15 September 2016
EMA/CHMP/538739/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zytiga

International non-proprietary name: abiraterone

Procedure No. EMEA/H/C/002321/X/0039

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
BCS	Biopharmaceutics Classification System
CFU	Colony Forming Units
CoA	Certificate of Analysis
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CRS	Chemical Reference Substance (official standard)
DoE	Design of Experiments
FC	Film-coated
FT-IR	Fourier Transform Infrared Spectroscopy
GMP	Good Manufacturing Practice
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control test
IR	Infrared
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
N/A	not applicable
ND	Not detected
NF	National Formulary (USP-NF)
NMT	Not more than
OOS	Out of Specifications
PAR	Proven Acceptable Range
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PP	Polypropylene
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by Design
QC	Quality Control
QOS	Quality Overall Summary
QTPP	Quality Target Product Profile
RH	Relative Humidity
RPM	round per minute
RRT	Relative retention time
RSD	Relative standard deviation
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UPLC	Ultra Pressure Liquid Chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet
Vs.	versus
XRD	X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 7 January 2016 an application for a line extension for Zytiga for a new film-coated (FC) tablet formulation of 500 mg to be used in the same currently approved indications of the marketed formulation of Zytiga.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008, Annex I 2.(c) Change or addition of a new strength/potency and Annex I 2.(d) Change or addition of a new pharmaceutical form.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the granting of a class waiver (CW/0001/2015).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.2. Manufacturers

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aranzazu Sancho-Lopez

- The application was received by the EMA on 7 January 2016.
- The procedure started on 28 January 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 April 2016.
- During the meeting on 13 May 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 13 May 2016.
- During the meeting on 26 May 2016, the CHMP agreed on the consolidated List of Questions to be sent

to the applicant. The final consolidated List of Questions was sent to the applicant on 26 May 2016.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2016.
- The CHMP Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 10 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zytiga on 15 September 2016.

2. Scientific discussion

2.1. Problem statement

Zytiga, in combination with prednisone/prednisolone-+- (hereafter referred to as prednisone), was approved in 43 countries as of 12 April 2012 for the treatment of men with mCRPC whose disease has progressed after a docetaxel-based chemotherapy regimen.

This submission is intended to obtain the Marketing Authorisation for a new film-coated (FC) tablet formulation of Zytiga 500mg tablets to be used in the same currently approved indications of the marketed formulation of Zytiga.

2.1.1. Disease or condition

Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen depletion therapy and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of preexisting disease, and/or the appearance of new metastases.

2.1.2. Epidemiology

Prostate cancer is the most common cancer and the second leading cause of cancer deaths among males in most Western countries. Prostate cancer-related deaths occur as a result of complications of metastatic disease. In 2008, 323,000 men were diagnosed with prostate cancer in the 27 EU markets, and 71,000 patients were lost to the disease (GLOBOCAN 2008 (IARC)).

2.1.3. Clinical presentation and prognosis

Treatment options for symptomatic bone disease are radiation or radionuclide agents and bisphosphonates or the RANK ligand inhibitor, denosumab. However, the prognosis of mCRPC patients is still poor, with a median survival of approximately 1 to 2 years.

Despite hormonal therapy, most patients with disease recurrence will progress within 12 to 18 months.

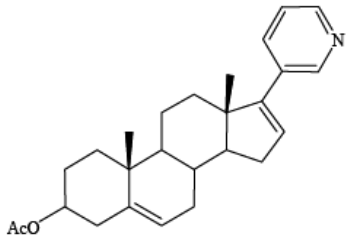
2.1.4. Management

Based on the results of 2 randomized controlled trials, it is currently recommended that for men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m^2 administered intravenously every 3 weeks with 5 mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation and quality of life.

2.2. About the product

Abiraterone acetate is a prodrug of abiraterone, an orally active inhibitor of the enzyme, CYP17α (17α-hydroxylase/C17,20-lyase). Abiraterone acts as an androgen biosynthesis inhibitor by blocking 2 important enzymatic activities in the synthesis of testosterone in the testes, adrenals, and within the prostate tumour.

Abiraterone acetate is 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene that is administered orally and is available as an immediate release 250 mg tablet. It has the following chemical structure:



Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Abiraterone selectively inhibits the enzyme CYP17∝. This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone (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.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as immediate-release, film-coated tablet, 20 mm long by 10 mm wide and debossed with “AA” on one side and “500” on the other side containing 500 mg of abiraterone acetate as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, croscarmellose sodium, hypromellose, sodium lauryl sulfate, silicified microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate.

Coating: titanium dioxide, macrogol 3350, talc, polyvinyl alcohol, iron oxide red (E172) and iron oxide black (E172).

The product is available in PVdC-PE-PVC blister with an aluminium foil backing as described in section 6.5 of the SmPC.

2.3.2. Active substance

The active substance used in the 500 mg film-coated tablets is identical to the one used in the manufacture of the currently authorised 250 mg tablet. No new information on the active substance has been provided within this line extension application.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical development

The quantitative composition of oval shaped, purple film-coated (FC) tablet is provided.

The first commercialized formulation containing abiraterone acetate is the 250 mg uncoated tablet. The aim of this line extension is to introduce the 500 mg strength of abiraterone acetate film-coated tablets. The new strength was developed in order to reduce the pill burden and improve patient comfort. The film-coat was introduced in order to eliminate dust formation and to differentiate tablet strengths by colour.

The Pharmaceutical development of the finished product contains QbD elements. The quality target product profile (QTPP) was defined as an immediate release film coated tablet, for oral administration, containing 500 mg of abiraterone acetate, bioequivalent to the commercial 250mg uncoated tablet, that meets microbial and impurity standards. The film-coated tablet stability should be at least 24 months and the container closure system should be blisters or bottles. The critical quality attributes (CQAs) identified were: appearance, identification, assay, chromatographic purity, microbial purity, uniformity of dosage units, and dissolution.

