22 April 2021
EMA/653711/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abiraterone Krka

International non-proprietary name: abiraterone acetate

Procedure No. EMEA/H/C/005649/0000

Note

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

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List of abbreviations

ADT	Androgen deprivation therapy
AE	Adverse event
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Applicant's Part (or Open Part) of ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
AUC	Area under the curve
BEQ	Bioequivalence
CI	Confidence interval
Cmax	Maximum measured analyte concentration over the sampling period
CoA	Certificate of Analysis
CRF	Case report form
CRS	Chemical Reference Substance (official standard)
CS	Clinically significant
CV	Coefficient of variation
CYP	Cytochrome P450
DAD	Diode-array
DHEA	Dehydroepiandrosterone
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HDPE	High-density polyethylene
HPLC	High Performance Liquid Chromatography
ICF	Informed consent form
ICH	International conference on harmonisation
ICH	International Council for Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IMP	Investigational medicinal product
IPC	In-process control
IR	Infrared
IRB	Institutional review board
Kel	Elimination rate constant
LDPE	Low-density polyethylene
LHRH	Luteinising hormone releasing hormone
LOD	Limit of Detection
LOQ	Limit of Quantification
LoQ	List of Questions

LQCT	Last quantifiable concentration time
LSM	Least-squares mean
MAH	Marketing Authorisation holder
mCRPC	metastatic castration resistant prostate cancer
mHSPC	metastatic hormone sensitive prostate cancer
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMT	Not more than
PE	Polyethylene
PET	Polyethylene terephthalate
Ph. Eur.	European Pharmacopoeia
PK:	Pharmacokinetic
PL	Patient Leaflet
PMRI	Pharma Medica Research Inc.
PSA	Prostate-specific antigen
PSMF	Pharmacovigilance system master file
PVC	Polyvinyl chloride
QA	Quality assurance
QOS	Quality Overall Summary
QP	Qualified Person
QPPV	Qualified person responsible for pharmacovigilance in the EU
R2	Coefficient of determination obtained from regression analysis
RH	Relative Humidity
RMP	Risk management plan
RP	Restricted Part (or Closed Part) of ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse event
SD or STD	Standard deviation
Thalf	The apparent elimination half-life
TLIN	Start time for linear regression
Tmax	Time of the maximum measured analyte concentration over the sampling period
ULN	Upper limit of normal
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 29 June 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Abiraterone acetate KRKA, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'.>. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.>

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Abiraterone acetate KRKA is indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Zytiga instead of non-clinical and clinical unless justified otherwise >The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 8 years in the EEA:

- Product name, strength, pharmaceutical form: Zytiga 250mg tablet and Zytiga 500mg film-coated tablet
- Marketing authorisation holder: Janssen-Cilag International N.V.
- Date of authorisation: 05-09-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/11/714/001 and EU/1/11/714/002-003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Zytiga 250mg tablet and Zytiga 500mg film-coated

tablet

- Marketing authorisation holder: Janssen-Cilag International N.V.
- Date of authorisation: 05-09-2011
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation numbers: EU/1/11/714/001 and EU/1/11/714/002-003
- Bioavailability study numbers: Study No. ARL/15/277 and Study No. ARL/18/135

Information on paediatric requirements

Not applicable

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.
>

Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Nevenka Trsinar Brodt

The application was received by the EMA on	29 June 2020
The procedure started on	16 July 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	5 October 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	19 October 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 November 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 December 2020
The Rapporteurs circulated the Joint Assessment Report on the	01 February 2021

applicant's responses to the List of Questions to all CHMP members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	07 April 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
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 Abiraterone acetate KRKA on	22 April 2021

2. Scientific discussion

2.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Abiraterone acetate Krka 500 mg film-coated tablets. The originator product is Zytiga 500 mg film-coated tablets first approved in Europe on 05th of September 2011 (MAA No: EU/1/11/714/001-003, Janssen-Cilag International NV).

Abiraterone acetate is an androgen biosynthesis inhibitor, converted in vivo to abiraterone. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals.

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Abiraterone acetate Krka is indicated in combination with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).

- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen.

To support this application, the applicant submitted one pivotal bioequivalence study (No.: 19-652), (fasting) and synopsis of pilot bioavailability study (No.: 19-624) as supportive study (fasting). Please refer to comments in section 3.3. Clinical aspects.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as well as the Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/09) and Abiraterone Product-specific Bioequivalence Guidance (EMA/CHMP/474712/2016 Rev. 1) and EMA`s Questions & Answers: Positions on specific questions addressed to the Pharmacokinetics Working Party (EMEA/618604/2008) in their current version.

The Applicant did not receive CHMP Scientific Advice pertinent to the clinical investigation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 500 mg of abiraterone acetate as active substance.

Other ingredients are:

Tablet core: lactose monohydrate, hypromellose (E464), sodium laurisulfate, croscarmellose sodium (E468), silicified microcrystalline cellulose, silica colloidal anhydrous and magnesium stearate (E470b).

Film coating: macrogol, poly(vinyl alcohol), talc (E553b), titanium dioxide (E171), red iron oxide (E172) and black iron oxide (E172).

The product is available in blister (PVC/PE/PVDC//Paper/Alu): 56, 60 film-coated tablets, and blister (PVC/PE/PVDC//Paper/Alu), calendar pack: 56 film-coated tablets, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of abiraterone acetate is 17-(Pyridin-3-yl)androsta-5,16-dien-3β-yl acetate corresponding to the molecular formula $C_{26}H_{33}NO_2$. It has a relative molecular mass of 391.55 g/mol and the following structure in Figure 1:

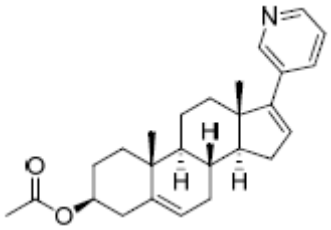

Figure 1: abiraterone acetate structure

The chemical structure of abiraterone acetate was elucidated by a combination of elemental analysis, UV spectroscopy, FT-IR spectroscopy, nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, thermal analysis (DSC) and thermo gravimetric analysis (TGA).

The active substance is a white to off-white powder practically insoluble in water and is insoluble in water and in aqueous buffers with pH 1.2-8.0.

Abiraterone acetate exhibits polymorphism. The polymorphic form of abiraterone acetate can be distinguished by XPRD.

Abiraterone acetate is a single enantiomer containing 8 stereochemical elements: 6 chiral centres and 2 centres of geometrical isomerism. Abiraterone acetate is produced as a single enantiomer. The optical purity is adequately controlled.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The manufacturing process consists of several synthetic steps.

Only one site is involved in the manufacture and micronisation of the active substance. The starting materials are acceptable and are controlled by suitable specifications. During the synthesis, several intermediates are isolated and are sufficiently controlled. In addition, acceptable specifications for reagents, solvents and other materials used in the synthesis have been provided. Critical steps of the process were identified and are controlled by justified and appropriate in-process controls.

The stability data for reprocessed batch has been included in stability section.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The information presented regarding potential impurities/degradation products controlled in the active substance is sufficient. Overall the defined control strategy is satisfactory.

Abiraterone acetate is packed in a suitable container. The primary packing material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identification (IR, HPLC), water content (Ph. Eur, in-house), specific optical rotation (Ph. Eur), sulphated ash (Ph. Eur.), content of abiraterone acetate (Ph. Eur, in-house), impurities (HPLC, in-house), residual solvents (GC), particle size (Ph. Eur, in-house) and microbiological quality (Ph. Eur).

