium 223 dichloride

In a randomised clinical trial in patients with asymptomatic or mildly symptomatic bone-predominant metastatic castration resistant prostate cancer, at the time of unblinding, the addition of radium 223 dichloride to ZYTIGA plus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture. Radium 223 dichloride is not

recommended for use in combination with ZYTIGA plus prednisone/prednisolone outside of clinical trials.

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). Blood glucose should be monitored in patients with diabetes.

Vaccination with live attentuated bacterial or viral vaccines

Prostate cancer patients on treatment should receive guidance on age and indication appropriate vaccinations, in particular live attentuated bacterial or viral vaccines. Patients should also be advised to take extra precaution should they come into contact with someone who has received a live vaccine.

Tuberculosis and/or HIV

Prostate cancer patients with tuberculosis and/or HIV, who are not well-controlled on treatment should be monitored closely.

Intolerance to excipients

Lactose

ZYTIGA contains lactose. Patients with rare hereditary problems of galactose intolerance; e.g. galactosaemia the Lapp lactase deficiency or glucose-galactose malabsorption should not take ZYTIGA.

Sodium

This medicine also contains more than 1 mmol (or 27,2 mg) sodium per dose of four 250 mg tablets or two 500 mg tablets. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Effect of food on ZYTIGA:

Administration of ZYTIGA with food significantly increases the absorption of abiraterone. The efficacy and safety of ZYTIGA given with food have not been established. **ZYTIGA must not be taken with food** (see sections 4.2 and 5.2).

Interactions with other medicines

Potential for other medicines to affect ZYTIGA 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 ZYTIGA 1 000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55 % (see section 4.3).

Other strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbitone, St John's wort) during treatment with ZYTIGA are to be avoided.

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 ZYTIGA.

Potential for ZYTIGA to affect exposures to other medicines

ZYTIGA is an inhibitor of the hepatic medicine-metabolising enzymes CYP2D6 and CYP2C8.

In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased by approximately 200 %. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33 %.

Caution is advised when ZYTIGA is administered with medicines activated by or metabolised by CYP2D6, particularly with medicines that have a narrow therapeutic index. Dose reduction of narrow therapeutic index medicines metabolised by CYP2D6 should be considered (e.g.paroxetine, propafenone, flecainide and haloperidol).
In the same study to determine the effects of ZYTIGA (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed).

In a CYP2C8 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 ZYTIGA. Patients should be monitored for signs of toxicity related to CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (see section 4.4 – Hypoglycaemia).

Concomitant use with Spironolactone

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

Concomitant use with eplenerone

There is no clinical study data related to concomitant use of eplenerone with ZYTIGA.

4.6 Fertility, pregnancy and lactation

Women should not use ZYTIGA.

Women of childbearing potential

There are no human data on the use of ZYTIGA in pregnancy and ZYTIGA is not for use in women of childbearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus.

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 until one week after the last dose of ZYTIGA.

Pregnancy

ZYTIGA is contraindicated in women who are or may potentially be pregnant (see section 4.3).

Pregnant women or women of child-bearing potential should handle ZYTIGA uncoated tablets with gloves.

Breastfeeding

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

Fertility

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

It is recommended to store semen before starting treatment with ZYTIGA in patients who might want to father a child.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trial data

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 increased alanine aminotransferase and/or increased aspartate aminotransferase.

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 effects were seen more commonly in patients treated with ZYTIGA versus patients treated with placebo: hypokalaemia 18 % versus 8 %, hypertension 22 % versus 16 % and fluid retention (peripheral oedema) 23 % versus 17 %, respectively. In patients treated with

ZYTIGA versus patients treated with placebo: Grades 3 and 4 hypokalaemia were observed in 6 % versus 1 %, grades 3 and 4 hypertension were observed in 7 % versus 5 %, and grades 3 and 4 fluid retention oedema 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 summary of clinical adverse reactions

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1 g 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 with ZYTIGA 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) and very rare (< 1/10 000).*

