EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/444189/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abiraterone Mylan

International non-proprietary name: abiraterone acetate

Procedure No. EMEA/H/C/005368/0000

Note

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

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List of abbreviations

3βHSD	3β-hydroxysteroid dehydrogenase/isomerase
AA	Abiraterone acetate
ACTH	Adrenocorticotrophic hormone
ADT	Androgen deprivation therapy
AIPC	Androgen-independent prostate cancer
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
Ames	Microbial mutagenesis
ANOVA	Analysis of Variance
AP	Applicant's Part of an ASMF
API	Active Pharmaceutical Ingredient
AR	Androgen receptor
AR	Assessment Report
ARE	Androgen-responsive elements
ARfl	Full-length AR
AR-V	AR variants
ARVs	AR splice variants
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
AST	aspartate aminotransferase
AUC	area under graph
AUC	Area Under Graph
BCS	Biopharmaceutical classification system
BE	Bioequivalence
CB	cannula blockage
CDSCO	Central Drugs Standard Control Organisation
CEP	Certificate of Suitability of the Ph.Eur.
CgA	Chromogranin A
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum concentration
CMS	Concerned Member State
CoA	Certificate of Analysis
CRPC	Castration-resistant prostate cancer
CRS	Chemical Reference Substance (official standard)
CTX	Carboxy-terminal collagen crosslinks
CV	coefficient of variation
D4A	Δ(4)-abiraterone
DCP	Decentralised Procedure
DD	Delivered Dose
DDI	Drug-drug interaction
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DP	difficulty in palpitation of vein
DPI	Dry Powder Inhaler

DSC	Differential Scanning Calorimetry
ECG	electrocardiogram
EDQM	European Directorate for the Quality of Medicines
EPAR	European public assessment report
ER	Oestrogen receptor
ESI	electrospray ionisation
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HN	Hormone-naive
HPLC	High Pressure Liquid Chromatography
HQC	Higher quality control
HRPC	Hormone-refractory prostate cancer
ICH	International Conference on Harmonisation
IGFIR	Insulin-like growth factor I receptor
IPC	In-process control test
IR	Infrared
IS	Internal standard
LA	late arrival
LBD	Ligand binding domain
LC	liquid chromatography
LH	Luteinizing hormone
LLOQ	lower limit of quantification
LOD	(1) Limit of Detection, (2) Loss on Drying
LOQ	(1) Limit of Quantification, (2) List of Questions
LQC	Lower quality control
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
mCRPC	Metastatic CRPC
MEB	(Dutch) Medicines Evaluation Board
MF	Matrix factor
mHSPC	metastatic hormone sensitive prostate cancer
MQC	Medium quality control
MS	mass spectrometry
MS	Mass Spectrometry
N	Number of observations
ND	Not detected
NED	Neuroendocrine differentiation
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NSE	Neurone-specific enolase
OBLs	Osteoblasts

OCLs	Osteoclasts
OECD	Organisation for Economic Co-operation and Development
OTC	over-the-counter
PCa	Prostate cancer
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PP	Polypropylene
ppb	pars per billion
PSA	Prostate-specific antigen
PTEN	Phosphatase and tensin homologue
QC	Quality control
QOS	Quality Overall Summary
R	Reference
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SD	Standard Deviation
S-D	Sprague-Dawley
SmPC	Summary of Product Characteristics
SNR	subject not reported
SOP	Standard Operating Procedure
T	Test
TAMC	Total Aerobic Microbial Count
TGA	Thermo-Gravimetric Analysis
TYMC	Total Combined Yeast/Mould Count
ULN	Upper limit of normal
ULN	upper limit of normal
UV	Ultraviolet
XRD	X-Ray Diffraction
XRPD	X-ray powder diffraction

This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan Ireland Limited submitted on 9 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Abiraterone Mylan, 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 26 April 2019.