The specification limits for impurities/degradation products and residual solvents are in accordance with the requirements of ICH guidelines Q3A and Q3C. All solvents used throughout the entire synthetic process, including those employed prior to the starting material, are routinely controlled in the specification and specified at levels below the ICH Q3C thresholds.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. The finished product manufacturer has adopted the analytical methods for content of abiraterone acetate and for related substances. For the test on residual solvents the same analytical procedure is used by the finished product manufacturer as followed by active substance manufacturer. All other analytical methods are Ph. Eur. Methods. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from several production scale batches generated by both active substance and finished product manufacturers was provided, demonstrating compliance with the proposed specifications. The batch data provided is considered to be sufficient. Consistency and uniformity of the active substance quality have been demonstrated.

Stability

Stability data from several commercial scale batches and micronisation validation batch stored for up to 60 months under long term conditions (25±2°C / 65±5% RH) and for up to 6 months under accelerated conditions (40±2°C / 75±5% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

All tested parameters were within the specifications.

Photostability studies were conducted in line with ICH Q1B requirements. Additionally, the force degradation study has been demonstrated to be stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period when stored in the proposed container with specified storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a film-coated tablet for oral administration containing 500 mg of abiraterone acetate. The film-coated tablets are presented as grey violet to violet oval biconvex film-coated tablets. Approximate tablet dimensions: tablets are 20 mm long by 10 mm wide.

The qualitative composition is listed below:

Active substance: Abiraterone acetate.

Tablet core: lactose monohydrate, hypromellose (E464), sodium laurisulfate, croscarmellose sodium (E468), silicified microcrystalline cellulose, silica colloidal anhydrous, magnesium stearate (E470b) and purified water.

Film coating: macrogol, poly(vinyl alcohol), talc (E553b), titanium dioxide (E171), red iron oxide (E172), black iron oxide (E172) and purified water.

Abiraterone Krka 500 film-coated tablets was developed with the objective of designing a bioequivalent, effective and safe generic equivalent to the originator medicinal product Zytiga 500 mg film-coated tablets of specified quality, manufactured by simple and reproducible technological process to consistently deliver the intended performance of the medicinal product – easily manufactured, stable formulation in the proposed packaging.

Abiraterone acetate is practically insoluble in water. Abiraterone acetate is a BCS class IV compound with low solubility and low permeability across physiological pH range.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with exception of some of them which are referred to USP/NF or 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. These are: lactose monohydrate; hypromellose; sodium laurylsulfate; croscarmellose sodium; cellulose, silicified microcrystalline (type 90) comprises of microcrystalline cellulose and colloidal anhydrous silica; silica colloidal anhydrous ; magnesium stearate. The coating material used for the 500 mg strength contains also polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide black (E172) and iron oxide red (E172). The selected ingredients for film coating have well known chemical, physical and microbial characteristics and comply with relevant Ph. Eur. Monographs and EU 231/2012 Regulation.

Silicified microcrystalline cellulose (type 90) (SMCC 90) is considered as co-processed excipient. A manufacturing process of SMCC 90 has been described in section 3.2.P.3.3 in the manufacturing process flowchart and detailed description of the manufacturing process including process settings and in process controls. It is composed of microcrystalline cellulose co-processed with colloidal silicon dioxide.

Because water is used during manufacturing process of silicified microcrystalline cellulose the applicant is strongly encouraged to change the quality to purified water, Ph. Eur., by a variation application post-approval. The requirements (Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)) for water used during the manufacture of active substances (point 5.2) could not be extrapolated to the excipients. Water, used during manufacture of medicinal products but not present in the final formulation, is recommended to be purified. See recommendation in section 2.2.6.

A compatibility study was performed to examine the interactions between the active substance and the proposed excipients. This was performed through the ICH stability studies under accelerated and long-term conditions. No significant increase in abiraterone acetate related substances was found in the compatibility study. From the results, it could be concluded that the active substance is compatible with the excipients used in Abiraterone 500 mg film-coated tablets.

In order to assess pharmaceutical equivalence, Abiraterone Krka 500 mg film-coated tablets was compared to Zytiga 500 mg film-coated tablets versus their quality characteristics – impurities and their *in vitro* performance – dissolution profiles. In the beginning of the development phase of Abiraterone 500 mg film-coated tablets and according to the "Guideline on the investigation of bioequivalence" (CPMP/EWP/QWP/1401 98 Rev.1/Corr**), solubility study of abiraterone acetate in physiological pH range from acidic to neutral pH was performed.

Solubility characteristics of abiraterone acetate were determined and selected dissolution media justified.

Development of the dissolution method was guided by the recommendations of the relevant chapters of the European Pharmacopoeia "Guidance on dissolution testing" and relevant sections of guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr**. In compliance with the above guidelines, the basic criteria, which governed the choice of the dissolution method (apparatus, medium, volume and stirring speed), were discriminatory power of the method, reflection of *in vivo* conditions, fulfilment of sink conditions, complete release of active substance within the specified time and appropriate robustness for routine QC testing. The dissolution testing was conducted using Ph. Eur. compliant equipment.

The selected dissolution method for Abiraterone 500 mg film-coated tablets has appropriate discriminatory power.

The bioequivalence study was conducted in order to compare the bioavailability of Abiraterone Krka 500 mg film-coated tablets and Zytiga 500 mg film-coated tablets. The study was a single-center, randomized, single-dose cross-over study conducted under fasting conditions with a 7 days washout period between the doses. The formulation used in the bioequivalence study were manufactured by the same manufacturer, same manufacturing process and same type of equipment. The assayed content of test batches does not differ more than 5% from that of the reference batches, there is also no observed difference in the impurity profile. The production batch size is the same as the size of batches in the bioequivalence study. Based on the results, bioequivalence is concluded between test and reference formulation.

The formulation used during clinical studies is the same as that intended for marketing.

Formulation development was initiated with an evaluation of the characteristics of the reference product, Zytiga film-coated tablets. Fluid bed granulating technique was selected for manufacturing the Zytiga 500 mg formulation as per EPAR. However, fluid bed granulating technique was later abandoned after scale-up experiment, and high-shear granulation was selected as the final manufacturing procedure for present formulation.

The primary packaging is blister (PVC/PE/PVDC//Paper/Alu): 56, 60 film-coated tablets, and blister (PVC/PE/PVDC//Paper/Alu), calendar pack: 56 film-coated tablets as stated in the SmPC. The material complies with Ph.Eur. and 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

There is only one manufacturer of the finished product. The manufacturing process consists of four main steps: dispensing; manufacturing of granulate; manufacturing of compression mixture; tabletting process and film-coating process. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), uniformity of dosage unit – mass variation (Ph. Eur), identification of abiraterone acetate (HPLC), content of abiraterone acetate (HPLC), dissolution, impurities (HPLC) and microbial quality (Ph. Eur).

The proposed specification is considered acceptable.

The potential presence of class 1 (As, Cd, Hg and Pb) and Class 2A (Co Ni, V) elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Furthermore Se, Sb, Ba, Mo, Cu, Sn and Cr were also included in the risk assessment, because of their naturally occurring as contaminants in mined substances (coating mixture (talc and titanium oxide), iron oxide). Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The applicant was requested to provide a risk evaluation concerning the presence of nitrosamine impurities in the product in question; this was raised as a MO during the procedure. In response to this MO, a risk assessment concerning the presence of nitrosamine impurities was performed for the finished product based on the combined recommendations from health authorities. A statement that there is no risk of N-nitrosamine contamination has been provided and it was concluded that there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Abiraterone Krka are necessary to mitigate potential contamination by nitrosamines. The nitrosamine impurities risk assessment of the finished product included evaluating contributions from abiraterone acetate active substance, excipients, finished product manufacturing facilities, and packaging components.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from several commercial batches of finished product stored for up to 12 months under long term conditions (25°C / 60% RH) and up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. For bulk product, adequate stability results at long term condition 25°C/60% RH supporting proposed bulk holding were also presented. The batches of Abiraterone Krka 500 mg film-coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

The analytical procedures used are stability indicating. A trend of increasing specified and total impurities was observed at accelerated and long-term conditions. Results for unspecified impurities are below reporting level ($\leqslant$0.05%). All results are within the proposed limits.