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

Table 1: Adverse reactions identified in clinical studies with ZYTIGA	
Infections and infestations	*very common*: urinary tract infection *common: sepsis*
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:* dysrhythmia
Vascular disorders	*very common*: hypertension
Gastrointestinal disorders	*very common:* diarrhoea *common:* dyspepsia
Hepatobiliary disorders	*very common*: increased alanine aminotransferase (ALT) and/or increased aspartate aminotransferase[a] (AST)
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*: peripheral oedema
Injury, poisoning and procedural complications	*common: fractures***

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

** *Fractures include osteoporosis and all fractures with the exception of pathological fracture.*

[a] *Increased alanine aminotransferase and/or increased aspartate aminotransferase includes increased ALT, increased AST, and abnormal hepatic function.*

The following 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. Grade 3 hypertriglyceridaemia and angina pectoris occurred in < 1 % of patients. 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.

Post-marketing data

Adverse reactions identified during the post-marketing experience based on spontaneous reports with ZYTIGA are described below.

Table 2 : Adverse reactions identified during post-marketing experience

Cardiac disorders Myocardial infarction, QT prolongation
Respiratory, thoracic and mediastinal disorders Allergic alveolitis
Hepatobiliary disorders Fulminant hepatitis, acute hepatic failure
Musculoskeletal and connective tissue disorders Rhabdomyolysis, myopathy
Immune System Disorders Anaphylactic reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

4.9 Overdose

There is no specific antidote. In the event of an overdose, administration of ZYTIGA should be stopped and general supportive measures undertaken, including monitoring for dysrrhythmias. Liver function should also be assessed. In cases of overdose, side effects may be exacerbated and exaggerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.21.12 Hormone inhibitors

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

Mechanism of action

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. 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 luteinising hormone-releasing hormone (LHRH) agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects

Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 38 % of patients treated with abiraterone acetate, versus 10 % of patients treated with placebo, had at least a 50 % decline from baseline in PSA levels.

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 1000 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 3 and Figure 1).

Table 3: Radiographic Progression-Free Survival - Stratified Analysis; Intent-to-treat Population (Study PCR3011)

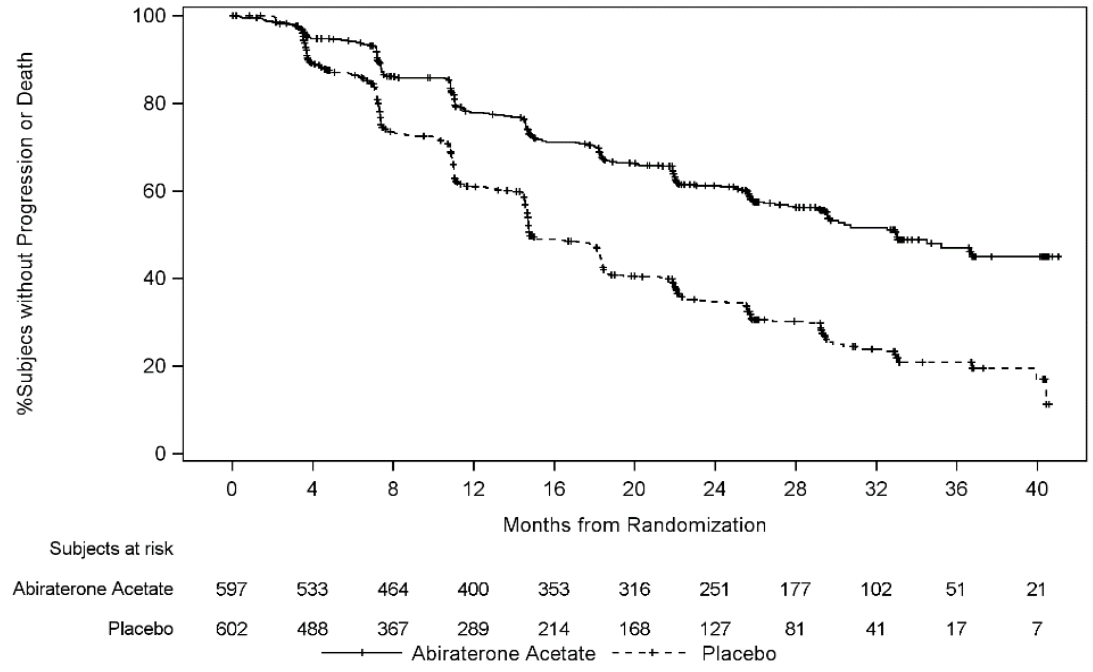
	AA-P	Placebo
Subjects randomised	597	602
Event	239 (40,0 %)	354 (58,8 %)
Censored	358 (60,0 %)	248 (41,2 %)
Time to Event (months)		
Median (95 % CI)	33,02 (29,57, NE)	14,78 (14,69, 18,27)
Range	(0,0+, 41,0+)	(0,0+, 40,6+)
p value[a]	< 0,0001	
Hazard ratio (95 % CI)[b]	0,466 (0,394, 0,550)	

