Attachment 1: Product information for AusPAR Zytiga Abiraterone acetate Janssen-Cilag Pty Ltd PM-2012-02706-3-4 Final 22 January 2014. This Product Information was approved at the time this AusPAR was published.

ZYTIGA®

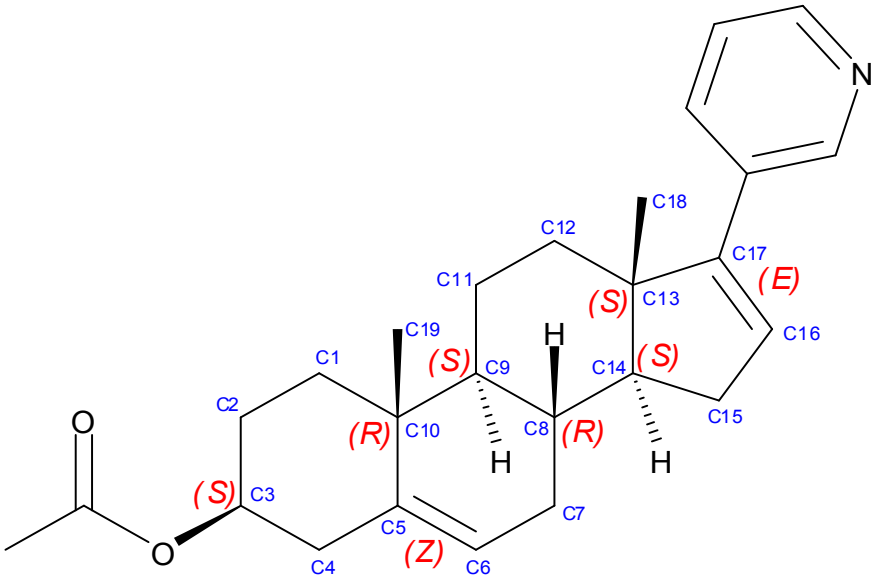
abiraterone acetate

PRODUCT INFORMATION

NAME OF THE MEDICINE

The chemical name of abiraterone acetate is 3β-Acetoxy-17-(3-pyridyl)-androsta-5,16-diene.

Abiraterone acetate has the following chemical structure:



Molecular formula: $C_{26}H_{33}NO_2$ Molecular weight: 391.55

CAS Registry Number: 154229-18-2

DESCRIPTION

ZYTIGA tablets contain 250 mg of the active ingredient abiraterone acetate. The tablets also contain the inactive ingredients: lactose monohydrate; microcrystalline cellulose; croscarmellose sodium; povidone; sodium lauryl sulfate; magnesium stearate and colloidal silicon dioxide.

PHARMACOLOGY

Pharmacodynamics

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 in prostatic tumour tissues. It 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 PRECAUTIONS).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with luteinizing 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 decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. 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, 29% of patients treated with abiraterone, versus 6% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Effects on the QT interval

In a cardiovascular safety study in patients with metastatic advanced prostate cancer there were no significant effects of abiraterone acetate on the cardiac QT/QTc interval.

Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone (see Pharmacodynamics).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the median time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Effect of food on absorption

Administration of ZYTIGA 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 should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see DOSAGE AND ADMINISTRATION).

Distribution

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed 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 represent approximately 43% of total radioactivity.

The major enzymes involved in the metabolism of abiraterone are CYP3A4 for phase I (oxidative) metabolites, the sulfotransferase (SULT) isozyme SULT2A1, and UDP-glucuronosyl transferase (UGT) UGT1A4. No studies have been conducted to determine if drugs that induce or inhibit these enzymes affect the metabolism of abiraterone.

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, 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).

Additional information on special populations

Hepatic impairment

The pharmacokinetics of abiraterone 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 dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk. ZYTIGA should not be used in patients with pre-existing severe hepatic impairment (see CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

For patients who develop hepatotoxicity during treatment with abiraterone suspension of treatment and dosage adjustment may be required (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal impairment

The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable hemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1 g dose did not increase in patients with end-stage renal disease on dialysis.

Administration of abiraterone in patients with renal impairment including severe renal impairment does not require dose reduction (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

The efficacy of abiraterone was established in two randomized placebo controlled multicenter phase 3 clinical studies (studies 301 and 302) of patients with metastatic castration resistant prostate cancer.

Study 302 enrolled patients who were asymptomatic or mildly symptomatic and had not received prior chemotherapy, whereas study 301 enrolled patients who received prior chemotherapy containing a taxane. In both studies patients were using a LHRH agonist or were previously treated with orchiectomy. In the active treatment arms, abiraterone was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone 5 mg twice daily. Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily.

Because changes in PSA serum concentration do not always predict clinical benefit, in both studies patients were maintained on abiraterone until specific discontinuation criteria were met for each study below.

Study 302 (asymptomatic or mildly symptomatic patients who did not receive prior chemotherapy)

In study 302, (n=1088) the median age of enrolled patients was 71 years for patients treated with abiraterone plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. 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.