Photostability study was conducted according to ICH Q1B, Option 2. Samples were tested for appearance, content of abiraterone acetate, dissolution and impurities. Test was performed on tablets stored outside the immediate packaging and exposed to light in a single layer on open Petri dish at controlled conditions 25°C/40%RH. Film-coated tablets outside the original packaging and exposed to light showed no sensitivity of the product to the light and no trends were observed on any of the tested parameters. Based on the results, it can be concluded that the finished product is found to be stable to light exposure.

According to the compliance of the results with the specification limits at accelerated conditions and according to photostability study results no special storage conditions is proposed. Therefore, based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

Lactose monohydrate is the only material of animal origin used in the production of Abiraterone film-coated tablets. 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. Valid TSE CEP is provided.

Magnesium stearate is of vegetable origin. Statement from manufacturer confirming origin of magnesium stearate is presented.

2.2.4. 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 MO raised during the procedure regarding the potential presence of nitrosamines in the finished product was resolved by performing and presenting a satisfactory risk assessment as per the relevant published guidance. 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.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the quality standard of the water used in the manufacturing process of silicified microcrystalline cellulose. This point is put forward and agreed as recommendation for future quality development (see section 2.2.6).

2.2.5. 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. Lactose monohydrate is the only material of animal origin used in the manufacture of Abiraterone Acetate film-coated tablets. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To submit a variation post-approval in 2 years' time frame after approval to change the quality of water used during manufacturing process of silicified microcrystalline cellulose to purified water. The requirements (Guideline on the quality of water for pharmaceutical use (EMA/CHMP/CVMP/QWP/496873/2018)) for water used during the manufacture of active substances

(point 5.2) could not be extrapolated to the excipients. Water, used during manufacture of medicinal products but not present in the final formulation, is recommended to be purified.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of abiraterone are well known. As abiraterone is a widely used, well-known active substance, additional studies and further studies are not required. Overview based on literature review is appropriate.

The impurity profiles of Abiraterone acetate Krka 500 mg tablets were compared to that of the reference product Zytiga 500 mg tablets. Both test and reference products exhibit similar impurity profiles. The specifications set for all impurities are in accordance with the currently valid USP monograph for abiraterone acetate tablets and the ICH Q3B guideline and thus acceptable.

The excipients used in drug formulation are conventional, well known and broadly used in other medicinal products.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product (Zytiga SmPC, 2020).

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Abiraterone KRKA is considered unlikely to result in any significant increase in the combined sales volumes for all abiraterone acetate containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

SmPC of the generic product, section 5.3 contains the same information as the innovator: "The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish."

2.3.3. Discussion on non-clinical aspects

In line with the requirements for generic products, no new non-clinical data was submitted. The non-clinical data, based on literature review of published studies, are acceptable since abiraterone is well-known active substance clinically used in humans for more than 10 years.

The presented Non-clinical Overview is considered sufficient for this type of MAA.

The impurity profile has been discussed and was considered acceptable.

The excipients used in drug formulation are conventional, well known and broadly used in other medicinal products.

The Applicant's justification for omission of environmental risk assessment studies is considered acceptable.

The non-clinical data is reflected in the appropriate sections of the SmPC (Sections 4.6 and 5.3). The non-clinical aspects of the SmPC are in line with the SmPC of the reference product (Zytiga SmPC, 2020).

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Abiraterone acetate KRKA and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was accepted by the CHMP. This is in accordance with the relevant guideline and additional non clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Abiraterone acetate Krka 500 mg film-coated tablets with abiraterone acetate as active substance. Essential similarity is claimed to Zytiga containing abiraterone acetate, Janssen-Cilag International N.V., Belgium approved via centralised procedure since 5th of September 2011 (EU/1/11/714/002-003).

A clinical overview has been provided, which is based on up-to-date and adequate scientific literature.

To support this application, the applicant submitted one pivotal bioequivalence study (No.: 19-652) in fasting condition. In addition, the applicant submitted the synopsis of the pilot bioavailability study (No.: 19-624) as supportive study (fasting).

The bioequivalence is based on the results of the pivotal study (No.: 19-652). The pilot study (No.: 19-624) is not discussed in this report.

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.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study (No: 19-652). In addition, the applicant presented synopsis of pilot bioavailability study (No: 19-624) as supportive information.

Table 1 Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen;	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report

					Route of Administration				
BE	***19-652***	Section 5.3.1.2.	To compare the rate and extent of absorption of abiraterone from the test and reference products	Crossover, semi-replicate, fasting state	**Test product:** Abiraterone 500 mg film-coated tablets (KRKA, d.d., Novo mesto) **Reference product:** Zytiga® (abiraterone acetate) 500 mg film-coated tablets (Janssen-Cilag International N.V.) One film-coated tablet per period; Oral	102	Healthy subjects	Single dose	Complete; Full

2.4.2. Pharmacokinetics

Study No.19-652, A Single-Dose, Semi-Replicate, Bioequivalence Study of Two Formulations of Abiraterone Acetate 500 mg Film-Coated Tablets under Fasting Conditions

Methods

Study design

Study No.19-652 was an open-label, single-dose, randomized, three-period, two-treatment, two-sequence, cross-over, semi-replicate study, designed to evaluate the bioequivalence of abiraterone in healthy, non-smoking, male subjects under fasted conditions with a washout period of 7 days between drug administrations. In each period, subjects were administered a single, oral dose of either the test or reference product, in accordance with the randomization scheme, after an overnight fast of at least 10 hours.

The primary objective of this study was to evaluate the bioequivalence between Abiraterone 500 mg film-coated tablets (MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU) and Zytiga ® (abiraterone acetate) 500 mg film-coated tablets (MAH: Janssen-Cilag International NV, Belgium, EU) after a single dose in healthy male subjects under fasted conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.

Summary of study information

Clinical Study Dates:	December 06, 2019 (ICF signature) - March 02, 2020 (Last Subject Assessment)

	Treatment Dosing Dates: Period-I: December 07, 2019 Period-II: December 14, 2019 Period-III: December 21, 2019 Last Pharmacokinetic (PK) Blood Sample: December 23, 2019
Date of the Clinical Study Report:	May 11, 2020
Bioanalytical Study Dates:	02 January 2020 – 17 January 2020

Both the clinical study site and the bioanalytical site have been inspected by an EU competent authority.

In order to assess the within-subject variability for C_{max} of the reference product and to justify widening of a confidence interval for C_{max}, this study included semi-replicate administration of the test and reference products in 3-period cross-over design, where treatments are given in the order sequences TRR, RTT. The within subject variability were estimated for both test and reference products. The TRR, RTT replicate design is considered appropriate to assess the within-subject variability for C_{max} of the reference product as more than 12 subjects were allocated in each arm. This complies with the EMA`*s* question number 19 of Questions & Answers Document (EMA/618604/2008 Rev. 13).

The study was conducted in three periods and in each period the subjects received either test or reference products randomly as per the predetermined computer-generated randomization scheme (procedure PLAN in SAS® version 9.4) and under open-label conditions. The dosing (treatment) of test and reference product were given in two sequences (TRR, RTT). Subjects who were assigned sequence TRR received test product (T) in period-1 and reference product (R) in period-2 and 3. Subjects who were assigned sequence RTT received R product in Period-1 and T product in period-2 and 3. Dosing occurred following an overnight fast of at least 10 hours. There was a 7-day washout period between dosing times for the two treatment periods. The pre-dose concentrations of abiraterone, which was less than 5% of their C_{max} were observed for 3 subjects before the period-2 or period-3 drug administration at time 0.00h.