Abiraterone acetate is a white to off-white powder practically insoluble in water. Abiraterone acetate is classified as Class IV compound (low solubility, low permeability) according to the biopharmaceutical classification system (BCS). Physico-chemical characteristics of the active substance that can affect the intended performance of the dosage form are solubility, particle size distribution, and polymorphism. These characteristics are controlled by the active substance manufacturing process and/or specifications and their limits are considered justified. Analysis of finished product samples by means of XRD has demonstrated that the manufacturing process of the finished product does not lead to polymorphic conversion of the active substance. Additionally, no change of the solid state form of the active substance was observed for finished product samples stored for up to 24 months in the warehouse.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, with the exception of silicified microcrystalline cellulose which is tested according to NF standards and of the film-coating material Opadry II purple which is tested according to an in-house specification. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The 500mg film-coated tablet includes excipients not used in the currently marketed 250mg tablet: hypromellose, silicified microcrystalline cellulose and coating powder Opadry Purple. Therefore compatibility of the active substance was studied in binary mixtures with

these excipients, as well as in a full blend mixture containing all ingredients in equal proportions. Selection and concentrations of the excipients are justified, and their function in the finished product described.

A dissolution method has been developed for quality control (QC) during release and stability testing of the finished product. The dissolution test is performed in a paddle instrument (USP type 2) and it is adequately described and designed. The method used for the 500 mg film-coated tablets is similar to the dissolution test for 250 mg tablets except for the rotation speed and filter used. The discriminatory power of the dissolution method was investigated with regards to changes in particle size, granulation process parameters, tablet hardness, and finished product stability changes. Differences in dissolution profiles are observed when different active substance particle size distributions or granulation parameters are used. However because the studied ranges were very close to the target values, some OOS-batches for particle size or granulation process parameters fulfilled the dissolution specifications. Changes in coating weight gain were not detected by the method. Nevertheless taking into account the type of product, the discriminatory power of the dissolution method is considered acceptable.

Two different 500 mg FC tablets have been developed initially. One was manufactured in a dose proportional way to the commercial 250 mg uncoated tablet using high-shear granulation, and was subsequently coated with a purple film-coat. Another one was manufactured using fluid-bed granulation. The excipient composition of the tablet manufactured by fluid-bed granulation was therefore adjusted to meet the manufacturability requirements of the new process, to reduce the tablet weight, and to meet the desired quality profile for dissolution and bioavailability. The second 500 mg FC tablet was given the same purple film-coat as the first formulation. In a relative bioavailability trial, the two new tablet formulations of 500 mg dosage strength were compared to the commercial 250 mg uncoated tablet. Based on the results the bioavailability study, the tablet using fluid-bed granulation was selected to be tested in a pivotal bioequivalence trial. Bioequivalence study was performed showing bioequivalence between the commercial 250 mg uncoated tablet and the proposed commercial formulation for the 500 mg film-coated tablet.

The finished product manufacturing process was systematically evaluated through the use of risk assessment to identify critical process parameters (CPPs). The risk identification was based on process development and manufacturing data from the product or on prior knowledge. The experimental studies performed to determine the criticality of process parameters, and to establish appropriate target settings and ranges, have been performed at both production scale sizes proposed. The critical process parameters have been adequately identified for the following steps: fluid bed granulation and drying, initial blending, final blending, compression, film-coating. Based on the outcome of this evaluation a risk-based control strategy is proposed. No design space has been proposed.

The primary packaging is PVdC/PE/PVC-alu blister. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: fluid bed granulation, blending, compression, and film-coating. The process is considered to be a standard manufacturing process.

Critical steps have been identified as being fluid bed granulation and drying, initial blending, final blending (lubrication), compression and film-coating. They are properly evaluated at the commercial scale. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Two production scale sizes are proposed. Proven acceptable ranges (PAR) have been defined for the following

steps of the medicinal product: granulation, blending and film coating. The available development data, the proposed control strategy and batch analysis data from both sizes of production scale batches fully support the proposed PARs.

Formal validation will be performed post-approval on the first three consecutive commercial batches, prior to launching the product. An acceptable validation protocol has been provided.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (FTIR), assay and purity (HPLC), uniformity of dosage units (Ph. Eur.), dissolution test (HPLC), and microbial purity (Ph. Eur.).

Finished product specifications are considered appropriate. They include parameters critical to finished product quality.

Impurities present at higher than the qualification threshold according to ICH Q3B were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Batch analysis results are provided for seven batches. Three of them have been manufactured at the proposed manufacturing site at the small production scale size using active substance manufactured by the two approved manufacturers. Results confirmed the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for three small production scale batches of finished product stored under long term conditions for 18 months at 25 ºC / 60% RH and 30 ºC / 75% RH, for 6 months under accelerated conditions at 40 ºC / 75% RH and for 12 months at 5 ºC according to the ICH guidelines. In addition, the three batches were exposed for three months at 50 ºC and one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The batches of medicinal product were identical to those proposed for marketing, were manufactured using both approved sources of the active substance and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, chromatographic purity, dissolution, microbial purity. Specifications are the same as the release specifications except for assay and chromatographic purity. In addition water content is monitored during stability testing. Analytical methods are the same as described for release testing, have been correctly validated and are stability-indicating.

No significant change was observed during storage of the finished product at the different storage conditions. Photostability study results demonstrated that the finished product is not light sensitive.

Based on available stability data, the proposed shelf-life of 24 with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.3.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product manufacturing process. However, no design space was claimed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendation(s) for future quality development

None.

2.4. Non-clinical aspects

2.4.1. Introduction

No new nonclinical pharmacology, pharmacokinetics and toxicology data have been submitted in this application.

2.4.2. Ecotoxicity/environmental risk assessment

An environmental risk assessment (ERA) of abiraterone was prepared in accordance with CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 1; EMA, 2006). This environmental risk was assessed as part of the initial MA application for Zytiga 250 mg tablets.

The MAH has submitted an environmental risk assessment to support this application (new strength and pharmaceutical form) for abiraterone acetate in Zytiga 500 mg film-coated tablets that can be summarised as follows:

Phase I assessment

Screening for persistence, bioaccumulation and toxicity

The octanol/water partition coefficient of abiraterone acetate is 5.12. Thus, according to EMA Guideline EMEA/CHMP/SWP/4447/00, a stepwise screening for persistence, bioaccumulation and toxicity for abiraterone acetate has been performed.

