



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Abiraterone Acetate

Proprietary Product Name: Zytiga

Sponsor: Janssen-Cilag Pty Ltd

January 2014

TGA Health Safety
Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
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List of abbreviations

Abbreviation	Meaning
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CIOMS	Council for International Organisations of Medical Sciences
CL	Clearance
ECG	Electrocardiograph
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
F	Absolute bioavailability
GnRH	Gonadotrophin Releasing Hormone
HR	Hazard Ratio
IDMC	Independent Data Monitoring Committee
ISS	Integrated Summary of Safety
ITT	Intention to Treat
mCRPC	Metastatic Castration Resistant Prostate Cancer
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group-2
PD	Pharmacodynamics
PFS	Progression-Free Survival
PK	Pharmacokinetics
PSA	Prostate Specific Antigen
RECIST	Response Evaluation Criteria In Solid Tumours
rPFS	Radiographic Progression-Free Survival
SCS	Summary of Clinical Safety
WHO	World Health Organisation

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Extension of Indications
<i>Decision:</i>	Approved
<i>Date of decision:</i>	20 August 2013
<i>Active ingredient:</i>	Abiraterone acetate
<i>Product name:</i>	Zytiga
<i>Sponsor's name and address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
<i>Dose form:</i>	Tablet
<i>Strength:</i>	250 mg
<i>Container:</i>	Bottle
<i>Pack size:</i>	120 Tablets
<i>Approved therapeutic use:</i>	<i>Zytiga is indicated with prednisone or prednisolone for the treatment of patients with metastatic castration resistant prostate cancer (mCRP) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT)</i>
<i>Route of administration:</i>	Oral (PO)
<i>Dosage:</i>	1 g daily
<i>ARTG number:</i>	180314

Product background

This AusPAR describes the application by the sponsor to extend the indications of Zytiga (Abiraterone acetate) to:

Zytiga is indicated with prednisone or prednisolone for:

- the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT)*
- the treatment of patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) who have received prior chemotherapy containing a taxane.*

Abiraterone inhibits the androgen biosynthesis enzyme 17 α -hydroxylase/C17, 20-lyase (CYP17), thereby decreasing androgen production in the testes, adrenals and prostate tumours and limiting progression of prostate cancer. Its effects are more wide-ranging

than traditional androgen deprivation therapies (ADT) such as Luteinizing-hormone-releasing hormone (LHRH) agonists and orchidectomy which only decrease androgen production in the testes.

The standard of care for a patient who has progressed after ADT, that is, has castration resistant prostate cancer (CRPC), is cytotoxic chemotherapy. Abiraterone is proposed as an alternative in CRPC patients who are asymptomatic or mildly symptomatic before introducing chemotherapy on the basis that abiraterone is less toxic and will give patients a better quality-of-life.

Relevant European Guidelines are the *Guideline on the Evaluation of Anticancer Medicinal Products in Man*¹, *Appendix 1* relating to the use of progression-free survival as a primary endpoint in confirmatory trials² and *Points to Consider* on applications with one pivotal trial³.

Regulatory status

The product received initial Australian Register of Therapeutic Goods (ARTG) Registration on 27 February 2012.

The following table summarises the international regulatory status (Table 1).

Table 1. International regulatory status of Zytiga

Country	Submission Date	Approval Date	Approved Indications
EU – Centralised Procedure*	14 June 2012	18 December 2012	ZYTIGA is indicated with prednisone or prednisolone for: <ul style="list-style-type: none"> the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1) the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen.
United States of America	14 June 2012	10 December 2012	ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.
Canada	15 June 2012	28 May 2013	ZYTIGA® is indicated in combination with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer) in patients who: <ul style="list-style-type: none"> are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy
Switzerland	16 August 2012	25 April 2013	Zytiga is indicated in combination with LHRH agonists and prednisone or prednisolone <ul style="list-style-type: none"> in asymptomatic or mildly symptomatic patients with metastatic castration resistant prostate cancer (mCRPC) without visceral or liver metastases, after failure of androgen receptor blockade and when chemotherapy is not clinically indicated. in patients with advanced metastatic prostate cancer with progression following treatment with docetaxel.
New Zealand	31 August 2012	20 June 2013	ZYTIGA is indicated with prednisone or prednisolone for: <ul style="list-style-type: none"> the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated (see Clinical Trials section) the treatment of patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) who have received prior chemotherapy containing a taxane

*The rapporteur for the EU centralised procedure is Spain and the co-rapporteur is the United Kingdom.

¹ CPMP/EWP/205/95/Rev.3/Corr. Guideline on the evaluation of anticancer medicinal products in man

² EMEA/CHMP/EWP/27994/2008 Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CPMP/EWP/205/95/Rev.3)

³ CPMP/EWP/2330/99 Points to consider on application with 1. Meta-analyses; 2. One pivotal study

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

Introduction

Studies were performed to assess the potential inhibition of CYP2C8 by abiraterone acetate, to characterise the mechanism by which resistance to abiraterone acetate is developed and to characterise impurity R601250. In the oral studies, abiraterone acetate was administered as a mixture in water of 0.5% weight/volume (w/v) Methocel A4M and 0.1% w/v Tween 80 with or without 0.9% w/v sodium chloride (NaCl).

Potential reproductive and juvenile toxicities of abiraterone acetate were also assessed. Although these are not required to support the proposed extension of indication, such studies may be required to support future applications. The sponsor stated in their *Nonclinical Overview* that these studies were performed in support of indications such as paediatric congenital adrenal hyperplasia and metastatic breast cancer.

None of the toxicity studies submitted specifically addressed the new indication, so this will have to be assessed clinically.

Pharmacology

Primary pharmacology

The production of testosterone involves cytochrome P450 (CYP450) isozyme 17 α -hydroxylase/C17,20-lyase (CYP17)-mediated conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone and androstenedione. Inhibition of CYP17 for the treatment of metastatic castration-resistant prostate cancer (mCRPC) aims to reduce testosterone production beyond that afforded by existing androgen-deprivation therapies. Studies submitted in this application gave some evidence of abiraterone binding to the androgen receptor (AR) and inhibiting AR activation induced by eplerenone, suggesting abiraterone may inhibit prostate cancer growth by AR binding, in addition to enzyme inhibition.

Atrophy of hormone-sensitive reproductive organs was consistently observed in repeat dose toxicity studies in rodents dosed orally with abiraterone acetate. These findings support the rationale for using abiraterone acetate to reduce circulating levels of androgens.

Resistance to treatment with abiraterone acetate

Resistance to abiraterone acetate treatment is a known phenomenon, although the mechanisms are not fully understood. Published studies investigating resistance to abiraterone acetate treatment were submitted and they showed that resistance to abiraterone can occur through increased expression of the abiraterone target CYP17A1, or

increased expression of androgen receptor and androgen receptor splice variants that confer ligand-independent receptor trans-activation.