In each study period, blood samples were collected within 60 minutes prior to dose administration (0 hour) and at intervals over 48.00 hours after administration of dose, totalling 22 samples in each period. Considering the expected time to peak concentration (approximately 2 hours) and the elimination half-life (approximately 15 hours), the sampling schedule and the sampling time period of 48 hours seems long enough to estimate PK parameters (C_{max}, $AUC_{0\text{-}t}$ and T_{max}).

The quantification of abiraterone in human plasma was performed using liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method.

Test and reference products

Product Characteristics	**Test product**	**Reference Product**
Name	Abiraterone 500 mg film-coated tablets	Zytiga® 500 mg film-coated tablets
Strength	500 mg	500 mg

Dosage form	Film-coated tablets	Film-coated tablets
Batch number	RA0258	IGZSB00
Expiry date (Retest date)	(17/01/2020)	06/2020
Location of Certificate of Analysis	Appendix 16.1.6	Appendix 16.1.6
Member State where the reference product is purchased from:		Germany, EU
This product was used in the following trials:	Sponsor Project N° 19-652 *CRO Project N° 2020-4801*	Sponsor Project N° 19-624 *CRO Project N° KRS-P6-263* Sponsor Project N° 19-652 *CRO Project N° 2020-4801*

Zytiga 500 mg film-coated tablets is an immediate release tablet formulation containing abiraterone, which was approved in Europa on 5th of September 2011, through a centralised marketing authorization procedure under Article 8.3 of Directive 2001/83/EC. Therefore, the choice of the reference medicinal product is acceptable. The member state where the reference product was purchased from is Germany, EU.

Satisfactory certificates of analysis of the test and reference products bio-batch are presented. The difference in the assay between the test and reference product is less than 5%, which is acceptable. This difference was not taken into account in the pharmacokinetic or statistical analysis.

Population(s) studied

A total of 102 non-smoker, healthy, adult, male volunteers 18 to 65 years of age, having a Body Mass Index (BMI) between ≥18.5 and ≤30.0 kg/m2 and weight ≥50 kg with normal clinical and laboratory results, were enrolled in the study. The population chosen was appropriate and in line with the *Guideline on the investigation of Bioequivalence/CMP/EWP/QWP/1404/98 Rev.1/Corr***. All the subjects were dosed as per the randomization. Male subjects participated in the study met the inclusion criteria and did not fulfil any of the exclusion criteria described in the study protocol.

Out of the **102 subjects**, **98 subjects** completed all 3 periods of the study**,101 subjects** completed at least two periods and were included in the **Pharmacokinetic** and **Statistical analysis**.

The **safety** assessment includes information for **all 102 subjects** who received at least one administration of any study treatment.

Drop-outs and missing samples:

Two subjects discontinued after completing period-1 and 2, due to AEs (libido decreased and scrotal discomfort; pyrexia). Plasma samples of both subjects were analysed as per protocol requirement. And data from both subjects were included in the PK and Statistical analyses.

One subject who discontinued after period-1 of drug administration due to personal reasons. was excluded from the PK and statistical analyses.

A fourth subject discontinued after completing period-1 due to personal reason but returned in period-3 to complete the study. The subject completed two periods (period-1 with test product and period-3 with reference product), hence the subject was included in the PK and Statistical analyses.

One subject completed the study with missing Period-3 sample of reference product at 48 hours post dose.

<u>Protocol Deviations</u>

Protocol deviations are presented in Table 2 Protocol Deviation Summary

Protocol Deviation Number	Protocol Section	Details
2020-4801-P01	10.12 Pharmacokinetic Sample Collection	The actual time of collection of the PK sample from period 1, 48 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results. The actual time of collection of the PK sample from period 3, 48 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results. The actual time of collection of the PK sample from period 1, 3.5 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results. The actual time of collection of the PK sample from period 2, 36 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results. The actual time of collection of the PK sample from period 2, 3.5 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results.

Protocol Deviation Number	Protocol Section	Details
2020-4801-P01	10.12 Pharmacokinetic Sample Collection	The actual time of collection of the PK sample from period 2, 36 hours postdose, could not be verified. The sample was collected, processed in accordance with the protocol, and the scheduled time of collection was used in the PK analysis. Therefore, this deviation had no significant impact on the integrity of the study results.
2020-4801-P01	10.12 Pharmacokinetic Sample Collection	No PK sample was collected during period 3 at 48 hours postdose because the subject did not return to the clinic. The corresponding abiraterone concentration value was set to missing for the purposes of the PK analysis and the impact on the integrity of the study results was not significant.
2020-4801-P01	10.12 Pharmacokinetic Sample Collection	The PK sample scheduled for collection at 48 hours postdose in period 3 was collected 186 minutes prior to the scheduled time. A PK scientist was not consulted to assess the continued participation of the subject in the study. The actual time of collection was used in the PK analysis and this deviation had no significant impact on the integrity of the study results.
2020-4801-P02	10.9 Vital Signs Measurements	Systolic and diastolic blood pressure, but not pulse rate, was documented in period 1, 4.5 hours postdose. A pulse rate within normal limits was obtained as part of an electrocardiogram recording 59 minutes prior to the time of the measurement of vital signs. The blood pressure measurements were within normal limits. This deviation had no significant impact on the safety of the subject or on the integrity of the study results. Vital signs measurements were obtained during period 3, 8 hours postdose, at 5 minutes before the earliest allowable time. The measurements were within normal limits. This deviation had no significant impact on the safety of the subject or on the integrity of the study results.

PK, pharmacokinetic.

Analytical methods

Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

Plasma concentrations of abiraterone in subject samples were measured utilizing Analyst® Software Version 1.6.3, according to an achiral, liquid chromatographic tandem mass spectrometric detection (LC-MS/MS) method.

The analytical method used for the study is the same as the validated method.

Calibration curve standards and quality control samples met the acceptance criteria for all the runs used for the final data, demonstrating satisfactory performance of the method during the analysis of study subject samples.

119 subject samples were repeated in accordance with. due to unacceptable internal standard response, injection error, extraction error, poor chromatography, above the Upper Limit of Quantitation and to confirm presence of peak in pre-dose. The reasons for reanalysis of samples in each of the sample analysis are considered justified.

385 study samples were re-assayed in accordance with SOP.

ISR was performed with more than 5 % of the samples as requested by the guideline for total number samples exceeding 1000 samples. The ISR assay complied with the acceptance criteria as all samples (100%) were within the acceptance criteria (±20%) indicating that the analysis is robust.

Deviations

Two deviation occurred during analysis of the study samples.

Pharmacokinetic variables

The PK parameters C_{max}, AUC_t, AUC_{inf}, T_{max}, K_{el}, and T_{half} estimated for abiraterone were computed using a noncompartmental approach in Phoenix™ WinNonlin®, Version 8.1.

Primary pharmacokinetic parameters: were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$

Secondary pharmacokinetic parameters wereT_{max}, K_{el}, and T_{half}

The selected primary pharmacokinetic variables are appropriate for a single dose bioequivalence study and in line with the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1)*.

Pharmacokinetic software and method for PK parameters estimation are considered acceptable.

Actual time of blood collection was considered for pharmacokinetic calculations.

Statistical methods

Descriptive statistics for the PK parameters of abiraterone were calculated and included number of observations, arithmetic mean, standard deviation (SD), geometric mean (where applicable), coefficient of variation (CV), median, minimum, and maximum.

Statistical analysis was performed on log-transformed pharmacokinetic parameters AUC_t, AUC_{inf}, and C_{max} of abiraterone using the SAS® package (Version 9.4, PROC MIXED of SAS).

Analysis of variance (ANOVA) was performed on log-transformed pharmacokinetic parameters AUC_t, AUC_{inf}, and C_{max} of abiraterone using PROC MIXED procedure in SAS®, Software, Version 9.4 or higher. The significance of the sequence, period, and treatment effects (all fixed) was tested.