In study 302, 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. Patients should not be discontinued based on PSA progression alone and should remain on treatment until fully confirmed clinical progression utilising multiple assessment criteria.

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

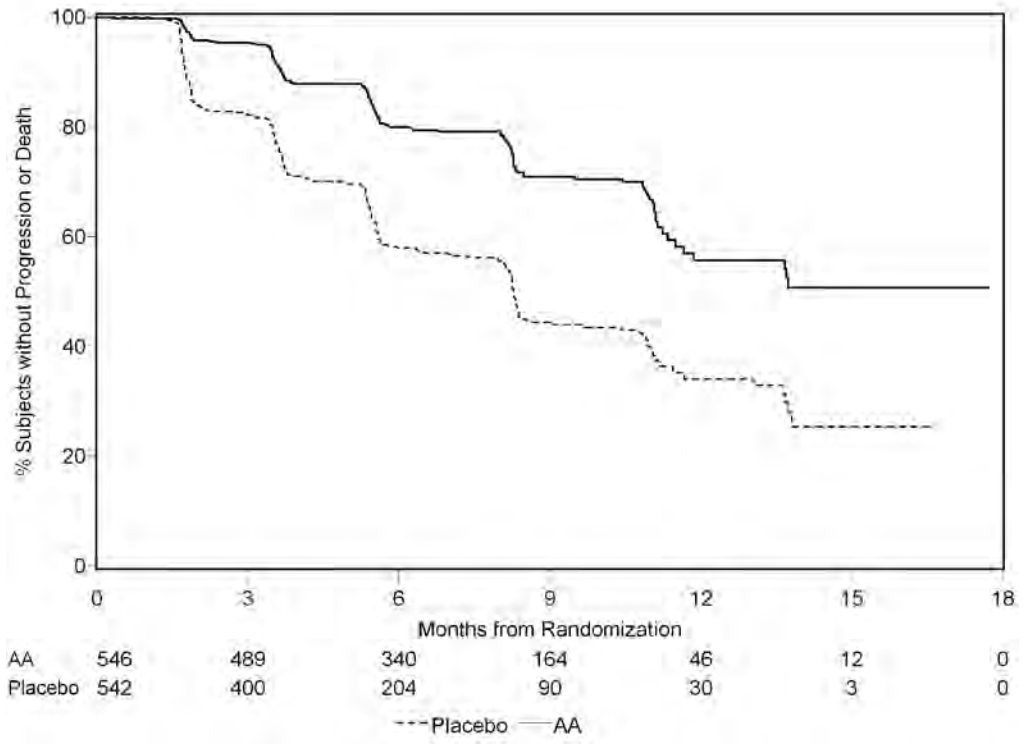
At the planned rPFS analysis there were 401 radiographic progression events; 150 (28%) of patients treated with abiraterone and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 1 and Figure 1).

Table 1: Study 302: Radiographic Progression-free Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy

	ABIRATERONE (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 (11.6, NE)	8.3 (8.12, 8.54)
p value*	< 0.0001	
Hazard ratio** (95% CI)	0.425 (0.347, 0.522)	