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 Mylan 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); Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and two bioequivalence studies 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 500 mg film-coated tablets
- Marketing authorisation holder: Janseen-Cilag International NV Ltd.
- Date of authorisation: 05-09-2011
- Marketing authorisation granted by:
  - Union
- Union Marketing authorisation number: EU/1/11/714/002-003

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Zytiga 500 mg film-coated tablets

- Marketing authorisation holder: Janseen-Cilag International NV Ltd.
- Date of authorisation: 05-09-2011
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: 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 500 mg film-coated tablets
- Marketing authorisation holder: Janseen-Cilag International NV Ltd.
- Date of authorisation: (05-09-2011)
- Marketing authorisation granted by:
  - Union
  - Marketing authorisation number(s): EU/1/11/714/002-003
- Bioavailability study numbers: 18-VIN-0695, 19-VIN-0187

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: John Joseph Borg

The application was received by the EMA on	9 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 June 2020

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 December 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	01 February 2021
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 to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	22 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 CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	24 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 June 2021
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 Mylan on	22 April 2021

2. Scientific discussion

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).

The pharmacotherapeutic group of abiraterone is endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX03

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Abiraterone Mylan 500 mg film-coated tablets, and a hybrid application according to

article 10(3) of Directive 2001/83/EC for Abiraterone Mylan 1000 mg film-coated tablets. The applicant is Mylan Ireland Limited.

The originator product is Zytiga 500 mg film coated tablets (EU/1/11/714/002-003) marketed by Janssen-Cilag International NV Ltd and registered within the community since 05 September 2011. A pilot bioequivalence (BE) study was carried out using the originator as reference product sourced from Germany (BE Study 18-VIN-0144). Two bioequivalence (BE) studies have been performed using the originator as a reference product sourced from Germany (BE Study 18-VIN-0695 and 19-VIN-0187). Zytiga 500 mg film coated tablets marketed by Janssen-Cilag International NV Ltd sourced from Germany and first authorised in the EU in 5 September 2011 (EU/1/11/714/002-003) was also used in both BE studies.

2.1. Quality aspects

2.1.1. Introduction

The finished product is presented as film-coated tablets containing 500 mg and 1000 mg of abiraterone acetate as active substance, equivalent to 446 mg and 893 mg of abiraterone respectively.

Other ingredients are:

Tablet core: croscarmellose sodium (E468), sodium laurilsulfate, povidone, cellulose microcrystalline (E460), lactose monohydrate, silica colloidal anhydrous (E551) and magnesium stearate (E470b).

Tablet coat: poly(vinyl alcohol), titanium dioxide (E171), macrogol (E1521) and talc (E553b).

In addition, Abiraterone Mylan 500 mg film-coated tablets contain iron oxide red (E172) and iron oxide black (E172) in the film-coat.

The product is available in the following packaging formats as described in section 6.5 of the SmPC:

Abiraterone Mylan 500 mg film-coated tablets:

- Aluminium-OPA/Alu/PVC blister packs.

- Aluminium-OPA/Alu/PVC perforated unit dose blister packs.

- Aluminium-PVC/PE/PVDC blister packs.

- Aluminium-PVC/PE/PVDC perforated unit dose blister packs.

Abiraterone Mylan 1000 mg film-coated tablets:

- High density polyethylene (HDPE) bottles with an oxygen absorbing canister and closed with a polypropylene (PP) child resistant closure.

- High density polyethylene (HDPE) bottles closed with a polypropylene (PP) child resistant closure.

2.1.2. Active substance

General information

The chemical name of abiraterone acetate is [(3S,10R,13S)-10,13-dimethyl-17-pyridin-3-yl-2,3,4,7,8,9,11,12,14,15-decahydro-1*H*-cyclopenta[a]phenanthren-3-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:

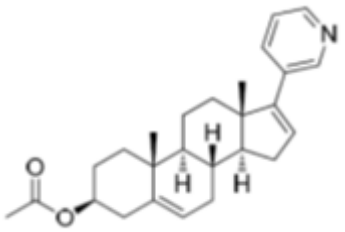


Figure 1: abiraterone acetate structure

The chemical structure of abiraterone acetate was inferred from the route of synthesis and elucidated by a combination of infra-red spectroscopy (IR), ultraviolet-visible spectroscopy (UV), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry and elemental analysis.

The active substance is a white to off-white powder practically insoluble in water and has no pH-dependent solubility in aqueous media.