Pharmacokinetics

Pharmacokinetic and toxicokinetic studies included determination of plasma levels of abiraterone and abiraterone acetate *in vivo* after single and/or repeated administration to transgenic mice, pregnant rats and juvenile rats. Presystemic elimination of abiraterone acetate and abiraterone was studied in portal-vein catheterised dogs after administration of abiraterone acetate. Pharmacokinetics and plasma levels of abiraterone acetate and of abiraterone were studied after oral (PO) and intravenous (IV) administration to dogs in the development of possible new formulations, which are not the subject of the current application, and to determine the effect of food on absorption.

The absorption of abiraterone acetate after oral administration was affected by food and vehicle. Exposure was significantly higher when abiraterone acetate was administered with food and also was higher when abiraterone acetate is administered in hydroxypropyl-beta-cyclodextrin compared with the commercial tablet.

Abiraterone acetate is extensively hydrolysed to abiraterone during absorption from the gastrointestinal tract (even before reaching the portal vein in dogs as demonstrated by very low concentrations of abiraterone acetate in the portal vein) and peak plasma concentrations of abiraterone are reached rapidly (within 1 hour) in dogs, mice and rats, consistent with results from the original submission in mice, rats and monkeys.

Exposure was decreased after repeated dosing in male and female mice and male rats. In juvenile rats, plasma levels were lower on Day 27 (dosing Day 10) than on Day 18 (dosing Day 1). The decrease in exposure in juvenile rats after repeated administration may have been due to the ageing of the experimental rats during the course of the study.

Pharmacokinetic drug interactions

In vitro studies of the effects of abiraterone acetate on CYP2C8, 2B6 and 2C19 were conducted. Both abiraterone and abiraterone acetate were strong inhibitors of CYP2C8 with 50% inhibitory concentration (IC₅₀) values of approximately 3 µM. Abiraterone and abiraterone acetate weakly inhibited CYP2B6 and CYP2C19, with IC₅₀ values ≥ 10 µM, which was the highest soluble concentration. It had previously been shown that abiraterone is a competitive, potent inhibitor of CYP1A2 and CYP2D6 (binding affinity constant (K_i) 0.39-0.44 µM), and a competitive moderate inhibitor of CYP3A4/5 (K_i 8 µM), CYP2C9 (K_i 29.8 µM) and CYP2C19 (K_i 46.3 µM).

Pharmacokinetic interactions with a CYP2D6 substrate, dextromethorphan have been observed in humans, though not with a CYP1A2 substrate, theophylline. Abiraterone has the potential to interact with CYP2C8 substrates.

Toxicology

A Good Laboratory Practice (GLP) compliant repeat-dose toxicity study of 4 weeks duration was conducted in mice as a preliminary dose range finding study in support for a future carcinogenicity study. Abiraterone acetate was administered PO once daily as a suspension in 0.5 % w/v Methocel A4M and 0.1 % w/v Tween 80 in demineralised water. Doses used in the mouse study were associated with exposure (area under the concentration time curve (AUC)) to abiraterone higher than that expected in humans, and were sufficient to cause observable pharmacological effects.

Consistent with the effects exhibited after repeat dose administration to rats and monkeys and in a dose range-finding 2 week study in mice (previous submission), the main effects observed at all dose levels (125-1500 mg/kg/day; exposure ratios 1-21) in the 4 week mouse study were atrophy of testes and oligospermia in the epididymides, vagina in various oestrous stages at different doses (related to steroid metabolism interference), hypokalaemia and hepatic toxicity (centrilobular hypertrophy, periportal subacute inflammation and multifocal subcapsular necrosis of hepatocytes, increased liver weight, increased serum alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin). Mild anaemia was observed at all doses, associated with extramedullary haematopoiesis of the spleen at ≥ 750 mg/kg/day. Some high dose male mice displayed transiently decreased motor activity and hunched appearance.

Table 2. Relative exposure

Duration, route, sex (sample time) (Study No.)	Abiraterone acetate dose (mg/kg/day)	Abiraterone C_{max} (ng/mL) at respective doses (respective animal:human exposure ratio) ¹	Abiraterone $AUC_{(0-\infty \text{ or } 24 \text{ h})}$ (ng.h/mL) at respective doses (respective animal:human exposure ratio) ¹
Mouse (CByB6F1, Tg.rasH2 non-transgenic littermate)(Fed) 28 days PO, (Day 27) (TOX9688)	125	582 / 507 (2.6 / 2.2)	886 / 1327 (0.89 / 1.3)
	375	858 / 660 (3.8 / 2.9)	3273 / 3690 (3.3 / 3.7)
	750	1203 / 1124 (5.3 / 5.0)	5086 / 10971 (5.1 / 11)
	1500	1862 / 2547 (8.2 / 11)	11187 / 20874 (11 / 21)

¹ Male/female data. Animal:human exposure ratios are based on human exposure data from clinical trial COU-AA-006, where peak plasma concentration (C_{max}) was 226 ng/mL and $AUC_{(0-24 \text{ h})}$ was 993 ng.h/mL after 1000 mg/day abiraterone acetate.

Reproductive toxicity

Fertility studies in male and female rats, embryofetal development studies in rats, and a preliminary toxicity study in juvenile rats, were submitted. These studies are not required to support the registration of abiraterone acetate for the proposed extension of indication, but such studies may be required for any future application to extend these indications to include women, juvenile patients or patients without cancer. The sponsor stated that the reproductive and developmental toxicity studies were performed in support of indications such as paediatric congenital adrenal hyperplasia and metastatic breast cancer.

Table 3. Relative exposure

Duration, route, sex (sample time) (Study No.)	Abiraterone acetate dose (mg/kg/day)	Abiraterone C_{max} (ng/mL); (respective animal:human exposure ratio) ¹	Abiraterone $AUC_{(0-24 \text{ h})}$ (ng.h/mL); (animal:human exposure ratio) ¹
Pregnant rat (SD) 11 days, PO (Day 9) (TOX10115)	10	10.8 (0.05)	34 (0.03)
	30	33.8 (0.15)	109 (0.11)
	100	55.7 (0.25)	367 (0.37)

¹ Animal:human exposure ratios are based on human exposure data from clinical trial COU-AA-006, where C_{max} was 226 ng/mL and $AUC_{(0-24 \text{ h})}$ was 993 ng.h/mL after 1000 mg/day abiraterone acetate.

Complete loss of fertility was observed in male rats (including loss of sperm motility) after treatment with 300 mg/kg/day for 4 weeks. Increased pre-implantation loss was observed in female rats after treatment with 300 mg/kg/day for 3 weeks. Oestrous cycles were disrupted with females showing extended periods of oestrus and increased cycle lengths, without effects on copulation, fertility indices and the pre-coital interval. A lower dose administered to both sexes (30 mg/kg/day) caused milder effects, which were also presumably related to the pharmacological effect of the drug. The effects in both sexes were reversible after 8 weeks (male) or 4 weeks (female) recovery.

In the embryofetal development studies, when administered to pregnant rats at 10-300 mg/kg/day, abiraterone acetate increased late resorptions and postimplantation loss, resulting in reductions in live fetuses. A reduction in ano-genital distance in male fetuses was observed as a result of inhibition of testosterone production.