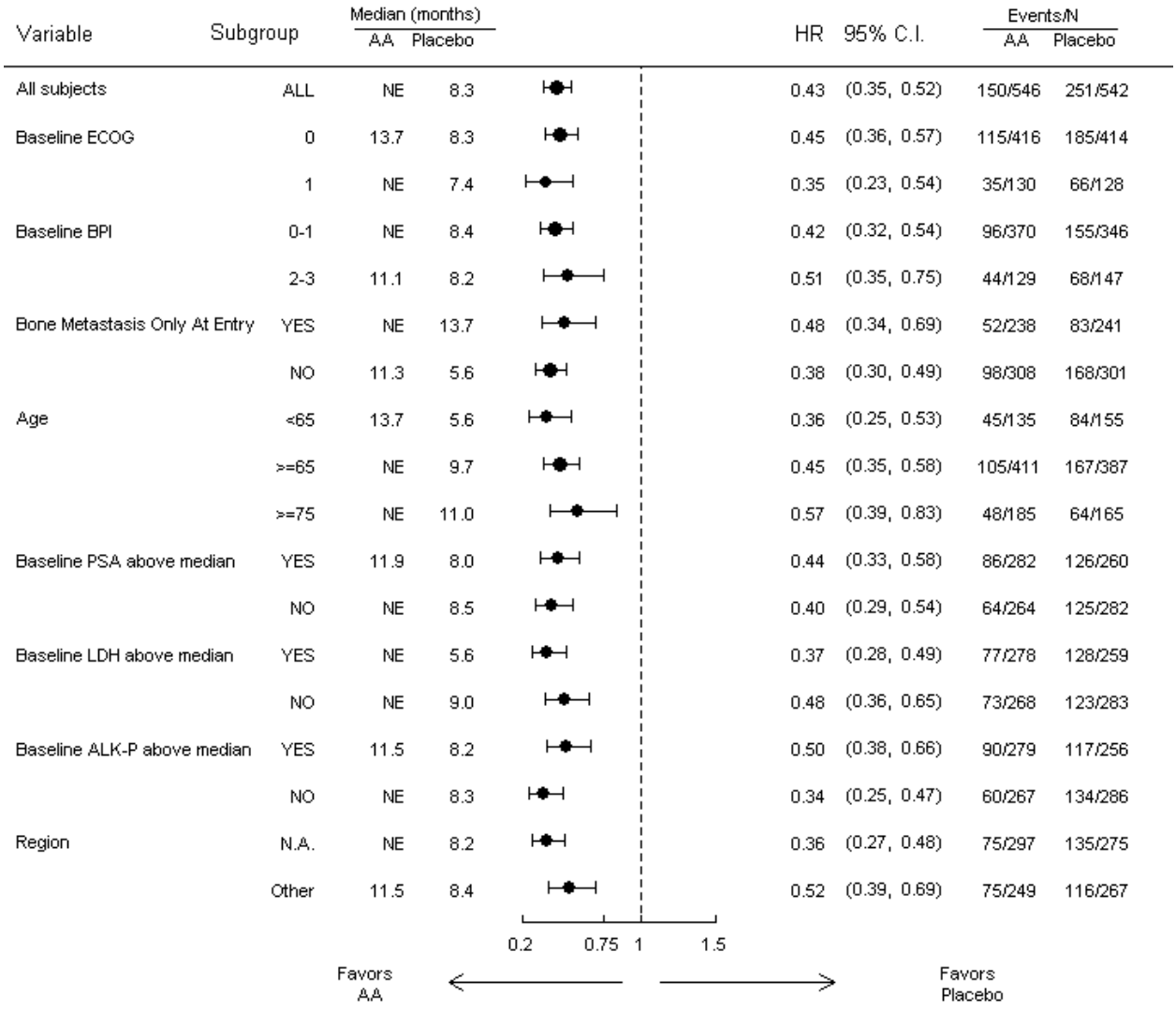
NE = Not estimated
*P value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favours abiraterone

Figure 1: Kaplan Meier curves of radiographic Progression-free Survival in patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH Agonists or prior orchiectomy



Subgroup analyses of rPFS are presented in Figure 2. The treatment effect of abiraterone on the co-primary endpoint of the independent review of rPFS was consistently favorable and highly robust across all subgroups.

Figure 2: **Radiographic Progression-Free Survival by subgroup cut-off date of 20 December 2010**



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.

AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

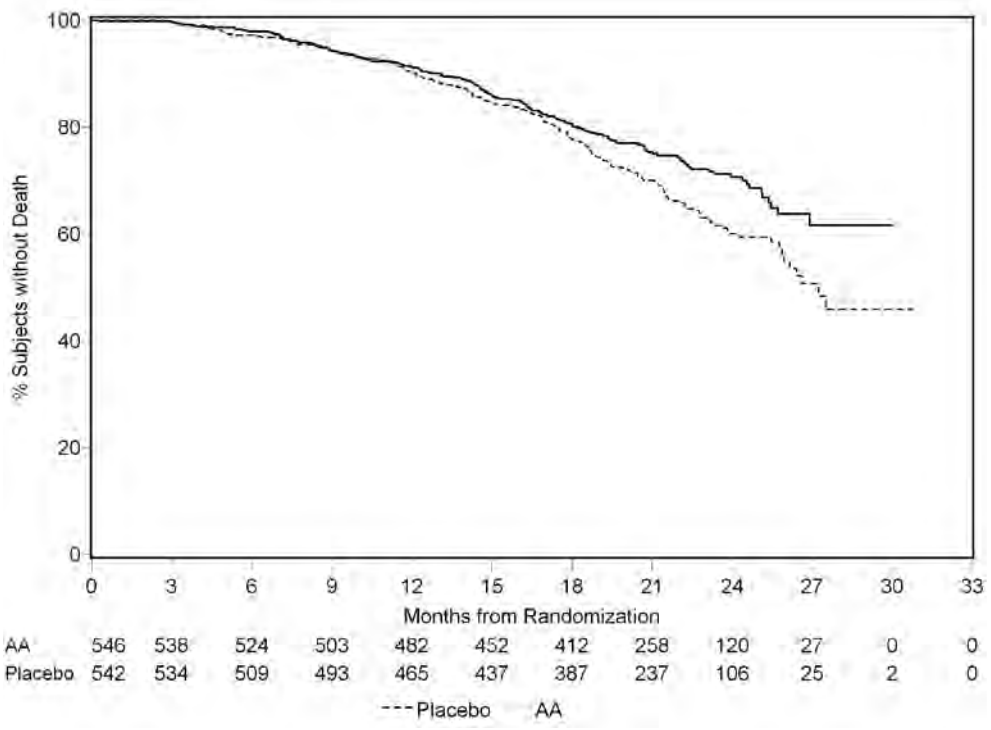
A planned interim analysis for overall survival was conducted after 333 deaths were observed. The study was unblinded, following the recommendation of the Independent Data Monitoring Committee (IDMC), based on the magnitude of clinical benefit observed. Twenty seven percent (147 of 546) of patients treated with abiraterone, compared with 34% (186 of 542) of patients treated with placebo, had died. Overall survival was longer for abiraterone than placebo with a 25% reduction in risk of death (Hazard Ratio = 0.752; 95% CI: 0.606 - 0.934). The p value was 0.0097 which did not meet the pre-specified level (0.0008) to claim statistical significance (see Table 2 and Figure 3).