Criterion	PBT Criteria	Results	References
Persistence	Half-life in freshwater DT_{50} > 40 days	DT_{50} freshwater = 2.3 days	Turk R, Lentz N. [14C]Abiraterone Acetate – Aerobic Transformation in Aquatic Sediment Systems Following OECD Guideline 308. Springborn Smithers Study No. 13674.6195. JNJ Study No. RMD 1078. 14 September 2010
Bioaccumulation	BCF > 2000	$BCF_{low\ conc}$ 0.13 µg/L = 625 $BCF_{high\ conc}$ 1.3 µg/L = 576	Lentz N. Abiraterone Acetate – Flow-Through Bioconcentration and Metabolism Study with Rainbow Trout (*Oncorhychus mykiss*). Springborn Smithers Study No. 13674.6215. JNJ Study No. RMD 1082. 10 November 2010.
Toxicity	Chronic NOEC < 10 µg/L	NOEC (fathead minnow partial life cycle) = 0.013 µg/L	York D. Abiraterone Acetate – Modified Partial Life-Cycle Exposure with Fathead Minnow (*Pimephales promelas*). Smithers Viscient Study No. 13674.6239. 7 August 2012

Substances are considered a PBT-substance when they fulfill the criteria for all three properties, i.e., persistence, bioaccumulation, and toxicity. Abiraterone acetate fulfills only the toxicity criterion and is therefore not considered a PBT-substance.

Calculation of the predicted environmental concentration (PEC)

The predicted environmental concentration in surface water ($PEC_{SURFACEWATER}$) has been calculated following the formula required by the current CHMP guidance document as follows.

$$PEC_{SURFACEWATER} = \frac{DOSEai * Fpen}{WASTEWinhab * DILUTION}$$

The values for these parameters were

DOSEai: = 1000 mg/day
Fpen: = 0.01 (=1% default)
WASTEWinhab: = 200 L (default)
DILUTION: = 10 (default)

Therefore, $PEC_{SURFACEWATER}$ of abiraterone acetate in surface water is 5 µg/L.

As the initial $PEC_{SURFACEWATER}$ value is above 0.01µg/L, a Phase II environmental fate and effects was performed, according to guideline EMEA/CHMP/SWP/4447/00.

On other hand, the applicant has performed a refinement of $PEC_{SURFACEWATER}$ based on metabolism data, waste water treatment plant removal (WWTP) data and estimation for the market penetration of the medicinal product in the EU. Thus, the refined $PEC_{SURFACEWATER}$ is 0.0046 µg/L.

Phase II assessment

Tier A: Initial environmental fate and effects analysis

- *Aquatic effect studies*

Study Type / Recommended Protocol – Guideline	Species / test protocol / duration	Results
Adsorption Desorption Using a Batch Equilibrium Method / OECD 121	HPLC-method	Koc > 22,387 L/kg
Ready Biodegradability Test / OECD 301	CO_2 evolution / 28 days	CO_2 evolved = 12.56% Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems / OECD 308	Taunton River and Weweantic River aerobic sediments/100 days	Half life in water for both Taunton and Weweantic Rivers = 2.3 days Half life in total system Taunton River = 4.9 days Half life in total system Weweantic River = 3.3 days
Algae, Growth Inhibition Test / OECD 201	Green algae *Pseudokirchneriella subcapitata*/static test/72 hours	Nominal concentrations tested: 0.13, 0.25, 0.50, 1.0, and 2.0 mg/L. Nominal conc. of 2.0 mg/L corresponds to a time weighted average conc. of 1.0 mg/L. EC_{50} (72h) > 1.0 mg/L; NOEC (72 h) = 1.0 mg/L;
Daphnia sp. Reproduction Test / OECD 211	Survival and reproduction of *Daphnia magna* / semi-static test/21 days	Nominal concentrations tested: 0.50, 1.0, 2.0, 4.0, and 8.0 µg/L. Nominal conc. of 2.0 µg/L corresponds to a mean measured conc. of 0.47 µg/L. NOEC (21-days) = 0.47µg/L;
Fish, Early Life Stage Toxicity Test / OECD 210	Fathead minnow (*Pimephales promelas*) / flow through test / 35 days	Nominal concentrations tested: 0.25, 0.50, 1.0, 2.0, and 4.0 µg/L. Nominal conc. of 2.0 corresponds to a mean measured conc. of 1.1 µg/L. NOEC = 1.1 µg/L;
Activated Sludge, Respiration Inhibition Test / OECD 209	Microorganisms of activated sludge/3 hours	Nominal concentrations tested: 0.2, 1.0, 10, 100, and 1000 mg/L. No inhibitory effect observed. EC_{50} (3h) > 1000 mg/L; NOEC (3h) = 1000 mg/L;

The MAH also calculated a Predicted Environmental Concentration in sediment (PECsediment) according to the EMA Guideline on Environmental Impact Assessment for Veterinary Medicinal Products (EMEA/CVMP/ERA/418282/2005-Rev1). The PECsediment for abiraterone acetate is 5.156 µg/kg

- *Calculation of PNEC*

$PNEC_{WATER}$	$\frac{\text{Lowest NOEC from long term toxicity}}{\text{Assessment factor}}$	$= \frac{0.013\ \mu g/L}{10} = 0.0013\ \mu g/L$

$PNEC_{MICROORGANISM}$	$\frac{\text{NOEC from microbial inhibition study}}{\text{Assessment factor}}$	$= \frac{1\,mg/L}{10} = 100\,\mu g/L$
$PNEC_{GROUNDWATER}$	$\frac{\text{NOEC from long - term toxicity Daphnia magna}}{\text{Assessment factor}}$	$= \frac{0.47\,\mu g/L}{10} = 0.047\,\mu g/L$

Also, the MAH has calculated a $PNEC_{SEDIMENT}$ whose value is 10 mg/kg, according the following formula:

$$PNEC_{sediment} = \frac{\text{NOEC from sediment dweller study}}{\text{Assessment factor}}$$

- *Groundwater assessment*

The predicted environmental concentration of abiraterone acetate in groundwater (PECgroundwater) was calculated using the following formula:

PECgroundwater = 0.25 × PECsurfacewater

Thus the $PEC_{GROUNDWATER}$ for abiraterone acetate is 0.0012 µg/L

- *Outcome of Tier A fate and effects analysis*
-

$PEC_{SURFACEWATER}$:$PNEC_{WATER}$	$= \frac{0.0046\,\mu g/L}{0.0013\,\mu g/L} = 3.56$	The ratio PECsurfacewater/PNECwater is above 1, no further testing in the aquatic conpartmen are needed
$PEC_{GROUNDWATER}$:$PNEC_{GROUNDWATER}$	$= \frac{0.0012\,\mu g/L}{0.047\,\mu g/L} = 0.025$	The ratio PECgroundwater/PNECgroundwater is below 1. Consequently, further evaluation on the fate of abiraterone acetate and/or its metabolites in the aquatic environment is not needed.
$PEC_{SURFACEWATER}$:$PNEC_{MICROORGANISM}$	$\frac{0.0046\,\mu g/L}{100\,\mu g/L} = = 4.6 \times 10^{-5}$	The ratio PECsurfacewater/PNECmicroorganisms is below 0.1. Consequently, further evaluation of the fate and effects of abiraterone acetate on microorganisms is not required.

On other hand, the low bioconcentration values (BCF) of 625 and 576 indicate that abiraterone acetate does not bioaccumulate in aquatic organisms.

The adsorption/desorption coefficient (Koc) for activated sludge and soils indicates that abiraterone acetate is immobile and will remain preferably in soil. Consequently, an environmental assessment of abiraterone acetate in the terrestrial compartment was conducted.

Tier B: Extended environmental fate and effects analysis

To estimate the terrestrial environmental concentrations and risk assessment, the MAH has calculated the PECSLUDGE. For abiraterone acetate, PECsludge was calculated as:

Type (i) STP = 0.36 mg/kg dry sludge (combined sludge, i.e., primary + surplus sludge);

Type (ii) STP = 0.28 mg/kg dry sludge (surplus sludge).

The PECsoil of abiraterone acetate just after the first year of sludge application is given by:

$$PEC_{soil} = \frac{C_{sludge} \times APPL_{sludge}}{DEPTH_{soil} \times RHO_{soil}}$$

Where:

C_{SLUDGE} = Concentration of abiraterone acetate in dry sludge (mg/kg); conservative value from SimpleTreat 3.1

$APPL_{SLUDGE}$ = Dry sludge application rate (kg/m2/year);default value of TGD = 0.5 kg/m2/year

$DEPTH_{SOIL}$ = Mixing depth in soil (m); default value of TGD = 0.20 m

Thus, PEC_{SOIL} of abiraterone acetate in soil after the first sludge application is 5.3 x 10^{-4} mg/kg.

The PNECsoil is based on the lowest NOEC result from the long-term toxicity tests, i.e., 100 mg/kg dry soil for terrestrial plants, i.e.,

$$PNEC_{soil} = \frac{\text{Lowest NOEC from long - term toxicity}}{\text{Assessment factor}}$$

$$= \frac{100\,mg/kg}{10} = 10\,mg/kg\ soil$$

Then, $PEC_{SOIL}/PNEC_{SOIL}$ = 5.3 X 10^{-5}

As, the ratio $PEC_{SOIL}/PNEC_{SOIL}$ is below 1, further testing in the terrestrial compartment is not required.

Table 3 - Summary of main study results

Substance (INN / Invented Name): To be assigned			
CAS-number (if available): 154229-19-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.12	Potential PBT YES
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.12	B
	BCF	625 (for low conc, 0.13 microg/L) 576 (for high conc, 1.3 microg/L	not B
Persistence	DT_{50} or ready biodegradability	$DT_{50,}$ freshwater= 2.3 days	not P
Toxicity	NOEC or CMR	NOEC (fathead minnow partial life cycle) = 0.013 µg/L	T
PBT-statement :	The compound is considered as T		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence,	0.005	µg/L	> 0.01 threshold (N*)

literature)					
Other concerns (e.g. chemical class)					N/A
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} > 22,387 Kg/L (log K_{oc} > 4.35)			List all values
Ready Biodegradability Test	OECD 301	12.56 %			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.3 days $DT_{50, sediment}$ = ND $DT_{50, whole\ system}$ = 4.9 and 3.3 days % shifting to sediment = sediment-bound residue 28.2% and 22.1%			Evidence of primary biodegradation was observed for [^{14}C]abiraterone acetate in the aerobic water/sedimen test samples.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC_{50}(72 h)	1000 > 1000	µg/L µg/L	*Pseudokirchneriella subcapitata.* NOEC value is the same for both measures of growth (biomass and growth rate)
Daphnia sp. Reproduction Test	OECD 211	NOEC	0,47	µg/L	21 days
Fish, Early Life Stage Toxicity Test/*Species*	Modified Partial Life-Cycle Exposure with Fathead Minnow (OECD 229)	NOEC	0.013	µg/L	*Pimephales promelas* (Fathead Minnow)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}(3 h)	> 10^6	µg/L	NOEC(3 h) = 1000 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	625 (for low conc, 0.13 µg/L) 576 (for high conc, 1.3 µg/L	L/kg	%lipids: Percent lipids at steady state (wet weight tissue basis) low = 3.46% and high 3.76 % Percent lipids at steady state (dry weight tissue basis) low = 19.65 % and high 22.74 %
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50} %CO_2	18 55.1 %	Days	Evolution of $^{14}CO_2$ (ultimate biodegradation) was 55.1% of the applied radioactivity accumulatively at Day 120. Metabolites identified were [^{14}C]abiraterone and dehydrogenated [^{14}C]abiraterone.
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	250	mg/kg	The nitrate production was inhibited by 3,9% on day 28. The empirical EC_{10}, EC_{25} and EC_{50} values for nitrogen transformation were estimated to be > 250 mg/kg dry soil

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100 for all species	mg/kg	Bean (*Phaseolus vulgaris)* Oat *(Avena sativa)* Tomato *(Lycopersicon esculentum)*
Earthworm, Acute Toxicity Tests	OECD 207	LC_{50} NOEC	> 1000 500	mg/kg mg/kg	*Eisenia fetida* / 14 days
Collembola, Reproduction Test	ISO 11267	NOEC	1000 for mortality; 500 for re-production	mg/kg	*Folsomia candida* / 28 days
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius* / 28 days

2.4.3. Discussion on non-clinical aspects

No new nonclinical pharmacology, pharmacokinetics and toxicology data have been submitted in this application, which was considered acceptable by the CHMP.