Using the same statistical model, the least-squares-means (LSMs), the differences between the treatments LSMs, and the corresponding standard errors of these differences were estimated for log-transformed AUC_t, AUC_{inf}, and C_{max} parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated.

To assess the within-subject variability of this drug, this study employed a replicate administration of the reference product. The intra-subject-within-reference variability, S_{WR}, was estimated using the data from subjects who completed 2 administrations of the reference product. The comparison of C_{max} (R1 versus R2) was carried out using PROC GLM procedure. The statistical model included sequence, subject-within-sequence, and period as factors. The residual variance corresponds to intra-subject-within-reference variability.

Standard bioequivalence criteria were proposed for AUC_{0-t} and AUC_{inf} while a wider bioequivalence interval was proposed for C_{max} if the reference product has a highly variable intra-subject variability (>30%) as indicated in the EMA *Guideline on the Investigation of Bioequivalence*.

Although the widening of the acceptance criteria for C_{max} has been adequately justified, the 90%CI for C_{max} of abiraterone lie within the acceptance range of 80 – 125% and therefore a justification for widening of the acceptance criteria for C_{max} is of no more relevance.

Protocol deviations/violations were not reported with regards the statistical analysis of the study.

Results

The pharmacokinetic parameters of abiraterone for Test Product (T) and Reference Product (R) are summarized in the following tables:

Table 2 : Pharmacokinetic parameters for abiraterone (non-transformed values) (Study No. 19-652)

Table 14–2 Descriptive Statistics for Plasma Abiraterone Pharmacokinetic Parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	**A**	303.605	356.722	209.707	58.79	315.976	60.575	1038.567	149
*(hr*ng/mL)*	**B**	316.680	378.234	229.061	60.56	318.335	79.085	1120.155	151
AUC_{inf}	**A**	329.882	383.914	219.458	57.16	337.266	64.458	1077.263	146
*(hr*ng/mL)*	**B**	344.688	407.283	238.656	58.60	346.437	92.026	1172.270	149
AUC_t/AUC_{inf}	**A**	92.74	92.88	4.67	5.03	93.91	58.60	99.38	146
(%)	**B**	91.99	92.30	6.86	7.44	94.56	53.05	98.56	149
C_{max}	**A**	56.932	69.089	44.785	64.82	56.000	9.420	282.000	149
(ng/mL)	**B**	60.409	72.542	43.408	59.84	64.100	14.400	216.000	151
T_{max}	**A**	1.71	1.98	1.18	59.74	1.67	0.67	7.00	149
(hr)	**B**	1.86	2.13	1.23	57.49	1.67	0.67	9.00	151
T_{half}	**A**	15.92	16.51	4.86	29.45	15.71	7.43	48.02	146
(hr)	**B**	16.08	17.11	7.10	41.48	14.74	8.48	50.76	149
K_{el}	**A**	0.0435	0.0450	0.0118	26.21	0.0441	0.0144	0.0932	146
(1/hr)	**B**	0.0431	0.0453	0.0131	29.03	0.0470	0.0137	0.0818	149
TLIN	**A**	15.35	16.17	5.28	32.62	16.00	7.00	24.03	146
(hr)	**B**	16.00	16.84	5.32	31.57	16.00	6.00	24.13	149
R^2	**A**	0.9749	0.9755	0.0344	3.53	0.9892	0.8269	1.0000	146
	B	0.9739	0.9746	0.0377	3.87	0.9891	0.8013	1.0000	149
LQCT	**A**	47.69	47.69	0.87	1.82	47.70	44.90	49.72	149
(hr)	**B**	47.64	47.66	1.29	2.71	47.75	35.00	49.12	151
Ct	**A**	0.883	1.031	0.559	54.23	0.912	0.108	3.080	149
(ng/mL)	**B**	0.909	1.078	0.619	57.39	0.916	0.170	3.100	151

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*

TLIN = start time for linear regression
R^2 = coefficient of determination for regression analysis
LQCT = time of the last quantifiable concentration
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity.

Treatment A: Abiraterone 500 mg film-coated tablets, Batch No.: RA0258
Treatment B: Zytiga® (abiraterone acetate) 500 mg film-coated tablets, Batch No.: IGZSB00

Table 3 : Statistical analysis for abiraterone (ln-transformed values) (Study No. 19-652)

Table 2–1 Summary of Study Results Based on Plasma Abiraterone Levels

Based on Log-transformed Data								
Parameter	***Trt***	***n***	***Arithmetic Mean (CV%)***	***Geometric Mean***	***Contrast***	***Ratio (%)***	***90% Confidence Interval***	***Intra-Sbj CV(%)***
AUC_t	**A1**	101	347.413 (58)	304.632	**A vs B**	96.67	91.17 - 102.50	30
*(hr*ng/mL)*	**A2**	48	376.312 (60)	.				
	B1	100	367.550 (62)	315.125				
	B2	51	399.181 (57)	.				
AUC_{inf}	**A1**	98	374.551 (57)	329.694	**A vs B**	95.76	90.57 - 101.24	28
*(hr*ng/mL)*	**A2**	48	403.028 (58)	.				
	B1	99	397.553 (60)	344.303				
	B2	50	426.548 (57)	.				
C_{max}	**A1**	101	69.117 (63)	57.561	**A vs B**	96.84	90.18 - 103.99	36
(ng/mL)	**A2**	48	69.029 (68)	.				
	B1	100	70.238 (59)	59.438				
	B2	51	77.059 (61)	.				

CV, coefficient of variation; n, number of subjects in statistical dataset; Sbj, subject; Trt, treatment.

Parameter	***Intra-Subject-within-Reference CV (%) B1 vs. B2***	***Wider Bioequivalence Range***
C_{max}	*34.8*	*77.34 - 129.30*

Treatment A (Test):	Abiraterone 500 mg film-coated tablets, Batch No.: RA0258
Treatment B (Reference):	Zytiga® (abiraterone acetate) 500 mg film-coated tablets, Batch No.: IGZSB00

Table 4 : Additional pharmacokinetic data for abiraterone (Study No. 19-652)

Plasma concentration curves where	**Related information**
- AUC_t/AUC_{inf}<0.8	Subject [redacted] period 2, R
	Subject [redacted] period 3, R
	Subject [redacted] period 1, R
	Subject [redacted] period 3, T
	Subject [redacted] period 1, R
	Subject [redacted] period 1, R
	Subject [redacted] period 2, R
	Subject [redacted] period 1, T
	Subject [redacted] period 2, R
- C_{max} is the first point	None
- Pre-dose sample > 5% C_{max}	None

The ANOVA output for treatment/sequence and period effects are presented below:

AUC_t

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Seq	1	99	0.11	0.7395
Per	2	196	4.41	0.0133
Trt	1	196	0.91	0.3401

AUC_{inf}

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Seq	1	99	0.02	0.8797
Per	2	191	4.15	0.0172
Trt	1	191	1.66	0.1994

C_{max}

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Seq	1	99	0.64	0.4242
Per	2	196	3.46	0.0333
Trt	1	196	0.55	0.4576

Based on the above table, treatment effect and sequence effect are found to be statistically insignificant (p-value > 0.05) for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{inf} of abiraterone.

Period effect is found to be statistically significant (p-value < 0.05) for ln-transformed pharmacokinetic parameters C_{max}, AUC_t and AUC_{inf} of abiraterone. A significant period effect could be an indication of an unequal carryover effect. However, there was no sequence effect and even in presence of an unequal carryover effect, the treatment comparison would not be invalidated since it would affect both treatments in the same way. Therefore, it is concluded that these finding does not affect the conclusion of the study.