Table 2: Study 302: Overall Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy

	ABIRATERONE (N=546)	PLACEBO (N=542)
Overall Survival		
Deaths	147 (27%)	186 (34%)
Median overall survival in months (95% CI)	Not reached (NE, NE)	27.2 (25.95, NE)
p value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606, 0.934)	

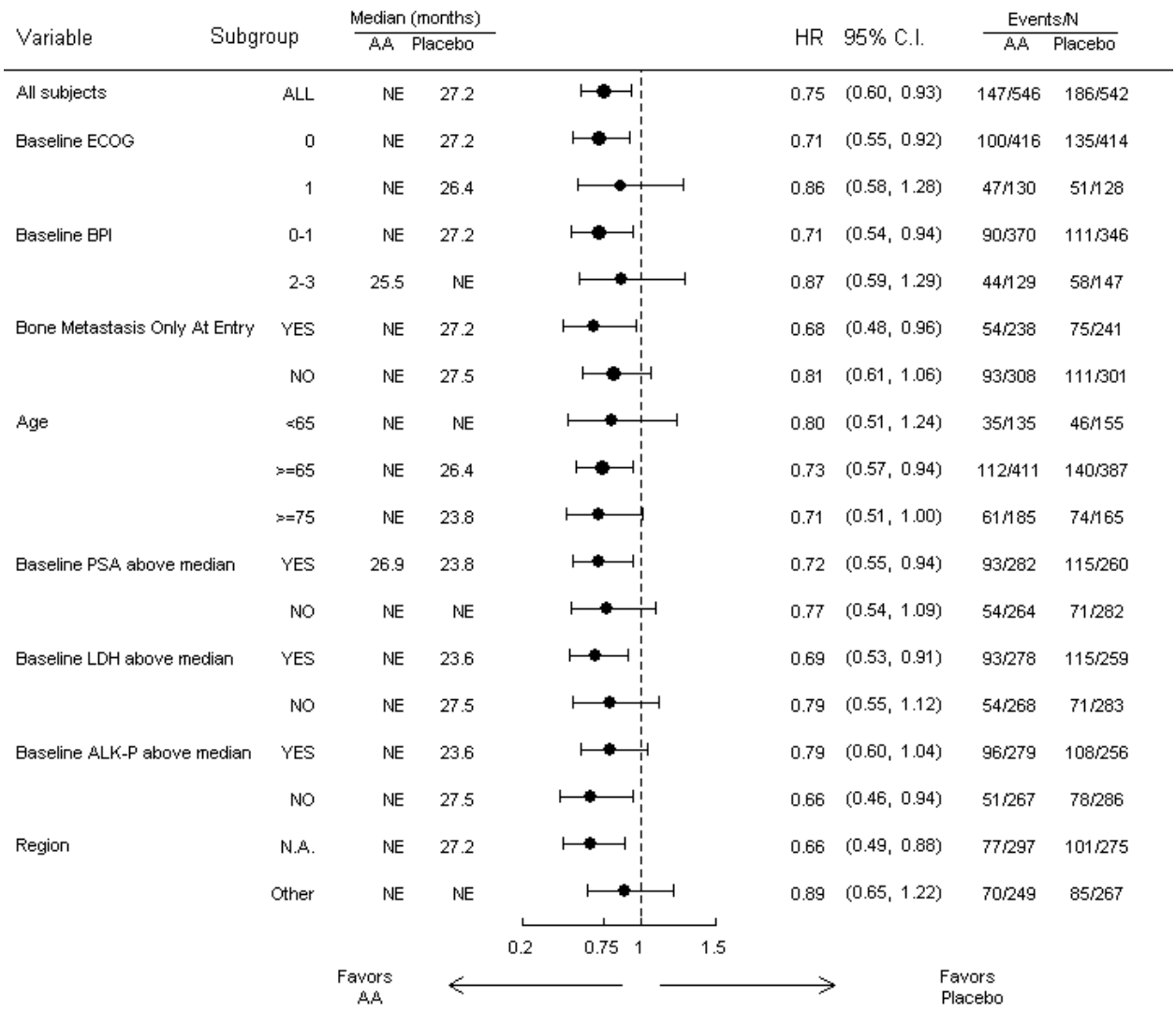
NE = Not estimated
*P value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favours abiraterone

Figure 3: Kaplan Meier Survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy



Subgroup analyses of overall survival are presented in Figure 4. The treatment effect of abiraterone on overall survival was favorable across all subgroups (all HR<1.0).