Abiraterone acetate exhibits polymorphism. The polymorphic form of abiraterone acetate can be distinguished by XPRD, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and the manufacturing process followed. This is confirmed by PXRD in the active substance specification.

Abiraterone acetate has 6 chiral centres. The overall and relative stereochemistry was confirmed by single crystal x-ray diffraction. All stereocentres originate in the starting material and are confirmed in the active substance by a test for specific optical rotation. The geometry of the 2 olefins is enforced by the fused ring system.

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 plus 1 acetylation, 1 purification and 1 isolation steps. The product may be micronised according to the customer requirement, and the micronisation process is validated.

Two sites are involved in the manufacture of the active substance. The starting materials introduced have been defined. The starting materials are acceptable and controlled by suitable specifications. Isolated intermediates are adequately 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.

Manufacturing process of abiraterone acetate active substance has been validated successfully.

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.

The applicant conducted a risk assessment on the possible presence of nitrosamine impurities in the active substance in line with the recommendations from the article 5(3) referral assessment report (EMA/369136/2020). The control strategy is considered suitable.

Abiraterone acetate is packed in bags, then sealed in a foil bag and placed in a well-closed drum. The primary packing material complies with the EC directives 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.), sulphated ash (Ph. Eur.), specific optical rotation (Ph. Eur.), related substances (HPLC), residual solvents (GC), assay (HPLC), particle size distribution (Ph. Eur.), polymorphic form (PXRD) and microbiological examination (Ph. Eur.).

The specifications adopted by the finished product manufacturer for the active substance, are the ones set by the active substance manufacturer with the addition of the following specification: microbiological examination.

The specification provided for particle size suggested that the product was either fine milled or micronised. However, a milling/micronisation process was neither described nor validated in the manufacturing process described in the ASMF. Since particle size is a critical material attribute, a question was raised as a MO at D120. In response, the process description for the micronisation process was added. A specification for PSD was not included as the requirement is considered customer specific. The specification included by the finished product manufacturer's specification is deemed sufficient to ensure adequate control of the active substance PSD.

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 ASMF holder's analytical methods. Analytical methods are Ph. Eur. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data analysed by both active substance and finished product manufacturers is 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 production scale batches under long term conditions (30±2ºC / 65±5% RH and 30±2°C/ 75±5%) for up to 6 months under accelerated conditions (40±2ºC / 75±5% RH) according to the ICH guidelines were provided.

Forced degradation studies were conducted and mass balance under different stressed conditions. The stress study has shown that that the analytical method for related substance in Abiraterone Acetate is stability indicating and is suitable for the impurities testing. The study has demonstrated that the analytical procedure is stability indicating and is suitable for the tested parameters.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months stored in the proposed container, with no special storage conditions.

2.1.3. Finished medicinal product

Description of the product and pharmaceutical development

The finished product is a film-coated tablet for oral administration containing either 500 mg or 1000 mg of abiraterone acetate. The film-coated tablets are presented as follows:

500 mg: brown, oval-shaped film-coated tablets, debossed with "500" on one side, with dimensions 18.9 mm x 9.5 mm ± 5%.

1000 mg: white to off-white, oval-shaped film-coated tablets, with a score line on one side and plain on the other side, with dimensions 23.1 mm x 11.1 mm ± 5%.

The score-line in the 1000 mg film-coated tablets is only to facilitate breaking for ease of swallowing and not to divide into equal doses. The applicant has discussed the rationale for the presence of a score-line on the 1000 mg strength film-coated tablets and it was considered acceptable. A compendial test for sub-division of tablets is included in the 1000 mg tablet specification The applicant further supported this by demonstrating the stability of three validation batches, sub-divided and stored at 30°C / 75% RH in Aluminium/Aluminium foil for 9 months and HDPE bottle without canister for a minimum of 10 months.

Abiraterone Mylan 500 and 1000 mg film-coated tablets were developed with the objective of obtaining a generic product, physically and chemically stable for the assigned shelf-life period, equivalent to the reference product Zytiga, achieving an immediate release formulation matching the reference product *in vivo*.

Based on the clinical and pharmacokinetic characteristics as well as the *in vitro* dissolution and physicochemical characteristics of the reference medicinal product, a quality target product profile (QTPP) was defined for Abiraterone acetate 1000 mg film-coated tablets.