Mean plasma concentration vs. time profiles (semi-log and linear) of Abiraterone 500 mg test and reference products under fasting conditions are depicted in figure 1.

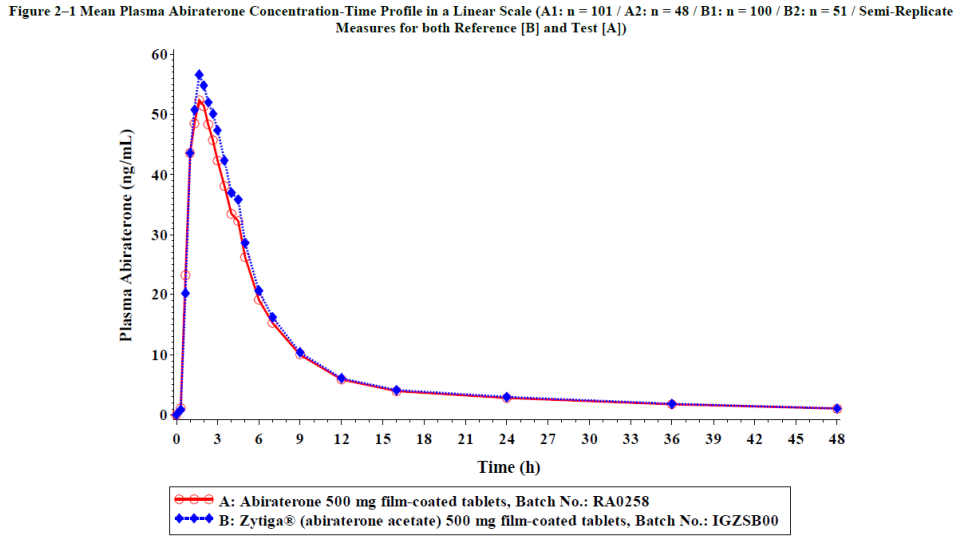

Figure 2 Mean Plasma Abiraterone Concentration-Time profile in linear Scale (*A*1:n=101/A2:n=48/B1:n=100/B2:n=51/Semi-Replicate measure*s for both Reference (B) and Test (A))*

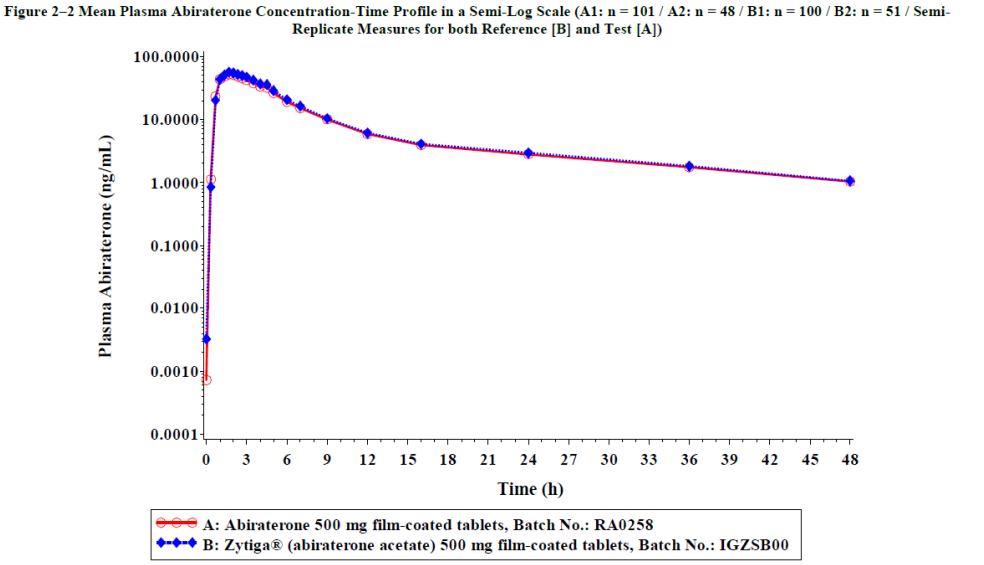

Figure 3 Mean Plasma Abiraterone Concentration-Time profile in Semi-logarithmic Scale (A1:n=101/A2:n=48/B1:n=100/B2:n=51/Semi-Replicate measures for both Reference (B) and Test (A))

As per EMA Guideline for highly variable drugs, the within-subjects variability was estimated using the data from subjects who completed 2 administrations of the reference product. Due to high intra-subject variability of the reference formulation (34.8%), a wider acceptance range of C_{max} was applied (77.34% - 129.30%). The request for widened interval was pre-specified in the protocol. The widening of the pharmacokinetic criteria C_{max} is in line with the requirements of the *Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **) section 4.1.10 Highly variable drugs*. The geometric least square mean ratio (T/R) was 96.84% for C_{max}, which was within the conventional acceptance range of 80.00% to 125.00%. As well as the 90% confidence intervals for the ln-transformed C_{max}, AUC_{inf} and AUC_{0-t} are within the acceptance range of 80.00 – 120.00%.

No pre-dose samples larger than 5% C_{max} have been reported. The pre-dose concentrations of abiraterone, which was less than 5% of their C_{max} were observed for subjects before period-2 or period-3 drug administration at time 0.00h (Period-2: subject: 0.108 ng /mL- test product; subject:

0.233 ng /mL- reference product and subject: 0.131 ng /mL-reference product and Period-3 subject: 0.130 ng /mL - reference product). Hence those subjects were considered for PK and Statistical analysis as per protocol, which is also in line with the *Guideline on the Investigation of Bioequivalence* and thus acceptable.

C_{max}/t_{max} is not reached at first sample point 0.33 h for any subjects, indicating that the sampling period is adequate.

According to *Guideline on the investigation of Bioequivalence/CMP/EWP/QWP/1404/98 Rev.1/Corr***, $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-\infty)}$. In this study most of the results demonstrated that the residual area was <20%, except seven subjects (treatment B), (treatment B), (treatment A), (treatment B), (treatment B), (treatment B) and (treatment A+B) exhibit extrapolation higher than 20%. As the number of profiles (8 out of 300 profiles) with extrapolation >20% is less than 20% of the profiles, no question is raised.

The statistical methodology using Method B (PROC MIXED procedure) could be acceptable for replicate design according to the *EMA`s Q&A document (EMA/582648/2016)* as long as all subjects provide data for all treatment periods. The EMA`s Q&A document states: "*Method B using PROC MIXED procedure may be acceptable as long as results obtained with the two methods (Method A and Method B) do not lead to different regulatory decisions. However, in borderline cases and when there are many included subjects who only provide data for a subset of the treatment periods, additional analysis using method A (PROC GLM) might be required*". Therefore, having consider the missing treatment periods for 3 subjects that could cause different results for two approaches (Method A and Method B), the applicant was asked to discuss this issue and if applicable, present additional analysis using method A (PROC GLM). In response to Day 120 LOQ, the applicant submitted the results from Method A (PROC GLM) and compared them with the results of Method B (PROC MIXED). The results of Method A were in agreement with those of Method B.

Subject had one missing PK blood sample at 48 hours post dose in period-3 after treatment with the reference product with no missing values affecting the test product. The corresponding abiraterone concentration value was set to be missing.

The terminal elimination phase could not be properly characterized for 3 subjects (in period-1, in period-2, in period-2 for treatment A and 2 subjects (in period-3 and in period-1 for treatment B. Hence, no value of elimination parameters was reported for these subjects.

The LLOQ of 0.100 ng /mL was sensitive enough to detect levels of 5% of the minimum C_{max} (0.471 ng /mL is 5% of the minimum C_{max}=9.420 ng) to exclude the possibility of a relevant carry-over effect.