An environmental risk assessment (ERA) has been submitted to support the line extension application dossier for Zytiga 500mg film-coated tablets. Formerly, the MAH submitted an ERA that was assessed as part of the initial MA application for Zytiga 250 mg tablets. Moreover, on 28th September 2012, as part of the application number II/00047G, an extended partial life cycle study with fathead minnow (*Pimephales promelas*) to assess the specific mode of action of abiraterone acetate according to the OECD recommendations for endocrine disrupting substances was submitted. And, with this study, a further updated ERA report in which the toxicity NOEC and PECSURFACEWATER were refined. In this way, since this application is intended to obtain the Marketing Authorisation for a new film-coated tablet formulation to be used in the same currently approved indications of the marketed formulation of Zytiga, the submission of a new ERA was not necessary. It is not expected an increase of potential risk of the medicinal product to the environment.

Regarding the ERA submitted in the current application, the CHMP noted the following:

- The MAH has refined the PECsurfacewater with metabolism data, waste water treatment depletion data, and estimation for the market penetration of the medicinal product in the EU. This is not correct. According to EMA/CHMP/SWP/44609/2010 guideline, market research data cannot be used for the refinement of the fraction of market penetration (Fpen). The refinement of the Fpen is based on prevalence of the disease and treatment regime.

- The MAH has calculated the Predicted Environmental Concentration in sediment (PECsediment) according to the EMEA guideline on environmental impact assessment for veterinary medicinal products (EMEA/CVMP/ERA/418282/2005-Rev1). This is not correct, since the evaluation of environmental risk of medicinal products for human use must be based in the guidelines EMA/CHMP/SWP/4447/00 and EMA/CHMP/SWP/44609/2010.

2.4.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of abiraterone acetate.

However, as it is mentioned in section 5.3 of Summary of Product Characteristics, it is known that the active substance abiraterone shows an environmental risk for the aquatic environment, especially to fish.

2.5. Clinical aspects

2.5.1. Introduction

This submission is intended to obtain the Marketing Authorisation for a new film-coated (FC) tablet formulation of Zytiga 500mg tablets to be used in the same currently approved indications of the marketed formulation of Zytiga.

Several formulation have been developed to improve the commercial formulation (minor changes in excipients were made, allowing for the design of a 500 mg tablet) which would reduce the tablet burden and potentially represent more convenient dosing for patients. Furthermore, coating the tablet would reduce the risk of unwanted exposure during handling.

A pivotal bioequivalence study 212082PCR1007 and the supportive relative bioavailability study (code 212083PCR1010) are being submitted in the current dossier. These studies compared the oral bioavailability of the 250 mg and 500 mg FC tablets with the commercial 250 mg uncoated tablets of abiraterone acetate.

In addition, for completeness, a Clinical Study Report (CSR) for study 212082PCR1006 (exploratory relative bioavailability study of 3 test FC tablets) was also submitted.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Number (Section of Module 2.7.1)	Number of Subjects	Study Description	Dosage Regimen and Formulation Numbers (Drug Product Batch Numbers)
Relative Bioavailability			
212082PCR1010 (Section 2.1)	32	A single-dose, open-label, randomized, 8-sequence, 4-period, 5-treatment, crossover design in healthy subjects	Abiraterone acetate 1,000 mg Single oral dose G002 (4367707): 4 x 250-mg G022 (4367700): 4 x 250-mg G023 (4367701): 2 x 500-mg G004 (4367702): 4 x 250-mg G005 (4367703): 2 x 500-mg
Bioequivalence			
212082PCR1007 (Section 2.2)	102	A single-dose, open-label, randomized, 6-sequence, 3-period, 3-treatment, crossover design in healthy subjects	Abiraterone acetate 1,000 mg Single oral dose G002 (PFTF): 4 x 250-mg G004 (SBCN): 4 x 250-mg G023 (4207): 2 x 500-mg

Source:Mod3.2.P.5.4; Mod5.3.1.1\PCR1010; Mod5.3.1.2\PCR1007

2.5.2. Pharmacokinetics

The Pharmacokinetic analysis includes all subjects who have at least 1 non compartmental PK parameter estimated. Conventional and standard statistical methods have been employed.

Relative Bioavailability

Clinical Study Report 212082PCR1006

This study was a randomized, open-label, single-center, 4-way crossover study of a single dose of 1,000 mg abiraterone acetate under fasted conditions in healthy male subjects with a wash-out period of 7 days to assess the relative bioavailability of 3 new abiraterone acetate tablet formulations with respect to the current commercial abiraterone acetate tablet under fasted conditions in healthy male subjects.

The main difference between formulations was the SLS content, which is lower in the new formulation (range of 0.5% to 2%) compared to the current formulation.

The results showed that the systemic exposure (assessed by the mean Cmax, AUClast, and AUC0-∞) to abiraterone was lower for all three coated tablets relative to the commercial uncoated tablet. The rate of absorption was lower in the test formulations approximately 33% to 43% and the extent of absorption approximately by 20% to 30% lower compared to the test formulation.

These observed differences could be associated with the differences in the content of SLS according to the Applicant. Interestingly, although treatment D exhibits a slower dissolution rate, *in vivo* it exhibits the higher Cmax. Therefore, the *in vitro* dissolution testing lacks of any predictive value.

Clinical Study Report 212082PCR1010

This was a single-dose, open-label, randomized, 4-period, 5-treatment crossover study to assess the relative bioavailability of 4 new abiraterone acetate tablet formulations with respect to the current commercial abiraterone acetate tablet under fasted conditions in healthy male subjects. An incomplete block design was

used in this study to reduce the number of treatment periods while keeping equal precision among all 4 paired comparisons between the test treatment groups vs. the reference.

Overall, mean systemic exposures to abiraterone, as assessed by Cmax, AUClast and AUC0-∞, after administration of abiraterone acetate in test formulations were comparable to the mean systemic exposure to abiraterone following the administration of the reference formulation.