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 38 % reduction in the risk of death compared to Placebo plus ADT (HR = 0,621; 95 % CI: 0,509, 0,756; p < 0,0001), crossing the pre-specified boundary for OS at Interim Analysis 1 of 0,010 (see Table 4 and Figure 2).

Table 4: Overall Survival, Stratified Analysis; Intent-to-treat Population (Study PCR3011)

	AA-P	Placebo
Subjects randomised	597	602
Event	169 (28,3 %)	237 (39,4 %)
Censored	428 (71,7 %)	365 (60,6 %)
Overall Survival (months)		
Median (95 % CI)	NE (NE, NE)	34,73 (33,05; NE)
Range	(0,1; 43,5+)	(1,4+, 43,5+)
p value[a]	< 0,0001	
Hazard ratio (95 % CI)[b]	0,621 (0,509, 0,756)	

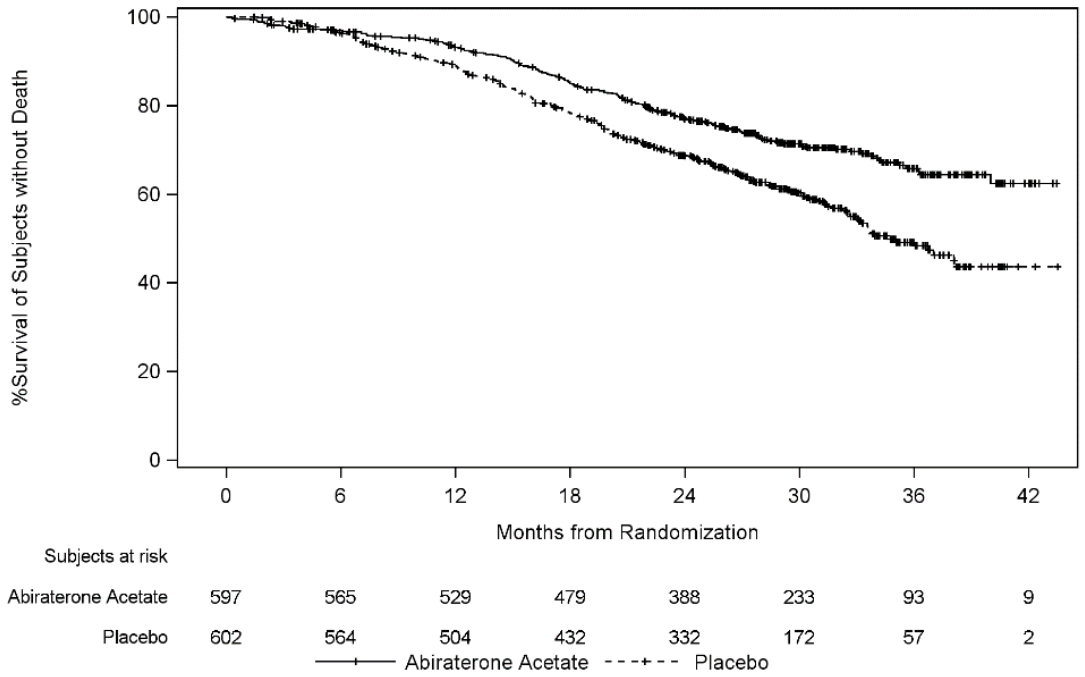
Table 4:	Overall Survival, Stratified Analysis; Intent-to-treat Population (Study PCR3011)	
	AA-P	Placebo

Note:+= censored observation, NE = not estimable. AA-P= subjects who received abiraterone acetate and prednisone

[a] p value is from 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 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study PCR3011)



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 endpoint measures as follows:

Time to skeletal-related event (SRE): There was a 30 % reduction in the risk of skeletal-related events (HR = 0,703; 95 % CI: [0,539; 0,916], p = 0,0086). The median time to SRE has not been reached for the ZYTIGA or placebo study arm.