Safety data

Safety analysis was carried out on all subjects who were dosed with the investigational product (a single oral dose of either the reference product or test product), which included 102 subjects. No serious adverse events (SAEs) were reported during the conduct of this study. None of the Adverse events (AEs) had a significant impact on the safety of the subjects or on the integrity of the study results. Forty-one (41) subjects (40.2% of subjects dosed) reported a total of 92 AEs. Thirty-one (31) subjects (30.7%) receiving the test product reported 42 AEs, and 27 subjects (26.5%) receiving the reference product reported 50 AEs. Of these, 33 AEs affecting 18 subjects (17.6%) were assessed as treatment related, with 14 subjects (13.9%) reporting 19 treatment-related AEs following administration of the test product and 11 subjects (10.8%) reporting 14 treatment-related AEs following administration of the reference product.

Eighty-eight (88) of the 92 AEs resolved prior to the end of the study.

The most frequent treatment related AE was headache (11 events affecting 6 subjects [5.9%]). All AEs were mild in severity with the exception of 1 AE (headache) which was moderate in severity.

End of Study

Twenty-four (24) AEs in 6 subjects (5.9% of subjects dosed) were detected by clinical laboratory tests. The AEs were mild in severity and 20 of these events resolved prior to the end of the study. The resolution of 4 of these AEs is unknown because the subject was lost to follow up. Four (4) of the AEs detected by clinical laboratory tests were assessed as having a possible relationship to the IMP, 2 were assessed as unlikely in relationship to the IMP and the other 18 were assessed as unrelated.

Vital Signs, Physical Findings and Other Observations Related to Safety

Adverse events detected by vital signs measurements include bradycardia (29 events affecting 21 subjects [20.6%]), ventricular extra systoles (1 event affecting 1 subject [1.0%]) and pyrexia (1 event affecting 1 subject [1.0%]). All AEs detected by vital signs measurements were assessed as unrelated or unlikely in relationship to the IMP.

Adverse events detected by ECG measurements include electrocardiogram PR prolongation (6 events affecting 4 subjects [3.9%]) and electrocardiogram QT prolonged (4 events affecting 4 subjects [3.9%]). All 6 events of electrocardiogram PR prolongation were assessed as possibly related to the IMP and all events of electrocardiogram QT prolonged were assessed as possibly related to the IMP.

A physical examination detected 1 AE (musculoskeletal stiffness) affecting 1 subject (1.0%). The AE was mild in severity, assessed as unrelated to the IMP, and resolved prior to the end of the study.

Conclusions

Based on the presented bioequivalence study 19-652, Abiraterone acetate Krka 500 mg film-coated tablets MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU, is considered bioequivalent with Zytiga (Abiraterone) 500 mg film-coated tablets MAH: Janssen-Cilag International NV, Belgium, EU..

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

Additional Data

The applicant presented synopsis of **pilot** bioavailability study (**No.: 19-624**) of Abiraterone 500 mg film-coated tablets as supportive data.

Pilot study (No.: 19-624)

Study title: Single Dose Crossover Comparative Bioavailability Pilot Study of Abiraterone 500 mg Film-Coated Tablets in Healthy Male Subjects Under Fasting Conditions

Study Initiation Date: 2019/05/22

Study Completion Date: 2019/07/25

Objectives:

The objective of this study was to evaluate the pharmacokinetics (PK) of four different formulations of abiraterone acetate after a single oral dose under fasting conditions.

Test-1

For the Test-1 (abiraterone 500 mg film-coated tablets, Batch number RA0236, MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU) versus Reference (Zytiga® [abiraterone acetate] 500 mg film-coated tablets, Janssen-Cilag SpA, Italy, EU) comparison, the resulting Test-1 to Reference ratio of geometric least-squares means (Lsmeans) for the C_{max} and AUC_{0-T} were 122.14% and 114.63%, respectively. Time to reach peak exposure (median T_{max}) was comparable for both products.

Test-2

For the Test-2 (abiraterone 500 mg film-coated tablets, Batch number RA0237, MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU) versus Reference (Zytiga® [abiraterone acetate] 500 mg film-coated tablets, Janssen-Cilag SpA, Italy, EU) comparison, the resulting Test-2 to Reference ratio of geometric LSmeans for the C_{max} and AUC_{0-T} were 127.26% and 124.75%, respectively. Median T_{max} was comparable for both products.

Test-3

For the Test-3 (abiraterone 500 mg film-coated tablets, Batch number RA0239, MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU) versus Reference (Zytiga® [abiraterone acetate] 500 mg film-coated tablets, Janssen-Cilag SpA, Italy, EU) comparison, the resulting Test-3 to Reference ratio of geometric LSmeans for the C_{max} and AUC_{0-T} were 93.76% and 93.26%, respectively. The Test-3 formulation showed comparable results to the reference with the mean C_{max} and the overall AUC within 7% of the reference product and the Test-3/Reference ratios of geometric LSmeans and the 90% CIs of C_{max} and AUC_{0-T} were within the 80.00 to 125.00 % range of bioequivalence. Median T_{max} was also comparable for both products.

Overall, out of the three test formulations, Test-3 formulation showed comparable PKs to the Reference formulation.

Results:

Test-1

Pharmacokinetic Parameters

Abiraterone

PARAMETER	TEST-1 (n=46)[b]		REFERENCE (n=46)[b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	93.160	(79.4)	74.824	(56.0)
T_{max} (hours)[a]	2.67	(1.00-6.02)	2.33	(0.67-6.00)
AUC_{0-T} (ng·h/mL)	485.578	(55.9)	426.904	(51.5)
$AUC_{0-\infty}$ (ng·h/mL)	505.795	(54.8)	445.849	(50.6)
Residual Area (%)	4.64	(89.6)	4.78	(63.6)
λ_Z (hours^{-1})	0.0538	(26.3)	0.0513	(23.4)
T_{half} (hours)	13.87	(29.8)	14.27	(24.2)

[a] Median and range are presented

[b] n=45 for AUC_{0-T}, $AUC_{0-\infty}$, residual area, λ_Z and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST-1 (n=46)[b]	REFERENCE (n=46)[b]		LOWER	UPPER
C_{max}	45.2	75.539	61.847	122.14	104.97	142.11
AUC_{0-T}	31.6	420.467	366.795	114.63	102.73	127.91

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

[b] n=45 AUC_{0-T}

Test-2

Pharmacokinetic Parameters

Abiraterone

PARAMETER	TEST-2 (n=47)[b]		REFERENCE (n=47)[b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	95.584	(63.6)	76.530	(56.3)
T_{max} (hours)[a]	2.33	(1.00-9.00)	2.33	(0.67-6.00)
AUC_{0-T} (ng·h/mL)	533.545	(50.6)	430.989	(50.8)
$AUC_{0-\infty}$ (ng·h/mL)	552.746	(49.8)	450.059	(50.0)
Residual Area (%)	4.14	(79.0)	4.76	(63.2)
λ_Z (hours^{-1})	0.0549	(23.1)	0.0512	(23.2)
T_{half} (hours)	13.32	(24.2)	14.29	(23.9)

[a] Median and range are presented

[b] n=46 for AUC_{0-T}, $AUC_{0-\infty}$, residual area, λ_Z and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST-2 (n=47)[b]	REFERENCE (n=47)[b]		LOWER	UPPER
C_{max}	34.1	80.592	63.327	127.26	113.43	142.79
AUC_{0-T}	26.0	464.238	372.136	124.75	114.06	136.44