Abiraterone acetate caused mortalities in pregnant rats at doses of 100 and 300 mg/kg/day. In a previous submission, mortality was observed only at 400 mg/kg/day in a 26 week study in non-pregnant rats. It is possible that pregnant rats are more sensitive to abiraterone acetate than non-pregnant rats.

No external, visceral or skeletal abnormalities were observed at up to 100 mg/kg/day; therefore abiraterone acetate is not considered teratogenic. However, abiraterone affect the development of reproductive organs. Pregnancy category D⁴ remains appropriate for abiraterone acetate.

Hormonal profiling

No significant changes in corticosterone concentrations were observed in male or female rats in a 2-week mechanistic study (non GLP study) in rats at abiraterone acetate doses of 50 or 400 mg/kg. Serum progesterone was increased by up to 43 fold in male rats only. Reflecting the pharmacological activity of abiraterone acetate, serum testosterone was decreased by up to 90% and serum luteinising hormone increased by up to 7 fold in males.

Impurities

Three new studies to qualify impurities were submitted. None of the studies identified safety concerns due to the presence of the impurities at the proposed limits.

Paediatric use

Studies in juvenile animals are not required to support the registration of abiraterone acetate for the proposed extension of indication but such studies may be required for any future application to extend these indications to include juvenile patients.

In a non GLP juvenile rat study with very limited parameters examined, treatment with abiraterone acetate at 300 mg/kg/day from day 18 of age for 10 days caused reductions in testis and epididymal weights in males. In males and females, body weight gain was reduced between days 18 and 22 of age.

Nonclinical summary and conclusions

- Abiraterone acetate is a prodrug for the active ingredient, abiraterone which inhibits cytochrome (CYP) 450 isozyme 17 α -hydroxylase/C17,20-lyase (CYP17) mediated

⁴ Drugs which have caused, or are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialised texts should be consulted for further details.

conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone and androstenedione.

- Nonclinical data for this application comprised well conducted pharmacokinetics, repeat dose toxicity, reproductive and embryofetal toxicity studies as well as studies with impurities which comprised a 1 month repeat dose toxicity study and genotoxicity studies. Pivotal studies were GLP compliant and all *in vivo* studies were performed with abiraterone acetate administered by the intended clinical route (PO). Doses used were adequate in terms of eliciting expected primary pharmacological effects, using higher doses than those used in studies previously submitted. Published pharmacology studies were also provided.
- It was shown in literature references submitted, that resistance to abiraterone can occur through increased expression of the abiraterone target CYP17A1 or increased expression of androgen receptor and androgen receptor splice variants. There was also some evidence of abiraterone binding to the androgen receptor (AR) and inhibiting AR activation induced by eplerenone.
- As previously demonstrated, after PO administration, the acetate is extensively hydrolysed to abiraterone during absorption from the gastrointestinal tract and systemic levels of the prodrug are negligible. Exposure was decreased after repeated dosing in male and female mice and male rats. In juvenile rats, plasma levels were lower than in adult rats after repeated dosing. The decrease in exposure in juvenile rats after repeated administration may have been due to the ageing of the experimental rats during the course of the study.
- Oral absorption of abiraterone acetate is enhanced by food and affected by the type of vehicle. Exposure was higher when abiraterone acetate is administered in hydroxypropyl-beta-cyclodextrin compared with the commercial tablet.
- Both abiraterone and abiraterone acetate were strong inhibitors of CYP2C8 with IC_{50} values of approximately 3 μ M. Abiraterone and abiraterone acetate weakly inhibited CYP2B6 and CYP2C19, with IC_{50} values \geq 10 μ M, which was the highest soluble concentration. Abiraterone has the potential to interact with CYP2C8 substrates.
- A new 4 week repeat dose toxicity study in mice showed no new target organ toxicity from previously evaluated studies in mice, rats and monkeys. Findings in the mouse study were atrophy of testes and oligospermia in the epididymides, vagina in various oestrous stages at different doses, hypokalaemia and hepatic toxicity (centrilobular hypertrophy, periportal subacute inflammation and multifocal subcapsular necrosis of hepatocytes, increased liver weight, increased serum ALP, ALT, AST and bilirubin), and mild anaemia (associated with extramedullary haematopoiesis of the spleen). Some high dose male mice displayed transiently decreased motor activity and hunched appearance.
- In a mechanistic study, decreases in testosterone and subsequent increases in luteinizing hormone (LH) levels (due to lack of negative feedback from testosterone on pituitary) were demonstrated in male rats where PO abiraterone acetate was associated with atrophy of male genital tract organs and increased pituitary weights. Atrophy of hormone-sensitive male reproductive organs and decreased systemic androgen levels had been consistently observed in the repeat dose toxicity studies of PO abiraterone acetate in rodents and monkeys. These findings continue to support the rationale for using abiraterone acetate to reduce circulating levels of androgens.
- In previously evaluated studies, abiraterone caused decreases in testosterone levels, atrophy, aspermia/hypospermia and/or hyperplasia in the reproductive system in mice, rats and monkeys. These effects, which are consistent with the antiandrogenic

pharmacological activity of abiraterone, were observed at exposure levels similar to or lower than the human clinical exposure.

- Increased pre-implantation loss in female rats and complete loss of fertility in male rats were observed after treatment with 300 mg/kg/day for 3 and 4 weeks, respectively. Oestrous cycles were disrupted with females showing extended periods of oestrus and increased cycle lengths, without effects on copulation, fertility indices and the pre-coital interval. All effects were reversible. Abiraterone acetate caused mortalities in pregnant rats at doses of ≥ 100 mg/kg/day. In an embryofetal development study in rats, abiraterone acetate at ≥ 10 mg/kg/day affected pregnancy including reduced fetal weight and survival, delayed/incomplete ossification, increase 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.
- Impurities in the finished product and the drug substance have been qualified by nonclinical studies.

Conclusions and recommendation

- There continues to be adequate nonclinical evidence to support the use of abiraterone acetate to reduce circulating androgen levels. Findings in new toxicity studies in mice and impurity qualification studies in rats given abiraterone acetate PO for up to 4 weeks were consistent with those previously evaluated in rodents and were associated with the pharmacology of the drug.
- The liver was a target organ for toxicity in the mouse and rat studies and was also observed in previously evaluated studies. Hepatotoxicity is unrelated to the pharmacology of abiraterone acetate. It is acknowledged that the proposed Product Information includes information about the potential for hepatotoxicity, which is to be monitored as part of the postmarket monitoring program.
- There were no novel toxicity findings that preclude approval of this application.
- The nonclinical evaluator proposed amendments to the draft Product Information.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Current methods of castration (GnRH agonists and antagonists, orchidectomy) inhibit production of testosterone from the testes. Abiraterone inhibits the production of testosterone from the testes and from other sites such as the adrenal and from prostate cancer tissue. The drug might therefore be expected to be effective in patients who have become castration resistant. The safety profile of abiraterone is also more favourable than that of taxanes. Hence the introduction of abiraterone prior to the use taxane chemotherapy is a logical rationale for the application.

Scope of the clinical dossier

The clinical submission to support the new indication included clinical efficacy and safety data from one large pivotal randomised controlled trial. Population PK data were also collected during this trial.