Treatments B and C showed the least difference in mean systemic exposures to abiraterone compared with Treatment A, with GMRs ranging from 99.07 to 101.23 for Treatment B and 101.94 to 103.67 for Treatment C, and the 90% CIs of GMR for AUCs falls completely within 80% to 125%.

Treatments D and E appeared to be lower in mean systemic exposures to abiraterone compared with Treatment A, with GMRs ranging from 94.52 to 96.09 for Treatment D and 90.66 to 91.68 for Treatment E, with lower bound of 90% CI falling below 80%.

Based on the PK results of this study, it is said that treatment B and C are selected for the pivotal study and at the same time it is said that the coated version of the current 250 mg formulation was tested in the pivotal study.

It was confirmed that Treatment D (G004, 250 mg coated tablet with current composition) and Treatment C (G023, 500 mg coated tablet with new composition) from Study 212082PCR1010 were used to establish bioequivalence in the pivotal Study 212082PCR1007.

Different treatment designations were used in the different studies. The formulations designated as Treatment D and C from Study 212082PCR1010 are referred to as Treatment B and C in Study 212082PCR1007.

Bioequivalence

Clinical Study Report 212082PCR1007

This was a single-dose, open-label, randomized, 3-way crossover pivotal study (Williams design) to assess the bioequivalence of 2 abiraterone acetate coated tablet formulations with respect to the current commercial abiraterone acetate uncoated tablet formulation under fasted conditions in healthy male subjects.

Maximum plasma concentrations of abiraterone were reached relatively rapidly with median tmax occurring 2 hours after drug administration across the 3 formulations. The apparent elimination phase profiles were also similar across the 3 formulations, with plasma concentrations declining in a biphasic manner and mean apparent terminal half-lives (t1/2, term) ranging from 16.3 to 16.6 hours across the 3 formulations (see the figures and table below).

Table 4 - Statistical analysis of pharmacokinetic data of abiraterone following single oral dose administration of abiraterone acetate to healthy fasting subjects

(Study 212082PCR1007: Pharmacokinetics Data Analysis Set)						
Parameter[a]	Treatment Group[b]	N	Geometric Mean	Ratio: Test/Reference (%)	90% Confidence Interval (%)	Intra-Subject CV
C_{max}(ng/mL)	Treatment A	99	87.70			39.6%
	Treatment B	99	81.52	92.96	(84.98 - 101.69)	
	Treatment C	99	90.14	102.77	(93.95 - 112.43)	
AUC_{last}(ng*hr/mL)	Treatment A	99	522.50			31.2%
	Treatment B	99	473.80	90.68	(84.42 - 97.40)	
	Treatment C	99	526.53	100.77	(93.82 - 108.24)	
AUC_{∞}(ng*hr/mL)	Treatment A	98	532.82			30.8%
	Treatment B	98	484.11	90.86	(84.63 - 97.55)	
	Treatment C	98	535.26	100.46	(93.57 - 107.86)	

[a]A: mixed-effect model with treatment, period, and sequence as fixed effects and subject within sequence as a random effect was used for analysis of each parameter on a log scale, and the results were presented at the original scale after anti-log transformation.

[b]A: Abiraterone 4 x 250 mg uncoated (current commercial formulation); B: Abiraterone 4 x 250 mg film-coated (current commercial formulation); C: Abiraterone 2 x 500 mg film-coated (new composition); Treatment A was used as the reference group.

The 90% CI geometric mean ratios of abiraterone C_{max}, AUC_{last}, and $AUC_{0-\infty}$ were within the 80% to 125% range, indicating that the two test formulations (Treatments B and C) were bioequivalent with respect to the reference formulation (Treatment A). However, the confidence level should have been corrected for multiplicity. The 93.93% CI have been calculated by the CHMP and the results are presented below:

C_{max}: Treatment B 83.90 - 103.00

Treatment C 92.75 - 113.88

AUC_{last}: Treatment B 83.56 – 98.40

Treatment C 98.87 – 109.35

AUC_{∞}: Treatment B 83.78 – 98.54

Treatment C 92.63 -108.96

Therefore, bioequivalence has been shown also after correction of the confidence level for multiplicity.

2.5.3. Pharmacodynamics

Non applicable.

2.5.4. Discussion on clinical pharmacology

The pharmacokinetic software and methods used for AUC0-t and Cmax estimation were considered acceptable. The non-compartmental linear-trapezoidal calculation was adequate. Pharmacokinetics variables are appropriate for a single dose bioequivalence study of an immediate release product.

The validation of the analytical method is apparently satisfactory for some validation parameters according to the data submitted. The Applicant has submitted the method validation report BA10183 as well as two amendments to the analytical method. The pre-study validation of the analytical method is satisfactory. The

method met the acceptance criteria for all the validation parameters evaluated, demonstrating acceptable performance.

A pivotal bioequivalence study 212082PCR1007 and the supportive relative bioavailability study (code 212083PCR1010) are being submitted in the current dossier. These studies compared the oral bioavailability of the 250 mg and 500 mg FC tablets with the commercial 250 mg uncoated tablets of abiraterone acetate. In addition, for completeness, a Clinical Study Report (CSR) for study 212082PCR1006 (exploratory relative bioavailability study of 3 test FC tablets) was also included.

The design of the relative bioavailability exploratory study of three new formulations compared to the current formulation is considered acceptable.

During the assessment the Applicant was requested to submit the dissolution profiles of formulation G011, G012 and G013 (for study PCR1006) in the proposed QC dissolution methods for the 250 mg and the 500 mg strength in order to assess if the proposed dissolution method is able to discriminate between formulations with different bioavailability.

The Applicant has acknowledged that the in vitro dissolution test employed as QC method is not able to discriminate between bioequivalent and non-bioequivalent formulations. The main reason is the use of a significant amount of surfactant to achieve “sink conditions”. In contrast, a more complex in vitro dissolution test, which tries to mimic the physiological conditions, is able to discriminate between bioequivalent and non-bioequivalent formulations. Therefore, it is important to highlight that variations of this product should not be approved based on the *in vitro* dissolution test QC method. *In vivo* bioequivalence studies are essential to ensure bioequivalence. If the physiologically based dissolution test exhibits poor reproducibility and incomplete dissolution as to be used as QC method, it should not be used to approve any variation.