Figure 4: Overall Survival by subgroup (Study COU-AA-302: ITT Population)



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.

AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone versus placebo treatment in all the secondary endpoint measures as follows.

Time to PSA progression based on PCWG2 criteria:

Median time to PSA progression was 11.1 months for patients receiving abiraterone and 5.6 months for patients receiving placebo (HR=0.488; 95%CI: [0.420, 0.568], p<0.0001). Time to PSA progression was approximately doubled with abiraterone treatment. The proportion of subjects with a confirmed PSA response was greater in the abiraterone group than in the placebo group (62% versus 24%; p<0.0001).

Time to opiate use for cancer pain:

The median time to opiate use for prostate cancer pain was not reached for patients receiving abiraterone and was 23.7 months for patients receiving placebo (HR=0.686; 95%CI: [0.566, 0.833], p=0.0001).

Time to initiation of cytotoxic chemotherapy:

The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving abiraterone and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], p<0.0001).

Time to deterioration in ECOG performance score by ≥ 1 point:

The median time to deterioration in ECOG performance score by ≥1 point was 12.3 months for patients receiving abiraterone and 10.9 months for patients receiving placebo (HR=0.821; 95% CI: [0.714, 0.943], p=0.0053).

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

Objective response:

Objective response was defined as the proportion of subjects with measurable disease achieving a complete or partial response according to RECIST criteria (baseline lymph node size was required to be ≥2 cm to be considered a target lesion). The proportion of subjects with measurable disease at baseline who had an objective response was 36% in the abiraterone group and 16% in the placebo group (p<0.0001).

Pain:

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

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

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

Study 301 (patients who had received prior chemotherapy)

Eleven percent of patients enrolled in study 301 had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with abiraterone.

It was recommended that patients be maintained on their study drugs 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. The primary efficacy endpoint was overall survival.

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

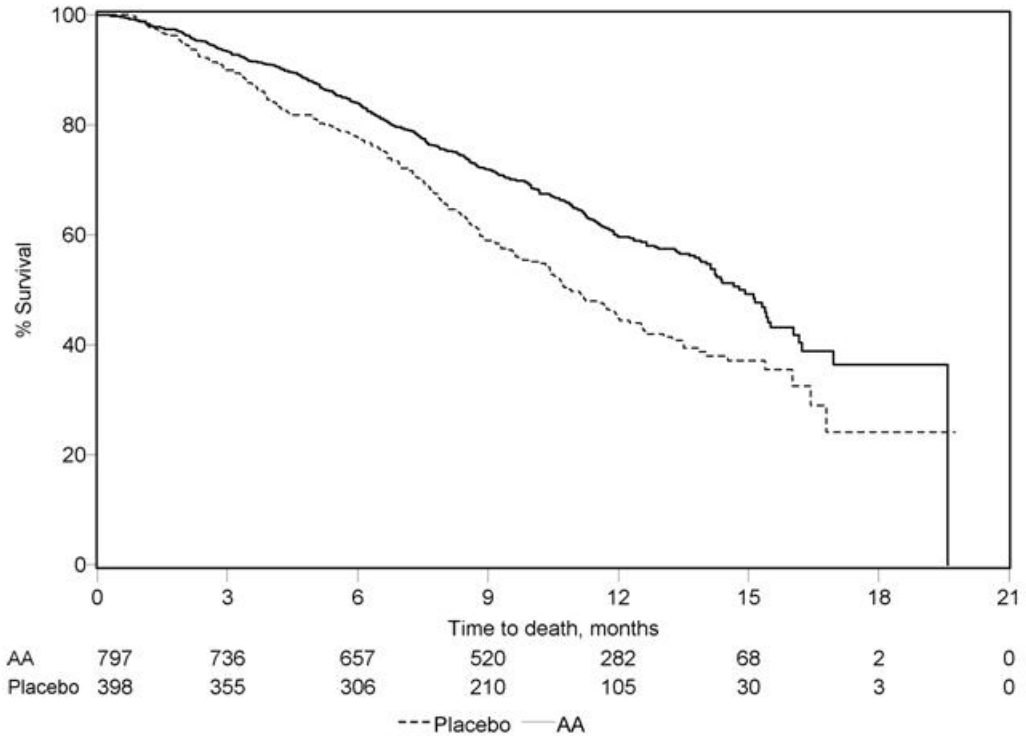
Table 3: Study 301: Overall Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy

	ABIRATERONE (N=797)	PLACEBO (N=398)
Deaths	333 (42%)	219 (55%)
Median overall survival in months (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p value	< 0.0001	
Hazard ratio* (95% CI)	0.646 (0.543, 0.768)	

*Hazard ratio <1 favours abiraterone

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone remained alive compared with the proportion of patients treated with placebo (see Figure 5).