The submission contained the following clinical information:

- 1 population pharmacokinetic analysis;
- 1 pivotal efficacy/safety study (Study 302) in chemotherapy-naïve metastatic Castration Resistant Prostate Cancer (mCRPC) subjects;
- Safety updates of several previously submitted phase I and II studies;
- An integrated summary of safety (ISS) which provided additional tabulations of safety data to those contained in the sponsor's *Summary of Clinical Safety*;
- Literature references.

Paediatric data

The submission did not include paediatric data. As prostate cancer is disease of adults, this is acceptable.

Good clinical practice

The report for the pivotal study included an assurance that the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with Good Clinical Practice and other applicable regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

The only new PK data in the submission come from a population PK analysis of plasma samples obtained from a subgroup of patients who participated in the pivotal study (Study 302).

Evaluator's overall conclusions on pharmacokinetics

The PK of abiraterone in patients who are naïve to chemotherapy is comparable to that previously documented for the drug.

Pharmacodynamics

No new PD data were submitted.

Efficacy

Dosage selection for the pivotal studies

The dose selected for use in the pivotal study (Study 302) was the same as that currently approved (that is, 1,000 mg daily). The original dose was justified on the grounds that, in dose-ranging studies:

- Dose limiting toxicity was not observed with doses up to 2,000 mg per day; and

- A plateau in the increase in upstream hormones (for example, corticosterone) was observed at a dose of 750 mg per day.

Comment: CYP17 activity is likely to be similar in the currently approved and proposed new populations. The decision to use the same dose is therefore acceptable.

Evaluator's conclusions on clinical efficacy

The pivotal study was well designed and conducted. The design generally complied with the relevant European Union (EU) guidelines^{5,6} adopted by the TGA. The use of the novel co-primary endpoint of rPFS was adequately justified.

The results for the co-primary endpoint of OS just failed to meet the pre-specified criterion for statistical significance. It might be expected that further analyses of OS, with more mature OS data, would establish a statistically significant effect on overall survival. However, the ability of patients in the placebo arm to now crossover and receive abiraterone may make demonstration of a survival benefit impossible.

There was a highly significant benefit with abiraterone treatment for the co-primary endpoint of rPFS. Although a novel endpoint, it is analogous to the conventional PFS endpoint that is accepted by the TGA. The novel aspects of the rPFS endpoint (determination of progression using bone scan criteria) are objective and have been recommended by an expert consensus group not associated with the sponsor.

The OS and rPFS data are supported by convincing results on the secondary endpoints, particularly those relating to the initiation of cytotoxic chemotherapy and opiate analgesia. The other endpoints suggest that abiraterone is likely to be also associated with maintenance of functional status/quality of life.

Overall the data from the pivotal study are considered to provide convincing evidence of the efficacy of abiraterone in chemotherapy-naïve patients with mCRPC.

Only one pivotal efficacy study was submitted. The TGA has adopted an EU "*Points to Consider*" document⁷ relevant to this situation. The pivotal study is considered to meet the prerequisites in section III.2 of this document. It could also be argued that the previously submitted Phase III trial (Study 301) was conducted in a similar population of patients and hence the EU document should not apply.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy study

In the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were assessed voluntary subject reporting and investigator review of subject history. For all AEs the investigator was required to assess causality of the event. A drug-related AE was defined as one that had an

⁵ European Medicines Agency. Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.); 2005.

⁶ European Medicines Agency. Appendix 1 To The Guideline On The Evaluation of Anticancer Medicinal Products In Man: Methodological Considerations For Using Progression-Free Survival (PFS) As Primary Endpoint In Confirmatory Trials For Registration (EMEA/CHMP/EWP/27994/2008); 2008.

⁷ European Medicines Agency. Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99); 2001.

unlikely, possible or related relationship to study medication. Severity of events was graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.

- Physical examination was conducted at regular intervals.
- Laboratory tests were performed at regular intervals.
- Full blood count: haemoglobin (Hb), haematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count (with differential), platelet count;
- Chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, direct bilirubin, gamma-glutamyl transferase (at screening only), glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, total bilirubin, total protein, uric acid. Liver function tests (LFTs) were measured at Day 15 of Cycles 2 and 3 only.
- Coagulation factors: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR); - performed at screening and Day 15 only.
- Serum lipids: cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides.
- Urinalysis: blood, protein, glucose (with microscopic examination if abnormal) was performed at baseline only.
- Electrocardiograms (ECGs) were performed at screening, at Cycles 3, 5, 7, and 10 and then every 3 cycles beyond Cycle 10, and at the End-of-Study Visit
- Left ventricular ejection fraction (LVEF) assessment by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan was performed at baseline only.

Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies assessing safety as a primary outcome.

Patient exposure

The extent of exposure to abiraterone/placebo in the pivotal study, as of 20 December 2011, is summarised in Table 4. Median duration of treatment was 13.8 months in the abiraterone arm and 8.3 months in the placebo arm.

Table 4: Pivotal Study 302 – Extent of exposure

	AA (N=542)	Placebo (N=540)
Total treatment duration (months)		
n	542	540
> 0 months	542 (100.0%)	540 (100.0%)
≥3 months	506 (93.4%)	452 (83.7%)
≥6 months	439 (81.0%)	322 (59.6%)
≥9 months	381 (70.3%)	250 (46.3%)
≥12 months	302 (55.7%)	184 (34.1%)
≥15 months	244 (45.0%)	144 (26.7%)
≥18 months	207 (38.2%)	117 (21.7%)
≥21 months	131 (24.2%)	72 (13.3%)
≥24 months	70 (12.9%)	29 (5.4%)
≥27 months	17 (3.1%)	5 (0.9%)
Mean (SD)	14.31 (7.665)	10.36 (7.541)
Median	13.80	8.28
Range	(0.3, 29.9)	(0.1, 28.1)

Postmarketing experience

There were no post-marketing data included in with the current submission. The sponsor's *Summary of Clinical Safety* included the following statement:

"The first marketing approval for abiraterone acetate was on 28 April 2011 in the United States. Based on the 2,245,830 grams distributed worldwide, the estimated post marketing exposure for abiraterone acetate from launch to 31 January 2012 is 2,245,830 person-days. No new ADRs have been detected for abiraterone acetate from post marketing data."

Safety Issues with the potential for major regulatory impact

Liver toxicity

See *Adverse events of special interest Hepatotoxicity* (Attachment 2). The additional analyses in the Summary of Clinical Safety (SCS)/ Integrated Summary of Safety (ISS), based on previously evaluated studies, gave similar results.

Haematological toxicity

Examination of the incidence of serious haematological AEs in the pivotal Study 302 did not suggest any increased risk for serious idiosyncratic haematological events with abiraterone. In a combined analysis of the two Phase III placebo-controlled studies (301 and 302) the incidence of pancytopenia was 0.2% with abiraterone and 0.3% with placebo.

Serious skin reactions

There was no suggestion of an increased incidence of severe skin reactions with abiraterone in the pivotal study. There were no cases of Stevens-Johnson syndrome or Toxic Epidermal Necrosis reported in the combined analysis of the two Phase III placebo-controlled studies.