Time to PSA progression based on PCWG2 criteria: The median time to PSA progression was 33,2 months for patients receiving ZYTIGA and 7,4 months for patients receiving placebo (HR = 0,299; 95 % CI: [0,255; 0,352], p < 0,0001).

Time to subsequent therapy: The median time to subsequent therapy at the time of interim analysis was not reached for patients receiving ZYTIGA and was 21,6 months for patients receiving placebo (HR = 0,415; 95 % CI: [0,346; 0,497], p < 0,0001).

Time to initiation of chemotherapy: The median time to initiation of chemotherapy was not reached for patients receiving ZYTIGA and was 38,9 months for patients receiving placebo (HR = 0,443; 95 % CI: [0,349; 0,561], p < 0,0001).

Time to pain progression: The median time to pain progression was not reached for patients receiving ZYTIGA and was 16,6 months for patients receiving placebo (HR = 0,695; 95 % CI: [0,583; 0,829], p < 0,0001).

The majority of exploratory endpoints favoured treatment with abiraterone acetate and prednisone (AA-P) over Placebo.

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 5 and Figure 3).

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

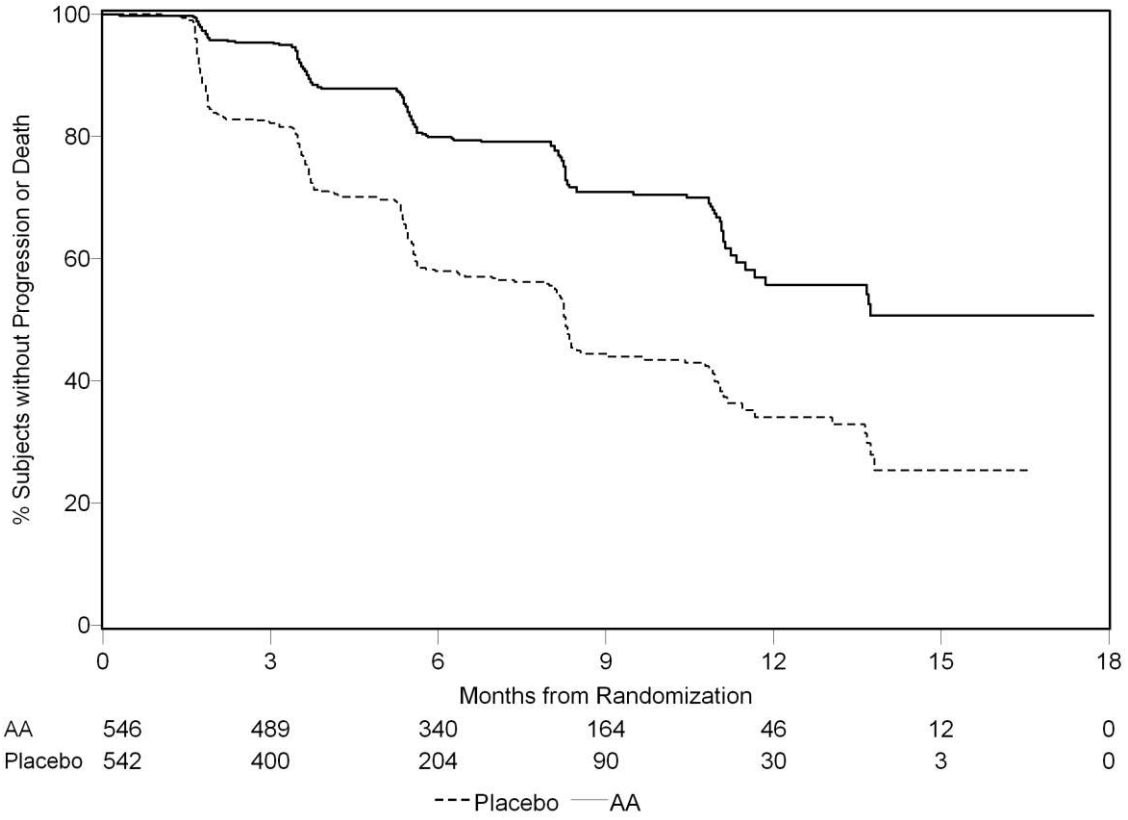
	ZYTIGA (N = 546)	Placebo (N = 542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28 %)	251 (46 %)
Median rPFS in months (95 % CI)	Not reached (11,66; NE)	8.3 (8,12; 8,54)
p-value*	< 0,0001	
Hazard ratio** (95 % CI)	0,425 (0,347; 0,522)	