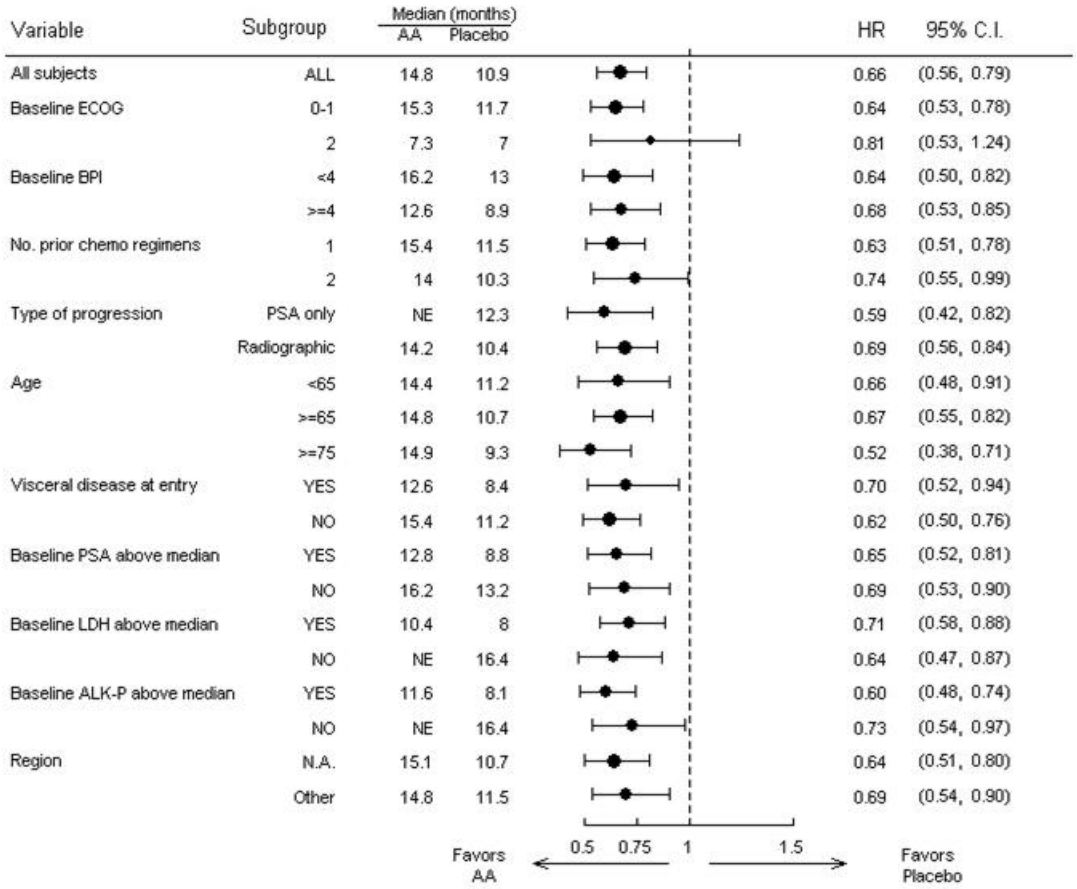
Figure 5: Kaplan Meier survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy



AA = abiraterone acetate

Subgroup survival analyses showed a consistent survival benefit for treatment with abiraterone (see Figure 6).

Figure 6: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval



AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable; No.=number

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

Patients receiving abiraterone demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo: 29% versus 6%, p<0.0001.

The median time to PSA progression was 10.2 months for patients treated with abiraterone and 6.6 months for patients treated with placebo (HR= 0.580; 95% CI: [0.462, 0.728], p< 0.0001).

The median radiographic progression free survival was 5.6 months for patients treated with abiraterone and 3.6 months for patients who received placebo (HR= 0.673; 95% CI: [0.585, 0.776], p<0.0001).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the abiraterone group than in the placebo group (44% versus 27%, p=0.0002).

A lower proportion of patients treated with abiraterone had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%). The time to pain progression at the 25th percentile was 7.4 months in the abiraterone group, versus 4.7 months in the placebo group.

Skeletal-Related Events

A lower proportion of patients in the abiraterone group had skeletal-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 abiraterone group was twice that of the control group at 9.9 months vs 4.9 months.

INDICATIONS

ZYTIGA is indicated with prednisone or prednisolone for the treatment of patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC):

- who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) or
- who have received prior chemotherapy containing a taxane.

CONTRAINDICATIONS

ZYTIGA is contraindicated in women who are or may potentially be pregnant.

ZYTIGA is contraindicated in patients with severe hepatic impairment [Child Pugh Class C]. (see PHARMACOKINETICS, PRECAUTIONS and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The safety of abiraterone in patients with left ventricular ejection fraction (LVEF) < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in study 301) or NYHA Class II to IV heart failure (in study 302) was not established. Before treatment with abiraterone, hypertension must be controlled and hypokalemia must be corrected.

Abiraterone may cause hypertension, hypokalemia and fluid retention (see ADVERSE EFFECTS) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Pharmacodynamics). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia.

Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see ADVERSE EFFECTS). Serum transaminase and bilirubin levels should be measured prior to starting treatment with abiraterone, 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 abiraterone should be interrupted immediately and liver function closely monitored.