The Applicant claims that the QC method is suitable for release and stability testing because of their discriminative power. It is claimed to be discriminative towards particle size and tablet hardness. If there were any other accidental modification in the manufacturing it is unknown if it would be detected with the current QC method. The Applicant claims that it is slightly discriminative towards the tested granulation process parameter ranges and it is able to pick up potential trends during the stability testing of the drug product. In any case, it is unknown if these changes in the particle size, hardness, granulation parameters or stability are affecting bioavailability. So it is unknown the value of these predictions. It may be possible that those in vitro differences have no impact on bioavailability and that other undetected in changes may change bioavailability of the drug product, like between the different tested formulations. However, this is accepted currently as QC tool.

The “sink conditions” are considered essential in QC methods (as pointed out in the “Reflection paper on the dissolution specifications for generic oral immediate release products”). Consequently, the QC method cannot be useful from an *in vivo* predictive point of view. Its limited value is acknowledged and this issue should not be pursued any further.

The bioavailability study (212082PCR1010) demonstrated comparable bioavailability between the current commercial uncoated tablet and 4 new FC tablet formulations. Based on the PK results of this study, it is said that treatment B and C are selected for the pivotal study (212082PCR1007) and at the same time it is said that the coated version of the current 250 mg formulation was tested in the pivotal study.

The Applicant confirmed that Treatment D (G004, 250 mg coated tablet with current composition) and Treatment C (G023, 500 mg coated tablet with new composition) from Study 212082PCR1010 were used to establish bioequivalence in the pivotal Study 212082PCR1007.

Different treatment designations were used in the different studies. The formulations designated as Treatment D and C from Study 212082PCR1010 are referred to as Treatment B and C in Study 212082PCR1007.

This pivotal bioequivalence study confirmed that the proposed to-be-marketed 250 mg and 500 mg FC tablets were bioequivalent to the current commercial 250 mg uncoated tablet of abiraterone acetate.

Although these studies are usually conducted at the highest strength (i.e., 2 x 250mg tablets and 1 x 500 mg tablets), the Applicant has conducted the studies at the therapeutic dose of 1000 mg (i.e., 4 x 250 mg and 2 x 500 mg), this is considered acceptable since abiraterone does not exhibit less than proportional pharmacokinetics when increasing the dose. The administration of several tablets simultaneously can increase variability due to different gastric emptying times of each unit, but it may represent the worst case scenario for a low solubility drug compared to the highest strength.

It was discussed, during the assessment, if the new 500mg formulation could give an altered food effect. CHMP agreed that the food effect of abiraterone is mainly drug dependent. However, it may also be product dependent. The applicant's claim that hypromellose and povidone have the same negligible food effect is speculative. Similarly the absence of information on the relationship between SLS and food effect is not demonstrative of absence of a food effect caused by SLS in the case of abiraterone. Furthermore, it is the whole formulation and not the isolated excipients that can alter the food effect on the drug bioavailability. Therefore, the Applicant justification was considered speculative and it is not able to ensure that the food effect will be similar in both strengths / formulations. However, as the new proposed strength of 500 mg is taken only in fasted state as the existing 250 mg strength, it is irrelevant if the food effect is different or not because the product should not be taken with meals. This issue would be relevant if a new formulation could be able to remove the food effect so that the new formulation can be taken with or without meals, but it is extremely unlikely and it is not the intention of the Applicant to modify the instructions of use.

2.5.5. Conclusions on clinical pharmacology

Based on the biopharmaceutical studies submitted, the proposed 500 mg abiraterone acetate film-coated tablet formulation was bioequivalent to the current commercial 250 mg uncoated tablet when administered at the therapeutic dose of 1000 mg, since the 90% and 93.93% confidence intervals for the geometric mean ratios of abiraterone C_{max}, AUC_{last}, and $AUC_{0-\infty}$ were within the 80% to 125% range

The Clinical programme to obtain the Marketing Authorisation for a new film-coated (FC) tablet formulation of Zytiga 500 mg tablets is considered acceptable.

2.6. Clinical efficacy

Not applicable.

2.7. Clinical safety

Study PCR1010

Thirty two healthy adult males were randomized into the study; 30 subjects completed the study, and 2 subjects terminated early. All of the 32 randomized subjects received at least 1 dose of abiraterone acetate and were included in the safety analysis.

An overview of TEAEs is presented in Table 5. All TEAEs were mild or moderate in severity. No deaths or serious adverse events (SAEs) were reported. One subject terminated the study early due to an investigator-reported adverse event (AE) of Grade 1 hypertriglyceridemia on Study Day 15 after completion of Period 2. The event was considered by the investigator to be possibly related to the study medication. The most common TEAEs observed were flatulence, nausea, upper respiratory tract infection, back pain, myalgia, headache, ocular hyperemia, and ecchymosis (each in 2 subjects [6.3%]).

A larger percentage of subjects from Treatment Group C (34.8%) were reported with TEAEs. The TEAEs were not all systematically in one System Organ Class (SOC), but rather, were spread across several SOCs. All were Grade 1 in severity, and no specific TEAE occurred in more than 1 subject.

Table 5 - Overall Safety Profile (Study 212082PCR1010)

	Treatment A[a]	Treatment B[a]	Treatment C[a]	Total
Analysis set: safety subjects	32	23	23	32
Treatment-emergent adverse events(TEAEs)	4 (12.5%)	3 (13.0%)	8 (34.8%)	13 (40.6%)
Drug-related[b]	1 (3.1%)	0	2 (8.7%)	5 (15.6%)
Toxicity Grade 1	4 (12.5%)	3 (13.0%)	8 (34.8%)	13 (40.6%)
Toxicity Grade 2	0	0	0	1 (3.1%)
Toxicity Grade ≥3	0	0	0	0

[a] A:Abiraterone 4 x 250 mg uncoated (current commercial formulation); B: Abiraterone 2 x 500 mg film-coated (new composition); C: Abiraterone 2 x 500 mg film-coated (same composition as current commercial formulation).

[b] Drug-related adverse events are adverse events with causality reported as possible, probable or very likely. A subject was counted once within each adverse event category and treatment.