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 6 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 6: 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)

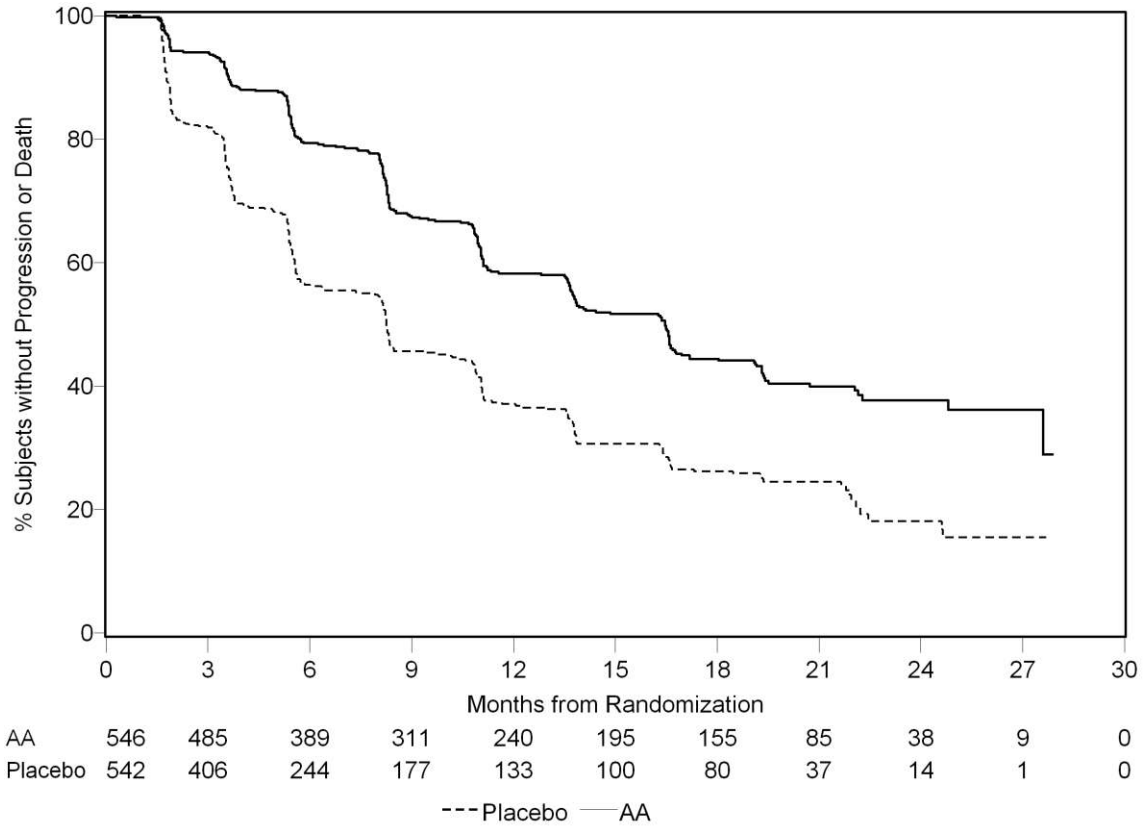
	ZYTIGA (N = 546)	Placebo (N = 542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50 %)	336 (62 %)
Median rPFS in months (95 % CI)	16,5 (13,80; 16,79)	8,3 (8,05; 9,43)
p-value*	< 0,0001	
Hazard ratio** (95 % CI)	0,530 (0,451; 0,623)	

* 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 5). 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 7 and Figure 5). This improvement was demonstrated even though 44 % of patients in the placebo arm received ZYTIGA as subsequent therapy.