Based on the QTPP, the critical quality attributes (CQAs) of the product were identified. These are still target elements of the QTPP and are ensured through an appropriate pharmaceutical quality system and the control strategy.

Abiraterone acetate is practically insoluble in water. Solubility testing of abiraterone acetate was carried out in different buffer aqueous media in a pH range of 1.2 to 9.8 showing non-pH dependent solubility. 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. 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 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 and EU1333/2008 (specifications for food additives).

A compatibility study was performed to examine the interactions between the active substance and the proposed excipients. The powder blend samples were analysed for related substances, using the analytical methods described in section 3.2.P.5.2, and the results indicated that the impurity profile of all samples was within the release specifications as described in section 3.2.P.5.1. Furthermore, the compatibility of abiraterone acetate with all the excipients was verified through the stability studies under accelerated and long-term conditions (section 3.2.P.8.3).

Solubility testing of abiraterone acetate was carried out in different buffer media in a pH range of 1.0 to 6.8 and in water, at 37°C.

The discriminatory power was assessed by the comparison of the dissolution profiles of "side batches" manufactured by changing aspects of the formulation and process parameters with the biobatch manufactured according to the proposed commercial formulation and process. The discriminatory power of the dissolution method has thus been demonstrated satisfactorily.

Essential similarity between the reference product and abiraterone acetate generic film-coated tablets has been shown through pharmaceutical equivalence testing and a pivotal bioequivalence study.

A clinical bioequivalence study was conducted in order to compare the bioavailability of Abiraterone acetate 500 mg film-coated tablets and Zytiga® 500 mg film-coated tablets in healthy, adult, male subjects under fasting conditions. Based on the results, bioequivalence is considered demonstrated between test and reference formulation.

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

The primary packaging is aluminium-OPA/Alu/PVC or aluminium-PVC/PE/PVDC blisters for the 500 mg film-coated tablets and HDPE bottles with or without oxygen absorbing canister and closed with a PP child resistant closure for the 1000 mg film-coated tablets. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure systems has been validated by stability data and they are adequate for the intended use of the product.

At D120 the applicant was requested to include information regarding the size of the oxygen canister and to consider whether to include a warning on it that it is not to be consumed. The applicant complied with the request, nevertheless, it is also suggested a clearer marking. The current version of the oxygen canister is accepted for granting a MA. However, it is recommended to consider the addition of the suggested markings to ensure a safer finished product. A recommendation with this regard has been included in section 2.1.6.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: dispensing; sieving; granulation; blending; compression and film coating. 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 IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification of abiraterone acetate (HPLC, UV), identification of titanium dioxide, identification of iron oxides, assay (HPLC), related substances (HPLC), dissolution (HPLC), uniformity of

mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dimension, microbiological examination (Ph. Eur.).

The proposed specifications are considered acceptable. 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 potential presence of class 1 and Class 2A elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on batches, 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 risk assessment for the active substance was previously discussed in section 1.1.2. The overall risk assessment also considered possible sources of nitrosamines in the finished product, such as excipients, the manufacturing process, packaging materials, utilities etc. and concluded that there was no additional risk. Therefore, no changes to the control strategy for Abiraterone Mylan are necessary to mitigate potential contamination by nitrosamines.

Batch analysis results were provided for industrial scale batches and pilot scale batch confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

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

Stability of the product

Stability data from production scale batches of 500 mg film-coated tablets stored in Aluminium-OPA/Alu/PVC blisters and Aluminium-PVC/PE/PVDC blisters, and production scale batches of 1000 mg film-coated tablets stored in HDPE bottles and HDPE bottles with oxygen absorbing canister stored under long term conditions (25ºC ± 2ºC / 60% ± 5% RH), under intermediate conditions (30°C ± 2°C, 65% ± 5% RH), and under accelerated conditions (40°C ± 2°C, 75% ± 5% RH) were presented according to the ICH guidelines. The batches of Abiraterone Mylan 500 and 1000 mg film-coated tablets are identical to those proposed for marketing and were packed in the primary packaging proposed. The analytical procedures used are stability indicating. The stability results have demonstrated that Abiraterone 500 and 1000 mg film-coated tablets are chemically and microbiologically stable No significant changes in assay of active substance, impurity content and all other tested parameters were observed.