Re-treatment with ZYTIGA may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see DOSAGE AND ADMINISTRATION).

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

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. ZYTIGA should not be used in patients with severe hepatic impairment (see PHARMACOKINETICS, CONTRAINDICATIONS and DOSAGE AND ADMINISTRATION).

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 abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage of a corticosteroid may be indicated before, during and after the stressful situation. 17α hydroxylase inhibition by abiraterone decreases glucocorticoid production.

Hyperglycaemia

The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Use with chemotherapy

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

Effects on fertility

In fertility studies in both male and female rats (4-and 3-weeks), abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In studies in mice (4 weeks), rats (4 up to 26-weeks) and monkeys (up to 39-weeks), decreases in testosterone levels, atrophy, aspermia/hypospermia, and/or hyperplasia in the reproductive system were observed at > 125 mg/kg/day in mice, ≥ 30 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed at exposure levels similar to or lower than the human clinical exposure, based on abiraterone AUC.

Use in Pregnancy
Category D

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

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

In an embryofetal developmental study in the rat, abiraterone acetate at ≥10 mg/kg/day affected pregnancy including reduced fetal weight and survival, delayed ossification, and increases in late resorptions and post implantation loss with a subsequent reduction in live fetuses. Effects on the external genitalia (decreased fetal ano-genital distance) 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.

It is not known if 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 child-bearing potential, a condom is required along with another effective contraceptive method.

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

Use in Lactation

ZYTIGA is not for use in women.

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

Use in children
This medicine is not for use in children.

Carcinogenicity

Carcinogenicity studies were not conducted with abiraterone acetate.

Genotoxicity

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests including, an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay. Genotoxicity studies have not been conducted with the main human metabolites of abiraterone.

INTERACTIONS WITH OTHER MEDICINES

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

In the same 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 200%. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when abiraterone is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered. There are no clinical data on the use of abiraterone with drugs that are substrates of CYP2C8.

Abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been investigated. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

Effect on Ability to Drive or Operate Machinery

No studies on the effects of abiraterone on the ability to drive or use machines have been performed. It is not anticipated that abiraterone will affect the ability to drive and use machines.

ADVERSE EFFECTS

Adverse Drug Reactions from Clinical Trials

The most common adverse reactions seen with abiraterone are peripheral edema, hypokalemia, urinary tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, dyspepsia, hematuria, fractures and hypertension.

Abiraterone may cause hypertension, hypokalemia 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 abiraterone versus patients treated with placebo; hypokalemia 18% versus 11%, hypertension 15% versus 11% and fluid retention (peripheral edema) 26% versus 20%, respectively. In patients treated with abiraterone, grades 3 and 4 hypokalemia and grades 3 and 4 hypertension were observed in 4% and 2% of patients, respectively. Mineralocorticoid effects generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse drug reactions (see PRECAUTIONS).

In a phase 3 study of patients with metastatic castration resistant prostate cancer who had received prior chemotherapy (study 301) who were using a LHRH agonist, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone (10 mg daily) in the active treatment arm; placebo plus low dose prednisone or prednisolone (10 mg daily) was given to control patients. Patients were intolerant to or had failed up to two prior chemotherapy regimens, one of which contained a taxane. The average duration of treatment with abiraterone was 8 months.

Adverse drug reactions due to abiraterone in study 301 that occurred at a rate of ≥1% (all grades) are shown in Table 4.

Table 4: Adverse drug reactions due to abiraterone in ≥ 1% of patients in a phase three study (Study 301)[a]						
	Abiraterone 1g daily with prednisone or prednisolone n=791[b]			Placebo with prednisone or prednisolone n=394[b]		
System Organ Class Adverse Drug Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions						
Edema peripheral	25	1	<1	17	1	0
Metabolism and Nutrition Disorders						
Hypokalemia	17	3	<1	8	1	0
Hypertriglyceridemia	1	<1	0	0	0	0
Infections and Infestations						
Urinary tract infection	12	2	0	7	1	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	3	1	0	1	<1	<1
Vascular Disorders						
Hypertension	9	1	0	7	<1	0
Injury, poisoning and procedural complications						
Fractures[d]	6	1	<1	2	0	0
Cardiac Disorders						
Cardiac failure[c]	2	2	<1	1	0	<1
Angina pectoris	1	<1	0	1	0	0
Arrhythmia	1	0	0	0	0	0
Atrial fibrillation	2	1	0	1	1	0
Tachycardia	3	0	0	2	0	0

[a] All patients were receiving an LHRH agonist or had undergone orchiectomy.
[b] n = patients assessed for safety
[c] Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased
[d] Fractures includes all fractures with the exception of pathological fracture.

In a second placebo-controlled, multicenter phase 3 clinical study (study 302), in asymptomatic or mildly symptomatic, chemotherapy naïve patients with metastatic advanced prostate cancer who were using a LHRH agonist or were previously treated with orchiectomy, abiraterone was also administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone 10 mg daily in the active treatment arm. Placebo plus low dose prednisone or prednisolone 10 mg daily was given to control patients. The average duration of treatment with abiraterone in study 302 was 13.8 months.