Cardiovascular safety

See *Adverse events of special interest Cardiac toxicity* (Attachment 2). The additional analyses in the SCS/ISS, based on previously evaluated studies, did not indicate any new cardiovascular safety issues.

Unwanted immunological events

There was no suggestion of an increased incidence of immunological reactions with abiraterone in the pivotal study or in the additional analyses in the SCS/ISS.

Evaluator's overall conclusions on clinical safety

The toxicity profile of abiraterone in Study 302 was comparable to that previously observed in the pivotal study (Study 301) that supported the original registration of the drug. It confirmed that the drug is associated with an increased incidence of AEs suggestive of mineralocorticoid excess (hypertension, hypokalaemia, fluid retention) and with hepatotoxicity. The study did not suggest that the drug is associated with an increased risk of cardiac toxicity, apart from cardiac failure.

The toxicity of the drug appears modest in the chemotherapy-naïve mCRPC setting. The difference between abiraterone and placebo in the incidences of AEs, Ggrade 3 or 4 AEs, serious AEs etc were typically < 7% (see Table 12 in Attachment 2). The difference in the rate of discontinuation due to AEs was approximately 1%. This suggests that the toxicity of the drug is manageable with dose interruptions or dose reductions. The safety profile of the drug appears more favourable than that of taxane chemotherapy.

Updated safety data from previously evaluated Phase I/II studies did not raise any new safety issues.

First round benefit-risk assessment

First round assessment of benefits

The benefits of abiraterone in the proposed usage are:

- A decreased risk of disease progression as assessed by bone scan/magnetic resonance imaging (MRI)/computed tomography (CT);
- A delay in the need for chemotherapy and opiate analgesia;
- Maintenance of functional status/quality of life.

A benefit in terms of prolongation of survival has not been definitively established. However, there was a trend in favour of abiraterone on this endpoint.

First round assessment of risks

The risks of abiraterone in the proposed usage are:

- Adverse events associated with mineralocorticoid excess (for example, hypertension, fluid retention, hypokalaemia);
- Hepatotoxicity.

First round assessment of benefit-risk balance

The benefit-risk balance of abiraterone, given the proposed usage, was considered to be favourable.

First round recommendation regarding authorisation

It was recommended that the application be approved.

List of questions

Efficacy

1. Please provide the results of the third interim and final analyses of overall survival from Study 302. If the results are not yet available, please provide an estimate of when these results will be available.
2. Please confirm that the formulation of abiraterone acetate used in Study 302 was identical to the currently marketed formulation in Australia.

Safety

1. In Study 302, coagulation parameters were to be tested at screening and Day 15. The results do not appear to have been included in the study report. Please provide the results of this testing.

Second round evaluation of clinical data submitted in response to questions

Updated analysis of overall survival

The sponsor provided an updated survival analysis, based on a data cut-off of 22 May 2012. At this time point, a further 101 deaths had occurred in the study. Results are shown in Table 5 and Figure 1, and a comparison of the initial and updated OS analyses is shown in Table 6.

Table 5: Pivotal study 302 – Results for OS co-primary endpoint (Updated analysis)

	AA (N=546)	Placebo (N=542)
Subjects randomized	546	542
Event	200 (36.6%)	234 (43.2%)
Censored	346 (63.4%)	308 (56.8%)
Overall survival (months)		
25th percentile (95% CI)	21.29 (19.15, 23.33)	18.86 (17.81, 20.60)
Median (95% CI)	35.29 (31.24, 35.29)	30.13 (27.30, 34.10)
75th percentile (95% CI)	35.29 (NE, NE)	34.69 (34.10, NE)
Range	(0.0+, 35.3)	(0.0+, 35.7+)
6-month event-free rate (95% CI)	0.980 (0.963, 0.989)	0.972 (0.954, 0.983)
12-month event-free rate (95% CI)	0.912 (0.884, 0.933)	0.901 (0.872, 0.923)
18-month event-free rate (95% CI)	0.807 (0.771, 0.838)	0.778 (0.740, 0.812)
24-month event-free rate (95% CI)	0.694 (0.653, 0.732)	0.628 (0.584, 0.668)
30-month event-free rate (95% CI)	0.570 (0.517, 0.619)	0.521 (0.470, 0.570)
36-month event-free rate (95% CI)	0.000 (NE, NE)	0.146 (0.014, 0.419)
p value ^a	0.0151	
Hazard ratio (95% CI) ^b	0.792 (0.655, 0.956)	

AA=abiraterone acetate; CI=confidence interval; ECOG PS=Eastern Cooperative Oncology Group Performance Status;

NE=not estimable

^a p value is from a log-rank test stratified by ECOG PS score (0 or 1).

^b Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors AA.

Figure 1: Pivotal study 302 – Kaplan-Meier curves for OS co-primary endpoint (Updated analysis)

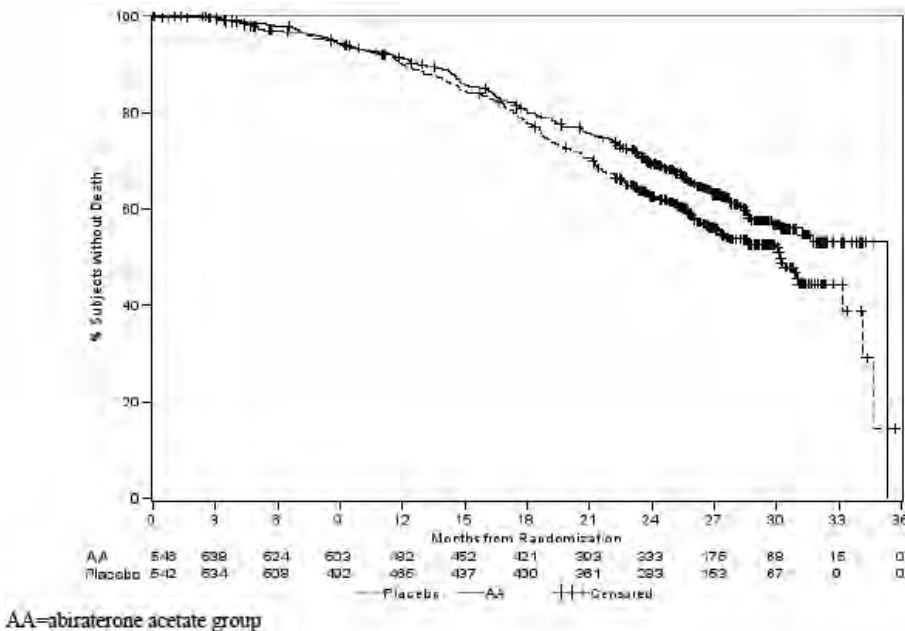


Table 6: Pivotal Study 302 – Comparison of results for OS co-primary endpoint (Initial versus Updated analysis)

	Initial (2 nd interim) analysis	Updated (3 rd interim) analysis
Data Cut-off	20 Dec 2011	22 May 2012
Report date	31 May 2012	6 Aug 2012
Median Follow-up	22.2 months	27.1 months
Deaths		
- Total	333 (30.6%)	434 (39.9%)
- Abiraterone	147 (26.9%)	200 (36.6%)
- Placebo	186 (34.3%)	234 (43.2%)
Hazard Ratio (95% CI)	0.752 (0.606 – 0.934)	0.792 (0.655 – 0.956)
p-value	0.0097	0.0151
Median OS – Abiraterone (95% CI)	NE (NE-NE)	35.29 months (31.24 – 35.29)
Median OS – Placebo (95% CI)	27.24 months (25.95 – NE)	30.13 months (27.30 – 34.10)

The results again showed a trend towards a survival benefit with abiraterone treatment. The hazard ratio for OS was 0.79 (95% CI: 0.655 – 0.956). Due to multiplicity of testing, the pre-specified statistical significance level for this analysis was $p = 0.0035$. The p-value obtained with the pre-specified log rank test was $p = 0.0151$, and hence the difference in OS was *not* statistically significant. In the updated analysis the median survival was reached for the abiraterone group (35.29 months; 95%CI: 31.24 – 35.29).