Stability testing of bulk product and intermediates packed in the intended storage containers as declared in the dossier, was conducted.

In addition, one batch of each strength of finished product in each proposed commercial packaging format was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the study indicate that upon direct exposure, the product is not sensitive to light, so for Abiraterone Mylan 500 mg and 1000 mg film-coated tablets in bottles and blisters, no special storage conditions with respect to light are required.

A forced degradation study was also carried out with tablets in HDPE bottles with oxygen absorbing canister, HDPE bottles, blisters and the bulk storage container. This study demonstrates the stability-indicating nature of the analytical methods.

According to the obtained stability results under accelerated and long-term conditions packed in HDPE bottles with oxygen absorbing canister and HDPE bottles, there is no indication that Abiraterone film-coated tablets are susceptible to deterioration and therefore no in-use stability studies have been performed in accordance with EMA's Q&A on Quality Part 2.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) are 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.

2.1.4. 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. A MO was raised in relation to re-definition of a starting material (SM) in the initial synthetic route; it has been resolved by providing an alternative new synthetic route that was concluded acceptable. Another MO was raised concerning the milling/micronisation process that was neither described nor validated in the manufacturing process description in the ASMF; it has been resolved by the provision of the micronisation process. A specification for particle size distribution (PSD) was not included in the ASMF as the requirement is considered customer specific and the specification already included in the finished product manufacturer's specification was deemed sufficient to ensure adequate control of the active substance PSD. 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. Abiraterone Mylan film-coated tablets have been shown to be bioequivalent to the reference product.

At the time of the CHMP opinion, there is one minor partially unresolved quality issue in relation to the marking of the canister in order to distinguish it from the film-coated tablets, having no impact on the Benefit/Risk ratio of the product. Based on that, a recommendation is issued.

2.1.5. 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.

2.1.6. 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 point for investigation:

1. Additional marking as requested during the procedure is recommended for Abiraterone Mylan 1000 mg film-coated tablets to ensure a safer finished product.

2. The applicant confirms that comparative dissolution testing will be undertaken on the first three production batches and the applicant will not market a batch until comparative dissolution testing has been completed.

3. The applicant has declared that they will base any future requests for scale-ups above the maximum batch size.

2.2. Non-clinical aspects

2.2.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.2.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Abiraterone Mylan manufactured by Mylan Ireland Limited 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.

2.2.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Abiraterone Mylan was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.3. Clinical aspects

2.3.1. Introduction

This is an application for film-coated tablets containing abiraterone acetate. To support the marketing authorisation application the applicant conducted bioequivalence studies with cross-over design under fasting conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

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 two bioequivalence studies. Study 18-VIN-0695 was to establish bioequivalence of Abiraterone Mylan 500 mg tablets and Zytiga 500 mg film-coated tablets. Study 19-VIN-0187 was to establish bioequivalence of Abiraterone Mylan 1000 mg tablets and Zytiga 500 mg film-coated tablets at a dose of 1000mg (2 tablets of 500mg).

Table 1: Tabular overview of clinical studies

Type of Study	Bioequivalence Study	Bioequivalence Study
Study Identifier	Project No.: 18-VIN-0695	Project No.: 19-VIN-0187
Objective(s) of the Study	To compare and evaluate the single-dose oral comparative bioavailability of Abiraterone Mylan 500 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions as well as to monitor the safety and tolerability of subjects.	To compare and evaluate the single-dose oral comparative bioavailability of Abiraterone Mylan 1000 mg film-coated tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000 mg (2 tablets of 500 mg) of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions as well as to monitor the safety and tolerability of subjects.
Study Design and Type of Control	An open label, balanced, randomised, two-treatment, two-sequence, four-period, single-dose, crossover fully replicate oral bioequivalence study of Abiraterone Mylan 500 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions.	An open label, balanced, randomised, two-treatment, two-sequence, four-period fully replicate oral bioequivalence study of Abiraterone Mylan 1000 mg film-coated tablets and Zytiga® (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000mg (2 tablets of 500mg) of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions.