Table 7: Study 302: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

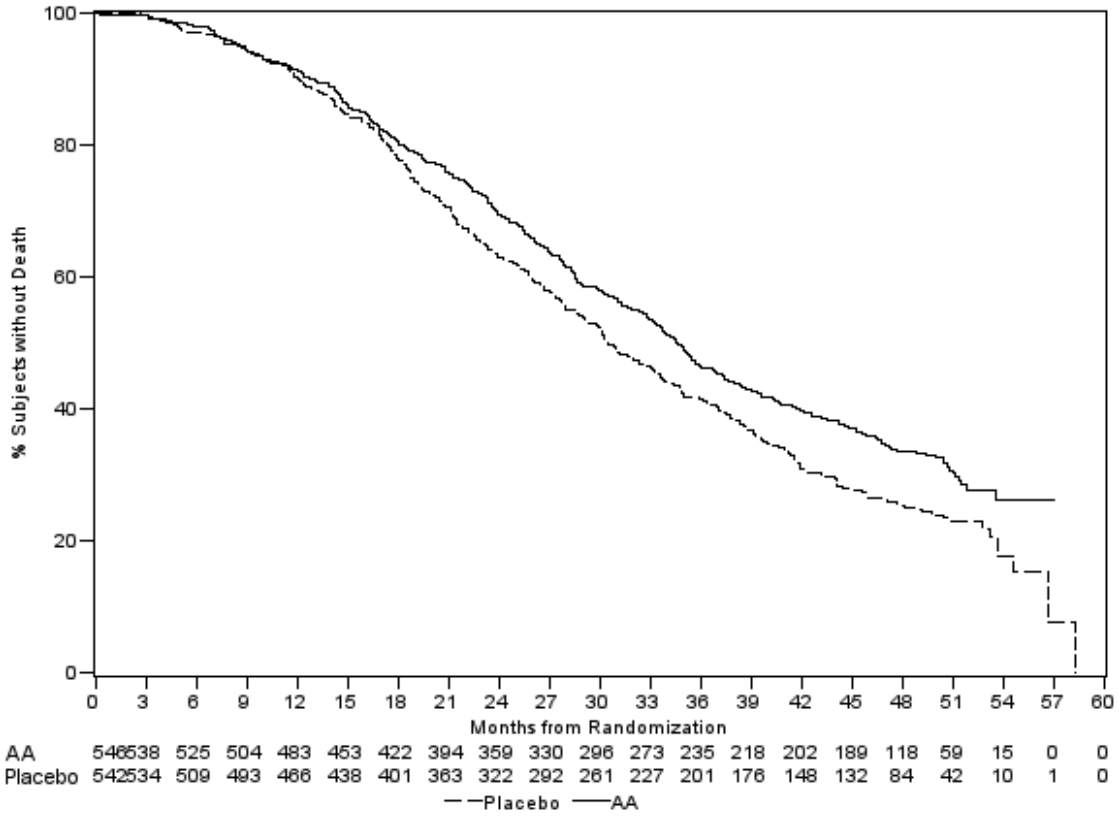
	ZYTIGA (N = 546)	Placebo (N = 542)
Interim survival analysis		
Deaths (%)	147 (27 %)	186 (34 %)
Median survival (months) (95 % CI)	Not reached (NE; NE)	27,2 (25,95; NE)
p-value*	0,0097	
Hazard ratio** (95 % CI)	0,752 (0,606; 0,934)	
Final survival analysis		
Deaths	354 (65 %)	387 (71 %)
Median overall 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 8).