Note: TEAEs that begin after administration of the dose in a given period to the time immediately prior to the dose in the next period (or up to 30 days from last dose if the event is in the last period), will be attributed to the treatment administered in the given period.

There were no clinically relevant changes in clinical chemistry or hematology parameters over time, and no apparent differences when comparing treatments. No clinically significant abnormalities in vital signs, physical examinations, or ECG parameters were reported during the study

Study PCR1007

One hundred-two healthy adult males were randomized into the study at one site in the US; 100 subjects completed the study, and 2 subjects terminated early. All of the 102 randomized subjects received at least 1 dose of abiraterone acetate and were included in the safety analysis.

An overview of TEAEs is presented in Table 6. All TEAEs were mild or moderate in severity. No deaths or SAEs were reported, and no subject discontinued treatment due to a TEAE. The most common TEAE observed was headache that occurred in 3 subjects (2.9%).

Table 7 - Overall Safety Profile; Safety Analysis Set (Study 212082PCR1007)

	Treatment A[a]	Treatment B[a]	Total
Analysis set: safety subjects	100	101	102
Treatment-emergent adverse events(TEAEs)	6 (6.0%)	10 (9.9%)	18 (17.6%)
Drug-related[b]	1 (1.0%)	4 (4.0%)	4 (3.9%)
Toxicity Grade 1	5 (5.0%)	10 (9.9%)	18 (17.6%)
Toxicity Grade 2	2 (2.0%)	1 (1.0%)	4 (3.9%)
Toxicity Grade >=3	0	0	0

[a] A: Abiraterone 4 x 250 mg uncoated (current commercial formulation); B: Abiraterone 2 x 500 mg film-coated (new composition)
[b] Drug-related adverse events are adverse events with causality reported as possible, probable or very likely. A subject was counted once within each adverse event category and treatment.
Note: TEAEs that begin after administration of the dose in a given period to the time immediately prior to the dose in the next period (or up to 30 days from last dose if the event is in the last period), will be attributed to the treatment administered in the given period.

There were no clinically relevant changes in clinical chemistry or hematology parameters over time, and no apparent differences when comparing treatments. No clinically significant abnormalities in vital signs, physical examinations, or ECG parameters were reported during the study.

2.7.1. Discussion on clinical safety

The safety profile of abiraterone is characterised by peripheral oedema, hypokalaemia, hypertension and urinary tract infection, as the most common adverse reactions. Other important adverse reactions include cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis.

The two clinical studies submitted in this variation are limited to two single dose clinical trials. The design of these ones is not definitely the best way to judge any new safety signal. In fact, bioequivalence studies do not usually offer any kind of safety discussions. With this premise in mind, it is not surprising that no new safety concerns have been identified with the new formulation, which is expectable given the aim of the variation and the results from that.

2.7.2. Conclusions on the clinical safety

The safety conclusions about this new formulation do not change the previous safety analysis for the already authorized formulation of 250 mg. The safety profile continues to be acceptable.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 12.0 (dated 15 September 2015) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report dated 13 May 2016.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 12.1 (dated 23 June 2016) with the following content:

Summary of the safety concerns

Important identified risks	• Hepatotoxicity • Cardiac disorders • Osteoporosis including osteoporosis-related fractures • Rhabdomyolysis/Myopathy • Allergic alveolitis • Increased exposure with food
Important potential risks	• Anaemia • Cataract • Drug-drug interaction (CYP2D6)
Missing information	• 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%

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Not applicable

Risk minimisation measures

Summary table of the risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks:		
Hepatotoxicity	Wording in SmPC Section 4.2, 4.4, 4.8	None
Cardiac disorders	Wording in SmPC Section 4.4, 4.8	None
Osteoporosis including Osteoporosis-related fractures	Wording in SmPC Section 4.4, 4.8.	None
Rhabdomyolysis/Myopathy	Wording in SmPC Section 4.4, 4.8	None
Allergic alveolitis	Wording in SmPC Section 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Increased exposure with food	Wording in SmPC Section 4.2, 4.5, 5.2	None
Important potential risks:		
Anaemia	Wording in SmPC Section 4.4	None
Cataract	The MAH considers that language in the SmPC is not warranted at this time	Not applicable
Drug-drug interaction (CYP2D6)	Wording in SmPC Section 4.5	None
Missing information:		
Use in patients with active or symptomatic viral hepatitis	Wording in SmPC Section 4.4	None
Use in patients with moderate/severe hepatic impairment and chronic liver disease	Wording in SmPC Section 4.2, 4.3, 4.4, 5.2	None
Use in patients with severe renal impairment	Wording in SmPC Section 4.2	None
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%.	Wording in SmPC Section 4.4.	None

2.9. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

The current commercial formulation of abiraterone acetate (Zytiga) is presented as 250 mg uncoated tablets.

This submission is intended to obtain the Marketing Authorisation for a new film-coated (FC) tablet formulation of Zytiga 500 mg tablets to be used in the same currently approved indications of the marketed formulation of Zytiga.

The use of the new tablet strength and formulation is supported by the results of two Phase I studies. Study 212082PCR1010 demonstrated comparable relative bioavailability of 2 new 500 mg FC tablet concepts compared to commercially available Zytiga (250 mg uncoated tablets). Study 212082PCR1007 demonstrated bioequivalence between the 500 mg FC tablets with respect to the current commercial 250 mg uncoated tablets of abiraterone acetate.

Based on the biopharmaceutical studies submitted, the proposed 500 mg abiraterone acetate film-coated tablet formulation was bioequivalent to the current commercial 250 mg uncoated tablet when administered at the therapeutic dose of 1000 mg, since the 90% and 93.93% confidence intervals for the geometric mean ratios of abiraterone Cmax, AUClast, and AUC0-∞ were within the 80% to 125% range.

As expected, no new safety concerns have been identified in the two clinical studies submitted.

The benefit risk balance remains positive

3.1. Conclusions

The overall B/R of Zytiga is positive

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers that the risk-benefit balance of Zytiga with prednisone or prednisolone in the following indications:

- 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)

- treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen.

is positive and therefore recommends the granting of the marketing authorisation for a new pharmaceutical form and strength (Zytiga film-coated (FC) tablet 500 mg) subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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