A subgroup analysis for OS again demonstrated consistent efficacy over all subgroups tested with all hazard ratios being less than 1.0 (that is, in favour of the abiraterone group).

Comment: The OS findings are essentially unchanged, with a non-significant trend in favour of abiraterone. Prior to the data cut-off of 22 May 2012 the sponsor had unblinded the study and patients who had been treated with placebo were offered abiraterone. As of the data cut-off, 14.4% of patients who had been randomised to placebo had received subsequent abiraterone treatment (compared with 10% on the previous analysis).

The final analysis of OS will be carried out when the number of death events reaches 773. The sponsor estimates this may occur sometime in 2014.

Formulation used in Study 302

The sponsor has provided an assurance that the formulation of abiraterone acetate used in Study 302 was identical to that currently marketed in Australia. This was considered to be acceptable.

Coagulation parameters

The sponsor provided summary data on coagulation testing (prothrombin time, activated partial thromboplastin time (APTT) and international normalized ratio (INR)) done at screening and Day 15 in Study 302. The incidence of abnormal results was comparable in the two treatment arms.

Second round benefit-risk assessment

The additional data provided in the sponsor's response does not alter the benefit-risk assessment, which remains favourable.

Second round recommendation regarding authorisation

It was recommended that the application be approved.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

Subject to the evaluation of the nonclinical aspects of the Safety Specification (SS) by the Toxicology area of the TGA's Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the TGA's Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 7):

Table 7. Important identified and potential risks and missing information.

Important Identified Risks	<ul style="list-style-type: none"> • Hypertension • Hypokalaemia • Fluid retention/oedema • Hepatotoxicity • Cardiac disorders • Osteoporosis including osteoporosis-related fractures
Important Potential Risks	<ul style="list-style-type: none"> • Cataract • Drug-drug interaction (CYP2D6) • Increased exposure with food
Important Missing Information	<ul style="list-style-type: none"> • Use in patients with active or symptomatic viral hepatitis • Use in patients with moderate/severe hepatic impairment and chronic liver disease • Use in patients with severe renal impairment • Use in patients with 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 III or IV heart disease or cardiac ejection fraction measurement of < 50% • Drug-drug interaction (CYP2C8) • Use in non-white patients

OPR reviewer comment:

Notwithstanding the evaluation of the nonclinical and clinical aspects of the SS, this was considered acceptable.

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 8.

Table 8. Activities additional to routine planned by the sponsor regarding certain safety concerns. Table continued across 2 pages.

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
<p>Trial COU-AA-006 (QTc)</p> <p>A QT/QTc and multi-dose PK Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer</p> <p>Protocol available</p>	<p>Cardiac disorders</p>	<p><i>Primary Objectives:</i></p> <p>To evaluate the effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using pharmacokinetic and time-matched ECGs in patients with metastatic castration resistant prostate cancer (CRPC)</p> <p><i>Secondary Objectives:</i></p> <p>To evaluate the pharmacokinetics (PK) of abiraterone acetate and abiraterone after multiple doses of abiraterone acetate</p> <p>To evaluate the anti-tumor effects of abiraterone acetate and prednisone</p> <p>To evaluate the effects of abiraterone acetate and prednisone on adrenal function as measured by the Cortrosyn stimulation test at baseline and after abiraterone acetate/prednisone administration</p>	<p>March 2013</p>

Targeted follow-up with reporter through a guided questionnaire	Hepatotoxicity Osteoporosis including osteoporosis-related fractures		
Trial 212082PCR2008 An Open-Label Study to Determine the Short-Term Safety of Continuous Dosing of Abiraterone Acetate and Prednisone in Modified Fasting and Fed States to Subjects With Metastatic Castration-Resistant Prostate Cancer. Protocol available	Increased exposure with food	<i>Primary Objective:</i> To establish the safety profile of oral abiraterone acetate and oral prednisone following short-term administration after standardized low-fat or high-fat meals to subjects with metastatic castration-resistant prostate cancer (mCRPC) <i>Secondary Objective:</i> To evaluate the exposure to abiraterone following short-term administration of oral abiraterone acetate in the modified fasting state and after standardized low-fat or high-fat meals to subjects with mCRPC	August 2013
Trial 212082PCR1004 Severe hepatic impairment (single dose PK trial). Protocol not available	Use in patients with moderate/severe hepatic impairment and chronic liver disease	<i>Protocol not available but study is nearly complete.</i>	March 2013
Trials: 212082PCR3001 212082JPN102 212082PCR2007 ABI-PRO-3001 ABI-PRO-3002	Use in non-White patients	<i>Multiple (see individual study protocols)</i>	Q4, 2014 Dec 2012 Jun 2014 Dec 2015 Sep 2013

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The sponsor mainly plans routine pharmacovigilance activities. Only some safety concerns have been assigned an additional activity.

The sponsor's proposed pharmacovigilance activities and milestones were considered to be acceptable. All relevant studies were ongoing at the time of this evaluation. The available study protocols submitted were considered to be acceptable in regard to the assigned safety concern for RMP purposes.

Risk minimisation activities

No additional risk minimisation activities are proposed for Zytiga. Some modifications of the Product Information document are planned.

OPR reviewer comment

The sponsor identifies hepatotoxicity as an important risk and, in Table 25 of the submitted RMP, states that *'[i]f patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy, treatment should be discontinued and patients should not be retreated (SmPC Sections 4.2 and 4.4).'*

Furthermore the sponsor states that *'[t]here 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 and abiraterone acetate should be avoided in these patients (see SmPC Sections 4.2 Posology and 5.2 Pharmacokinetic properties).'* It was noted that the sponsor was conducting a trial to investigate this (Trial 212082PCR1004 (An Open-Label Pharmacokinetic Study of Abiraterone Acetate Suspension in Subjects with Severe Hepatic Impairment Compared with Matched Control Subjects with Normal Hepatic Function)).

Given that hepatotoxicity is a known risk and that patients with severe hepatotoxicity should discontinue the drug, abiraterone should be contraindicated in severe hepatic impairment.

In regard to the proposed routine risk minimisation activities, it was recommended to the Delegate that the draft product information document be revised. The details of the proposed changes are however beyond the scope of this AusPAR.