Table 8: Overall survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy

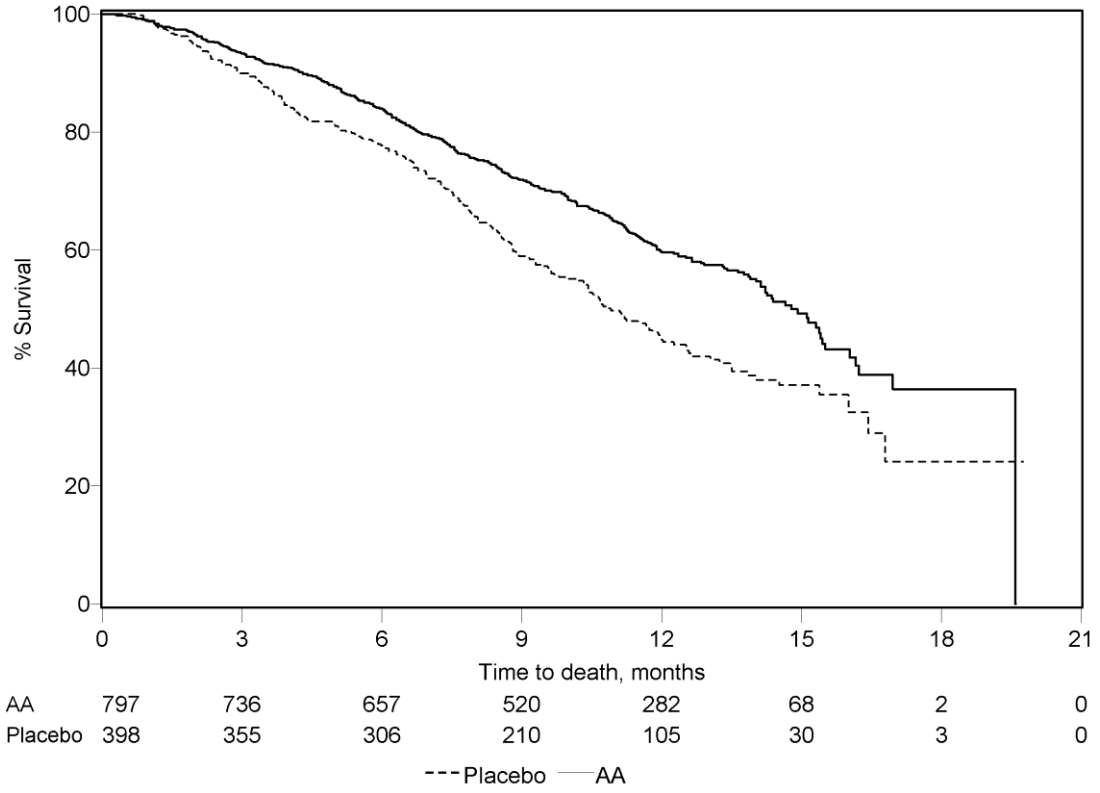
	ZYTIGA (N = 797)	Placebo (N = 398)
Primary Survival Analysis		
Deaths (%)	333 (42 %)	219 (55 %)
Median survival (months) (95% CI)	14,8 (14,1; 15,4)	10,9 (10,2; 12,0)
p-value[a]	< 0,0001	
Hazard ratio (95 % CI)[b]	0,646 (0,543; 0,768)	
Updated Survival Analysis		
Deaths (%)	501 (63 %)	274 (69 %)
Median 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).