Test product(s): Dosage regimen, Route of Administration	Abiraterone acetate 500 mg film-coated tablets, single dose, oral	Abiraterone acetate 1000 mg film-coated tablets, single dose, oral
Number of Subjects	Enrolled:28 Dosed Completed: 27	Enrolled:30 Completed:28
Healthy Subjects or Diagnosis of Patients	Healthy subjects	Healthy subjects
Duration of treatment	Single dose	Single dose
Study Status	Complete; Full	Complete; Full

2.3.2. Pharmacokinetics

To support the application, the applicant has submitted two bioequivalence studies.

Study 18-VIN-0695

An open label, balanced, randomised, two-treatment, two-sequence, four-period, single-dose, crossover fully replicate oral bioequivalence study of Abiraterone Mylan 500 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions.

Methods

CRO	**Clinical study site, PK and statistical analysis** Veeda Clinical Research Pvt. Ltd., India Shivalik Plaza, Near I.I.M., Ambawadi Ahmedabad – 380 015, India **Bioanalytical study site** Veeda Clinical Research Pvt. Ltd., India Rev. Sur. No. 12/1, Insignia, Corporate House, Nr. Grand Bhagvati Hotel, Sindhu Bhavan Road, S. G. Highway, Bodakdev, Ahmedabad – 380 054, India
Protocol identification No.	18-VIN-0695
Clinical phase	16 January 2019 to 10 February 2019
Bioanalytical phase	12 February 2019 to 27 February 2019

Study design

This was an open label, balanced, randomised, two-treatment, two-sequence, four-period, single-dose, crossover fully replicate oral bioavailability study to establish bioequivalence of Abiraterone Mylan 500 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets (MAH: Janssen-Cilag International NV, Belgium and sourced from Germany) in 28 healthy, adult, male subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

Randomisation was done in blocks such that the design was balanced. The order of receiving the Test (T) and Reference (R) product for each subject during each period of the study was determined according to the randomisation schedule. The dosing (treatment) of Test (T) and Reference (R) product was divided into two sequences (TRTR/RTRT). Subjects who were assigned sequence TRTR received Test product T in period 1 and 3 and reference product R in period 02 and 04. Subjects who were assigned sequence RTRT received Reference product R in Period 01 and 03 and Test product T in period 2 and 4.

Subjects took their assigned formulation, designated by the randomisation scheme, after at least a 10-hour fast. Tablets were administered orally at scheduled dosing time in sitting posture with 240±2mL of water at ambient temperature. Tablets were swallowed as a whole and were not chewed, crushed or divided. A washout period of 7 days was kept between drug administrations.

The pre-dose blood sample of 2.0mL (0.00 hr) was collected within one hour prior to scheduled time for dosing. The post-dose blood samples of 2.0mL each was drawn at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after dosing in study.

Test and reference products

Abiraterone Mylan 500 mg tablets was compared to Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV.

Population(s) studied

28 healthy adult male human subjects were enrolled in two groups as per the protocol to ensure dosing of 24 subjects. The study was conducted in two Groups as per following:

In group 01: 27 (Subject no. 01 to 27) healthy, adult, human male subjects were enrolled.

In group 02: 01 (Subject no. 28) healthy, adult, human male subject was enrolled.

A total of 25 subjects completed all the periods of the study as per the protocol. The dropouts are discussed below. Samples collected from 28 subjects were analysed for abiraterone plasma concentrations.

Twenty-eight (28) subjects were enrolled in the study and 25 subjects completed all the periods of the study. However Pharmacokinetic analyses were performed over 27 subjects who completed at least two periods of study as per approved protocol. One subject completed only one period of the study, hence excluded from Pharmacokinetic and Statistical analyses.

Analytical methods

A validated LC-ESI-MS/MS bioanalytical method developed for the quantification of abiraterone in plasma was employed for subjects' sample analysis. The quality control samples showed % Bias (mean accuracy) of -4.73 to -2.33 and % Precision (Coefficient of Variation - CV) of 1.75 to 2.80.