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

[b] n=46 AUC_{0-T}

Test-3

Pharmacokinetic Parameters

Abiraterone

PARAMETER	TEST-3 (n=46)[b]		REFERENCE (n=46)[b]	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	70.103	(57.7)	74.824	(56.0)
T_{max} (hours)[a]	2.50	(1.00-6.05)	2.33	(0.67-6.00)
AUC_{0-T} (ng·h/mL)	397.478	(52.4)	426.904	(51.5)
$AUC_{0-\infty}$ (ng·h/mL)	413.861	(51.8)	445.849	(50.6)
Residual Area (%)	4.52	(68.5)	4.78	(63.6)
λ_Z ($hours^{-1}$)	0.0535	(23.4)	0.0513	(23.4)
T_{half} (hours)	13.77	(27.5)	14.27	(24.2)

[a] Median and range are presented

[b] n=45 for AUC_{0-T}, $AUC_{0-\infty}$, residual area, λ_Z and T_{half}

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS[a]		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST-3 (n=46)[b]	REFERENCE (n=46)[b]		LOWER	UPPER
C_{max}	33.0	57.985	61.847	93.76	83.76	104.94
AUC_{0-T}	25.7	342.078	366.795	93.26	85.24	102.03

[a] units are ng/mL for C_{max} and ng·h/mL for AUC_{0-T}

[b] n=45 AUC_{0-T}

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This application concerns a centralised procedure for the generic Abiraterone acetate Krka 500 mg film-coated tablets with abiraterone acetate as active substance. Essential similarity is claimed to Zytiga containing abiraterone acetate, Janssen-Cilag International N.V., Belgium approved via centralised procedure since 5th of September 2011 (EU/1/11/714/002-003).

Abiraterone is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on up-to-date and adequate scientific literature.

To support the application, the applicant has submitted one **pivotal** bioequivalence study (No.: 19-652), (fasting) and **synopsis** of **pilot** bioavailability study (No.: 19-624) as supportive study (fasting). The results of the pilot study were in agreement with those of the pivotal study. Since batch size used in the pilot study (No.: 19-624) is not representative, bioequivalence of the to-be-marketed formulation is based solely on pivotal bioequivalence study.

The pivotal study (No.: 19-652) was designed as an open-label, single-dose, randomized, three-period, two-treatment, two-sequence, cross-over, semi-replicate study to evaluate the bioequivalence of abiraterone in healthy, non-smoking, male subjects under fasted conditions with a washout period of 7 days between drug administrations.

Abiraterone can be considered as a highly variable drug, therefore a replicate design was more appropriate to assess within-subject variability. The study design employed (as a randomized fasting

single dose semi replicate design 3-period cross-over) is thus considered appropriate for the evaluation of highly variable drug products and therefore acceptable. The semi-replicate design employed is appropriate for the bioequivalence study of highly variable drug products according to the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **). Overall design of this study is acceptable and in line with pharmacokinetic properties of abiraterone.

Data regarding the test and reference products were adequate.

The population studied is considered appropriate and the main inclusion and exclusion criteria are in line with the requirements of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01). Only male subjects were included in the study since abiraterone is contraindicated in women who are or may potentially be pregnant due to safety concerns.

The sampling periods are acceptable upon review of the graphs with sample time points around T_{max} (approximately 2 hours) and with an adequate wash-out period at greater than five times the half-life (approximately 15 hours).

Protocol deviations listed in the report were considered minor and do not have a negative effect of the study results. An updated section 16.2.2. including deviation for one subject's missing blood samples has been provided and considered acceptable.

The concomitant medication taken by one subject was accounted for in the bioanalytical method.

As the parent compound, abiraterone acetate, is almost immediately metabolised after oral administration hence, the demonstration of bioequivalence based on the active metabolite, abiraterone is acceptable.

The Analytical method (liquid chromatographic tandem mass spectrometric method) used for the determination of abiraterone in human plasma has been adequately validated. Pre-study and in-study validations were performed according to the requirements of the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/09).

The pharmacokinetic variables chosen for the study are adequate. The sampling schedule provides adequate estimation of C_{max}. No C_{max} was observed in the first time point and no pre-dose samples larger than 5% C_{max} have been reported.

The statistical methodology using Method B (PROC MIXED procedure) could be acceptable for replicate design according to the EMA`s Q&A document (EMA/582648/2016) as long as all subjects provide data for all treatment periods. Therefore, having consider the missing treatment periods for 3 subjects that could cause different results for two approaches (Method A and Method B), results from Method A (PROC GLM) were compared with the results of Method B (PROC MIXED). The results of Method A were in agreement with those of Method B.

According to EMA Guideline on the investigation of Bioequivalence/CMP/EWP/QWP/1404/98 Rev.1/Corr**, AUC0-t should cover at least 80% of AUCinf. In this pivotal study, they are only 8 out of 300 profiles with extrapolation >20% (seven subjects (treatment B), (treatment B), (treatment A), (treatment B), (treatment B), (treatment B) and (treatment A+B)). The number of profiles with extrapolation >20% is less than 20% of the profiles.

One Subject had one missing PK blood sample at 48 hours post dose in period-3 after treatment with the reference product with no missing values affecting the test product. The corresponding abiraterone concentration value was set to be missing.

Based on possible high intra-subject variability in abiraterone absorption a wider acceptance range of C_{max} (77.34% - 129.30%) was proposed. As the request for wider acceptance interval was

prospectively specified in the study protocol and study designed accordingly (i.e., semi replicate 3-period crossover design), the widening of acceptance criteria for C_{max} was considered acceptable. This complies with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **) section 4.1.10 Highly variable drugs. The geometric least square mean ratio (T/R) was 96.84% for C_{max}, which was within the conventional acceptance range of 80.00% to 125.00%. As well as the 90% confidence intervals for the ln-transformed C_{max}, AUC_{inf} and AUC_{0-t} were within the acceptance range of 80.00 – 120.00%.

Safety evaluation performed for study (No.: 19-652) demonstrated that the test and the reference products were relatively well tolerated by healthy subjects, as a single dose (500 mg tablets) administration. None of the AEs had a significant impact on the safety of the subjects. No new safety concerns related to the administered formulations were noted during the conduct of the study.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence study 19-652, Abiraterone acetate Krka 500mg film-coated tablets MAH: KRKA, d.d., Novo mesto, SLOVENIA, EU is considered bioequivalent with Zytiga (Abiraterone) 500mg film-coated tablets MAH: Janssen-Cilag International NV, Belgium, EU.

2.5. Risk management plan

Safety concerns

Table SVIII.1: Summary of safety concern

Summary of 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

There are no on-going or planned additional pharmacovigilance activities.

Risk minimisation measures

The safety information in the proposed product information is aligned to the reference medicinal product.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.1 is acceptable.

2.6. 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.

Periodic Safety Update Reports submission requirements

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.

2.7. Product information

2.7.1. User consultation

The applicant provided the bridging report with the comparison of the contents with the Product Leaflet (PL) of reference product Zytiga (EMEA/H/C/002321), and proof of the user testing of the reference product PL (i.e. EPAR).Considering that both Parent and Daughter PLs are sufficiently similar to justify the bridging,the Bridging report is acceptable.

3. Benefit-risk balance

This application concerns a generic version of Abiraterone Krka 500 mg film-coated tablets. The reference product Zytiga is indicated for metastatic prostate cancer. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant’s clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with an open-label, single-dose, randomized, three-period, two-treatment, two-sequence, cross-over, semi-replicate study healthy, non-smoking, male subjects under fasted conditions with a washout period of 7 days between drug administrations. The

study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Abiraterone Krka met the protocol-defined criteria for bioequivalence when compared with the Zytiga. The geometric least square mean ratio (T/R) was 96.84% for C_{max}, which was within the conventional acceptance range of 80.00% to 125.00%. The 90% confidence intervals for the ln-transformed C_{max}, AUC_{inf} and AUC_{0-t} are within the acceptance range of 80.00 – 120.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Abiraterone KRKA is favourable in the following indication:

Abiraterone Krka is indicated with prednisone or prednisolone for:

- the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT)
- the treatment of metastatic castration resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other 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.