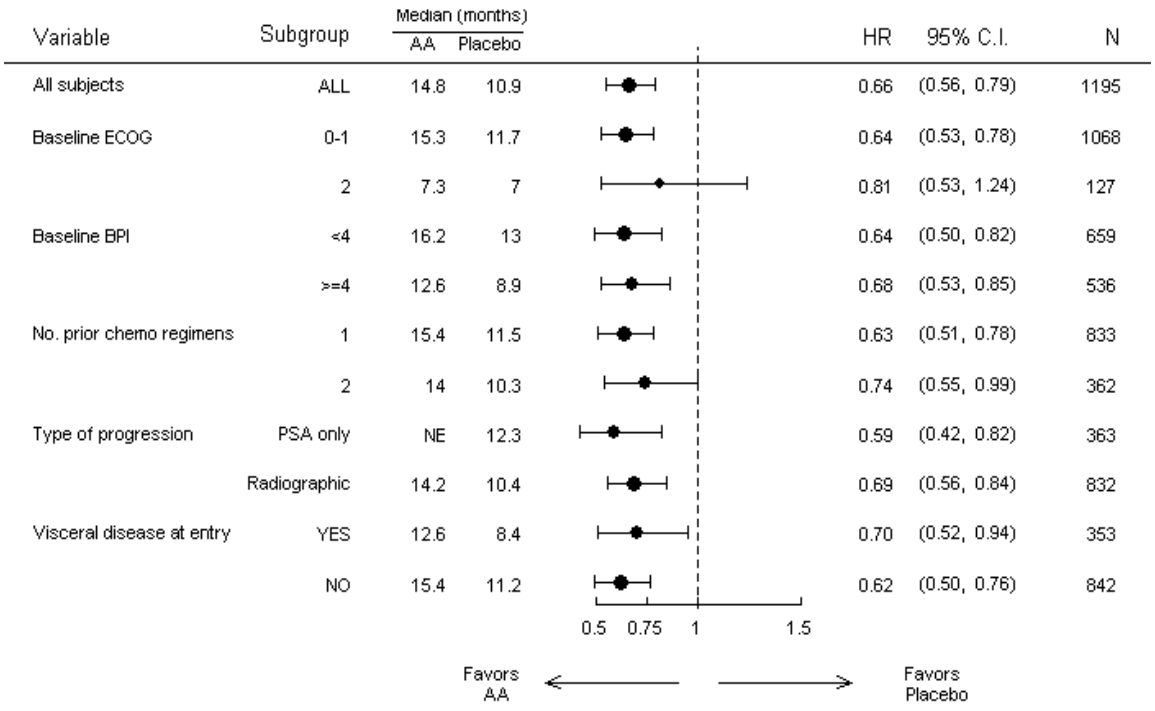
Figure 6: Kaplan Meier survival curves of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy



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 25^{th} 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

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 17-fold 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 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.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92 %) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represents approximately 43 % of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1 g, 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).

Patients with 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 g dose increased by approximately 11 % and 260 % in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. Abiraterone acetate should not be used in patients with moderate to severe hepatic impairment (see section 4.3).

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

Patients with 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 g dose did not increase in subjects with end-stage renal disease on dialysis. Administration of abiraterone acetate in patients with renal impairment, including severe renal impairment, does not require dose reduction (see section 4.2).

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.

The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZYTIGA 250 mg uncoated tablets

Colloidal anhydrous silica

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium lauryl sulfate

ZYTIGA 500 mg film-coated tablets

Tablet core:

Microcrystalline cellulose (silicified)

Croscarmellose sodium

Hypromellose 2910 (15 mPa.S)

Lactose monohydrate

Magnesium stearate

Colloidal anhydrous silica

Sodium lauryl sulfate

Film-coat:

Polyvinyl Alcohol

Titanium Dioxide

Macrogol 3350

Talc

Iron Oxide Red

Iron Oxide Black

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ZYTIGA 250 mg: 24 months

ZYTIGA 500 mg: 36 months

6.4 Special precautions for storage

Store at or below 30 °C. Keep well closed.

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

ZYTIGA 250 mg tablets are supplied in high density polyethylene round white bottles fitted with a white polypropylene cap and packed into an outer carton. Package size is 120 tablets.

Zytiga 500 mg tablets are available in blister packs of 60 tablets. Individual PVdC-PE-PVC/aluminium blister strips are packed inside a folding carton.

6.6 Special precautions for disposal and other handling

Women who are pregnant or women who may be pregnant should not handle ZYTIGA 250 mg tablets without protection, e.g. gloves (see section 4.6).

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements. This medicine may pose a risk to the aquatic environment (see section 5.3).

7. HOLDER OF CERTIFICATE OF REGISTRATION

JANSSEN PHARMACEUTICA (PTY) LTD

(Reg No.: 1980/011122/07)

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Halfway House, Midrand, 1685

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8. REGISTRATION NUMBERS

ZYTIGA 250 mg tablets: 46/21.12/0379

ZYTIGA 500 mg tablets: 52/21.12/0284

ZYTIGA 250 mg tablets:

Namibia Reg. No.: 15/21.12/0085

NS 2

Zimbabwe Reg. No.: 2016/9.5.2/5202

PP

9 DATE OF FIRST AUTHORISATION

Date of registration

ZYTIGA 250 mg tablets: 31 July 2014

ZYTIGA 500 mg tablets: 16 March 2021

10 DATE OF REVISION OF THE TEXT

Date of the most recently revised Professional Information as approved by SAHPRA: 15 November 2022.