Adverse drug reactions due to ZYTIGA in study 302 that occurred at a rate of ≥1% (all grades) are shown in Table 5.

Table 5: Adverse drug reactions due to abiraterone in ≥ 1% of patients in a phase three study (Study 302)[a]						
	Abiraterone 1g daily with prednisone or prednisolone n=542[b]			Placebo with prednisone or prednisolone n=540[b]		
System Organ Class Adverse Drug Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Dyspepsia	11	0	0	5	<1	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	12	5	1	5	1	<1
Aspartate aminotransferase increased	11	3	0	5	1	0
Renal and Urinary Disorders						
Hematuria	10	1	0	6	1	0
[a] All patients were using an LHRH agonist or had undergone orchiectomy. [b] n = patients assessed for safety						

The most common adverse drug reactions that resulted in drug discontinuation in combined data from phase 3 studies were alanine aminotransferase increased and aspartate aminotransferase increased (each in < 1% of patients taking abiraterone).

The adverse drug reaction, adrenal insufficiency, occurred in the phase 3 clinical studies at a rate 0.5% in patients taking abiraterone and at a rate of 0.2% inpatients taking placebo.

In the phase 3 studies, 73% of patients were 65 years and over, and 30% were 75 years and over. Adverse effects were more common in patients ≥ 75 years old in both the abiraterone and placebo groups.

Cardiovascular effects

Both phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, 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 (study 302) or cardiac ejection fraction measurement of < 50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominately with the use of LHRH agonists, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the phase 3 studies in patients taking abiraterone versus patients taking placebo were as follows: atrial fibrillation 3.4% vs. 3.4%, tachycardia 2.8% vs. 1.7%, angina pectoris 1.9% vs. 0.9%, cardiac failure 1.9% vs. 0.6% and arrhythmia 1.1% vs. 0.4%.

Hepatotoxicity

Drug-associated hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone. Across all clinical studies, liver function test elevations (ALT or AST increases of > 5 X ULN or bilirubin increases > 1.5 X ULN) were reported in approximately 4% of patients who received abiraterone, typically during the first 3 months after starting treatment. In the 301 clinical study, 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 was withheld or discontinued. Hepatic metastases and baseline elevations in alkaline phosphatase associated with prostate cancer were present in a few of these patients. In two instances marked increases in liver function tests occurred (see section PRECAUTIONS). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone, both patients had normalization of their liver function tests and one patient was re-treated with abiraterone 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. 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). Treatment discontinuations due to ALT and AST increases were reported in 1.7% and 1.3% of patients treated with abiraterone and 0.2% and 0% of patients treated with placebo, respectively. No deaths were reported due to hepatotoxicity event.

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 301 trial, patients with baseline ALT and AST ≥ 2.5X ULN in the absence of liver metastases and > 5X ULN in the presence of liver metastases were excluded. In the 302 trial patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2.5 X ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see DOSAGE and ADMINISTRATION). Patients with elevations of ALT or AST > 20X ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity associated with abiraterone is not understood.

Post-marketing experience

Adverse drug reactions identified during the post-marketing experience based on spontaneous reports with ZYTIGA are described below. The frequencies are provided according to the following convention:
Rare ≥ 1/10000 and < 1/1000

System Organ Class Respiratory, thoracic and mediastinal disorders
Rare: Allergic alveolitis

DOSAGE AND ADMINISTRATION

The recommended dosage of ZYTIGA is 1 g (four 250 mg tablets) as a single daily dose that **must not be taken with food**. ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see Pharmacokinetics – Absorption).

ZYTIGA is used with low-dose prednisone or prednisolone. The recommended dosage of prednisone or prednisolone is 10 mg daily.

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 PRECAUTIONS).

Patients started on ZYTIGA who were receiving a LHRH agonist should continue to receive a LHRH agonist.

Hepatic impairment

No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk. ZYTIGA should not be used in patients with pre-existing severe hepatic impairment (see PHARMACOKINETICS, CONTRAINDICATIONS and PRECAUTIONS).

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 normalize (see PRECAUTIONS). 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 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, discontinue treatment with ZYTIGA. Reduced doses should not be taken with food.

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 dosage adjustment is necessary for patients with renal impairment.

OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

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 arrhythmias. Liver function also should be assessed.

Contact the Poisons Information Centre (telephone 131126) for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

ZYTIGA tablets are white to off-white, oval tablets, debossed with "AA250" on one side.

ZYTIGA tablets are provided in high density polyethylene round white bottles fitted with a polypropylene cap. A bottle contains 120 tablets. Store below 25°C.

NAME AND ADDRESS OF SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd Macquarie Park NSW 2113 Australia
NZ Office: Auckland New Zealand

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

1 March 2012

DATE OF MOST RECENT AMENDMENT

3 December 2013

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