Summary of recommendations

It was considered that the sponsor's response to the TGA's request for further information has adequately addressed the issues identified in the RMP evaluation report.

Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA's consolidated request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these included a consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Outstanding issues***Issues in relation to the RMP***

No outstanding issues were identified.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration***RMP***

Implement Risk Management Plan (in EU-RMP format) Version 5.0 (dated 07 June 2012, DLP 27 April 2012) with Australian Specific Annex (ASA), and any future updates as a condition of registration.

PSUR

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). The reports are to meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report. Each report must have been prepared within 90 days of the datalock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

No fewer than three annual reports are required.

The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

The findings in new toxicity studies were consistent with previously submitted data. The evaluator supported approval.

Clinical

Pharmacokinetics

The pharmacokinetics of abiraterone in patients who have not received chemotherapy is comparable to that previously reported for other patients.

Efficacy

Efficacy was assessed in a double-blind, randomised controlled trial, COU-AA-302 in CRPC patients who are asymptomatic or mildly symptomatic after conventional androgen deprivation therapy. Subjects were required to be castrate (serum testosterone < 1.7 nmol/L) and have evidence of disease progression after discontinuation of anti-androgen therapy. Evidence of progression was based on rising serum Prostate Specific Antigen (PSA) (using PCWG2⁸ criteria) or radiographic imaging (using modified Response

⁸ Prostate Cancer Clinical Trials Working Group 2.

Evaluation Criteria In Solid Tumours (RECIST) version 1.0 criteria⁹). The median age of subjects was 70 years; range 44-95. The trial was conducted in the USA, Canada, Europe and Australia.

Subjects were randomly assigned to abiraterone plus prednisone/prednisolone or placebo plus prednisone/prednisolone. Randomisation was stratified by ECOG performance status¹⁰ (0 or 1). The dose of abiraterone was 1,000 mg once daily and the dose of prednisone/prednisolone 5 mg twice daily. Treatment was continued until clinical progression of disease or, at the discretion of the investigator, radiographic progression. The median duration of treatment was 13.8 months (range 0.3-29.9) with abiraterone and 8.3 months (range 0.1-28.1) with placebo.

There were co-primary efficacy endpoints, radiographic progression-free survival (rPFS) and overall survival (OS). rPFS is a non-standard endpoint; however, its use was adequately justified. The level of significance of 0.05 was allocated as follows: 0.01 for rPFS and 0.04 for OS.

The criteria for rPFS were adapted by the sponsor from the PCWG2 criteria. One of the following by independent radiographic review was required for rPFS:

- ≥ 2 new lesions on bone scan < 12 weeks from randomisation and second scan ≥ 6 weeks later shows ≥ 2 additional new lesions (≥ 4 new lesions)
- ≥ 2 new lesions on bone scan ≥ 12 weeks from randomisation and verified on second scan ≥ 6 weeks later
- Progression of soft tissue lesions measured by CT or MRI as defined by modified RECIST criteria
- Death from any cause.

Abiraterone significantly increased rPFS and there was a trend to increased OS (Table 9). The OS analysis was the second interim analysis at which 31% of subjects had died. rPFS and OS in the subgroups tested were consistent with the overall results. Despite the increase in overall survival with abiraterone not being statistically significant the independent data monitoring committee allowed unblinding and crossover from placebo to abiraterone. The third interim analysis of OS (at which 40% died) was presented during the evaluation. The result was similar to the second analysis. The final analysis is due in 2014.

Evidence of clinically relevant benefit with abiraterone was supported by secondary endpoints (Table 9). There was no adjustment for multiplicity of endpoints.

⁹ RECIST: The Response Evaluation Criteria in Solid Tumors (RECIST) is a voluntary, international standard using unified, easily applicable criteria for measuring tumor response using X-ray, CT and MRI.

¹⁰ ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:

- 0 - Fully active, able to carry on all pre-disease performance without restriction
- 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
- 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- 5 - Dead

Table 9. TRIAL COU-AA-302 Results; Intent-to-Treat Population

	Abiraterone + Prednisone/ Prednisolone n=546	Placebo + Prednisone/ Prednisolone n=542	Hazard Ratio/ Difference [95% CI] Log-Rank p
rPFS median <i>months</i> ¹	Not Reached	8.3	0.43 [0.35, 0.52] p<0.0001
OS median <i>months</i> – 2 nd interim analysis ²	Not Reached	27.2	0.75 [0.61, 0.93] p=0.0097 ³
OS median <i>months</i> – 3 rd interim analysis ⁴	35.3	30.1	0.79 [0.66, 0.96] p=0.0151 ⁵
Time to Opiate Use for Cancer Pain median <i>months</i>	Not Reached	23.7	0.69 [0.57, 0.83] p<0.0001
Time to Initiation of Cytotoxic Chemotherapy median <i>months</i>	25.2	16.8	0.58 [0.49, 0.69] p<0.0001
Time to ECOG Performance Scale Deterioration by ≥ 1 median <i>months</i> ⁶	12.3	10.9	0.82 [0.71, 0.94] p=0.0053

¹ Data cut-off 20 December 2010 (median follow-up 8.3 months). ² Data cut-off 20 December 2011 (median follow-up 22.2 months). ³ Not significant – pre-specified significance level 0.0008 based on O'Brien-Fleming. ⁴ Data cut-off 22 May 2012 (median follow-up 27.1 months). ⁵ Not significant – pre-specified significance level 0.0035 based on O'Brien-Fleming. ⁶ Confirmed at next visit (post-hoc analysis). Medians are Kaplan-Meier estimates and hazard ratios are from the proportional hazards model.

Safety

The primary safety data is from the pivotal trial COU-AA-302 (safety population n=542 abiraterone, n=540 placebo). Common adverse events with a notably higher incidence with abiraterone than placebo included (abiraterone versus placebo): infection (54% versus 39%), vascular disorders (47% versus 34%) in particular hypertension (22% versus 13%), hypokalaemia (17% versus 13%), ALT increased (12% versus 5%), AST increased (11% versus 5%), rash (8% versus 4%) and cardiac failure (2.0% versus 0.4%).

Severe (Grade 3-4) adverse events were marginally greater with abiraterone (48%) than placebo (42%) in particular infections (7.4% versus 6.1%), vascular disorders (6.3% versus 5.6%), hypokalaemia (2.4% versus 1.9%), ALT increased (5.4% versus 0.7%) and AST increased (3.0% versus 0.9%). The incidences of fatal and serious adverse events considered related to study drug were comparable for abiraterone and placebo.

The safety data from other trials was consistent with the pivotal trial.

The clinical evaluator supported approval.

Risk management plan

The sponsor satisfactorily addressed issues raised by the RMP evaluator.

The evaluator recommended the Risk Management Plan as a condition of registration (see above *Pharmacovigilance Findings*).

Risk-benefit analysis**Delegate considerations**

In the pivotal trial in asymptomatic or mildly symptomatic patients after failure of ADT, abiraterone significantly increased rPFS, delayed the need for chemotherapy and opiate analgesia and delayed deterioration in ECOG performance status. The magnitude of these effects was clinically significant. There was a trend to increased overall survival. Overall survival was a co-primary endpoint with rPFS. The trial was unblinded early and crossover from placebo to abiraterone allowed. Therefore, further analysis of overall survival is likely to be confounded and statistical and clinical significance may not be achieved. Based on the significant clinical benefits in rPFS (the other co-primary endpoint) and the secondary endpoints, the Delegate concluded that the efficacy of abiraterone in the proposed indication was established.

Abiraterone was associated with adverse events suggestive of mineralocorticoid excess (hypertension, hypokalaemia, fluid retention) and hepatotoxicity. This was consistent with the known safety profile.

The European Union (EU) restricted the indication to asymptomatic or mildly symptomatic patients in whom chemotherapy is not yet clinically indicated. This restriction seems unnecessary since the risks of chemotherapy are likely to exceed the benefits in asymptomatic or mildly symptomatic patients and therefore chemotherapy is unlikely to be clinically indicated.

The benefit-risk balance of abiraterone in the proposed indication was considered to be positive.

Advisory Committee on Prescription Medicines (ACPM) Advice sought

The Committee was asked to provide advice on the following specific issues:

1. The pivotal trial was unblinded and crossover allowed before demonstration of significantly increased overall survival. Overall survival was a co-primary endpoint. Is the demonstration of clinical benefit on the other co-primary endpoint, radiographic progression-free survival and the secondary endpoints sufficient to conclude that efficacy was satisfactorily established?
2. Should the indication be restricted to asymptomatic or mildly symptomatic patients in whom chemotherapy is not yet clinically indicated as in the EU?
3. What is the Committee's opinion of the benefit-risk balance of abiraterone in the proposed indication?
4. The Committee was also asked to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Delegate's Pre ACPM preliminary assessment

The Delegate considered that the application should be approved for registration subject to finalisation of the product information.

Response from sponsor

This document has been prepared in response to the Delegate's Request for ACPM Advice received from the TGA on 21 June 2013 for Janssen-Cilag's application to extend the indications for Zytiga/Janssen Abiraterone abiraterone acetate 250 mg tablet (Submission number: PM-2012-02706-3-4).

Indications

The sponsor agreed with the TGA Clinical Evaluator's and TGA Delegate's recommendations to approve abiraterone for the extended indication (underlined):

"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."*

Janssen agreed with the editorial rearrangement of the *Indications* section to remove duplication of text as suggested by the TGA Delegate as it aids readability.

Janssen also agreed with the Delegate's assessment that the EU restriction of the indication to asymptomatic or mildly symptomatic patients in whom chemotherapy is not yet clinically indicated is unnecessary. The proposed Australian indication reflects the patient population studied in COU-AA-302 (specifically patients were asymptomatic or mildly symptomatic and had not received prior chemotherapy). The language adopted by the EU regarding acceptability or appropriateness for chemotherapy could be confusing to the prescriber and could be misinterpreted to indicate that only patients who are unfit for chemotherapy are the appropriate population. The study protocol did not request that the investigator consider whether cytotoxic therapy was acceptable or appropriate in assessing the patient's eligibility for study. With the potential for the EU indication wording to cause confusion for the prescriber, there is the possibility that if adopted in Australia, this may lead to patients being denied access that could potentially derive benefit from abiraterone. Finally, as the Delegate outlined, the risks of chemotherapy are likely to exceed the benefits in asymptomatic or mildly symptomatic patients and therefore chemotherapy is unlikely to be clinically indicated.

Study endpoints and results

Abiraterone demonstrated a clinically and statistically significant benefit in the co-primary endpoint of radiographic progression free survival (rPFS) in the pivotal trial (COU-AA-302), together with statistically and clinically relevant improvements in the secondary endpoints: time to opiate use for cancer pain; time to initiation of cytotoxic chemotherapy and time to deterioration in ECOG performance status. The TGA clinical evaluator accepted Janssen's justification for the use of the nonstandard primary endpoint of rPFS and concluded "*the use of rPFS as a primary endpoint for the trial is considered acceptable*". A trend to increased overall survival was also observed, with a 25% reduction in the risk of death and despite this increased overall survival not achieving statistical significance, the Independent Data Monitoring Committee (IDMC) recommended unblinding of the study and crossover from placebo to abiraterone. The IDMC recommendation was based on an assessment of the efficacy data in totality (rPFS and the secondary endpoints combined). Due to the unblinding of the trial and crossover from placebo to abiraterone, further analysis of overall survival is likely to be confounded and statistical significance may not be achieved. It is not uncommon in oncology trials to not achieve statistical significance for overall survival at the interim analysis time point. Despite this, the point estimate of the hazard ratio (0.75) was lower than the hypothesised effect of 0.80 and represents a clinically meaningful result.

However when the efficacy results are viewed in totality, Janssen concurred with the clinical evaluator's and Delegate's assessment that efficacy has been established in the proposed indication. The EU, whose guidelines TGA adopts, also agreed that efficacy had been established as evidenced by their approving of the extension of indications. The new indication has also been approved in the USA, Canada and New Zealand.

The safety profile in Study COU-AA-302 was consistent with abiraterone's well established favourable toxicity profile, especially when compared to chemotherapy. For a patient with incurable mCRPC, treatment with an oral medication as an outpatient, without the side effects of cytotoxic chemotherapy, is clinically meaningful in the context of the limited available treatment options.

Conclusion

Given the positive benefit/risk profile, Janssen agreed with the Delegate's recommendation to approve Zytiga/Janssen Abiraterone in line with the proposed extended indication for use in metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT).

Janssen has also incorporated the changes to the product information requested by the nonclinical evaluator.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Zytiga/Janssen Abiraterone tablets containing 250 mg of abiraterone to have an overall positive benefit-risk profile for the following proposed indication;

Zytiga is indicated with prednisone or prednisolone for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC)

Due consideration should first be given to a chemotherapy option

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zytiga/Janssen Abiraterone tablets (250 mg abiraterone acetate) for oral administration, indicated for:

Zytiga is indicated with prednisone or prednisolone for the treatment of patients with metastatic castration resistant prostate cancer (mCRP) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT).¹¹

Specific conditions applying to these therapeutic goods

Implement Zytiga/Janssen Abiraterone Risk Management Plan On EU RMP format Version 5.0 dated 7 June 2012 (data lock point 27 April 2012 with Australian Specific Annex (AsA) and any subsequent revisions agreed with the TGA.

An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). The reports are to meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-Periodic Safety Update Report. Each report must have been prepared within 90 days of the datalock point for that report.

Unless agreed separately between the supplier who is the recipient of the approval and the TGA, the first report must be submitted to TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report until the period covered by such reports is not less than three years from the date of this approval letter.

No fewer than three annual reports are required.

The annual submission may be made up of two PSURs each covering six months. If the sponsor wishes, the six monthly reports may be submitted separately as they become available.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

¹¹Full indications are: *Zytiga is indicated with prednisone or prednisolone for the treatment of patients with metastatic castration resistant prostate cancer (mCRP) Who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT). Who have received prior chemotherapy containing a taxane.*

Therapeutic Goods Administration

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