Incurred Sample Reanalysis

180 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Pharmacokinetic variables

Primary parameters: AUC_{0-t} and C_{max}

Secondary parameters: AUC_{0-inf}, AUC_%Extra_obs, Tmax, $t_{1/2}$, λ_Z

Statistical methods

Descriptive statistics: Number of observations (N), mean, standard deviation (SD), minimum, median, maximum, percentage co-efficient of variation (%CY) and geometric mean was calculated for concentration profile at each time points and pharmacokinetic parameters for each formulation.

Statistical analysis: Statistical analyses was performed on ln-transformed pharmacokinetic parameters Cmax and AVCo_t of Abiraterone using the SAS® package (SAS Institute Inc., Cary, NC, VSA, Version 9.4 or higher).

Analysis of Variance: ln-transformed pharmacokinetic parameters Cmax and AUCo_t was analysed by analysis of variance (ANOVA) using PROC GLM in SAS® Software, Version 9.4 or higher.

The Sequence effect was tested using the Subject (Sequence) effect as the error term. The sequence effect was tested at the 0.10 level of significance and other main effects related to treatment and period was tested at the 0.05 level of significance. Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference.*Power:* The power of the ANOVA test to detect a 20% mean difference between test and reference formulations was reported.

Two One-Sided test for bioequivalence: Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for ln-transformed data of Cmax and AUC0-t.

If the intra-subject co-efficient of variation of the reference formulation for Cmax was less than or equal to 30%, the conventional acceptance range of 80.00% - 125.00% for bioequivalence would apply to Cmax. The 90% confidence interval of the relative mean Cmax and AUC_{0-t} of the test to reference formulation for ln-transformed data was to be within 80.00% to 125.00% for Abiraterone. For Cmax, the intra-subject co-efficient of variation for the reference formulation was evaluated.

If the intra-subject co-efficient of variation of Cmax for the reference formulation was greater than 30%, the acceptance range for 90% confidence interval is widened to a maximum of 69.84 – 143.19%, which was applied with an intra-subject variability of ≥50% for the reference formulation. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **) applicable for highly variable drugs.

Results

Bioequivalence was demonstrated between the test Abiraterone Mylan 500 mg tablets and the reference Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV in healthy male volunteers under fasted conditions for abiraterone.

Table 2: Pharmacokinetic parameters for Abiraterone 500mg tablets (n=27) (non-transformed values)

Pharmacokinetic parameters (units)	Arithmetic mean ± SD (%CV)	
	Reference product (R) (N=53)	Test product (T) (N=53)
C_{max} (ng/mL)	74.125 ± 51.9487 (70.08%)	71.338 ± 44.3545 (62.18%)
T_{max} (hr)[#]	2.000 (0.67 - 5.00)	1.500 (0.67 - 5.00)
AUC_{0-t} (hr*ng /mL)	355.220 ± 258.1216 (72.67%)	358.820 ± 240.9315 (67.15%)
AUC_{0-inf} (hr*ng /mL)	369.844 ± 260.7150 (70.49%)	373.482 ± 245.5084 (65.73%)
$t_{½}$ (hr)	11.122 ± 3.3259 (29.90%)	10.607 ± 3.5395 (33.37%)
λ_Z (1/hr)	0.072 ± 0.0417 (57.49%)	0.076 ± 0.0417 (54.75%)
AUC_%Extrap_obs	5.110 ± 3.4577 (67.66%)	5.319 ± 4.8336 (90.88%)

[#]For T_{max} Median (min – max)

Table 3: Statistical analysis for Abiraterone 500mg tablets (n=27)

PK parameters (units)	Geometric least squares means and ratio			ISCV of reference formulation (%)	Acceptance range 90% confidence interval	Calculated 90% confidence interval	Power (%)
	Test product (T) (N=53)	Reference product (R) (N=53)	(T/R) %				
C_{max} (ng/mL)	59.175	59.705	99.11	34.01	77.77% - 128.59%	85.19% - 115.31%	78.38
AUC_{0-t} (hr*ng /mL)	285.558	291.157	98.08	24.62	80.00%- 125.00%	86.60% - 111.07%	90.48

Figure 2: Mean Plasma Concentration Time Curve of Abiraterone in semi-log scale following single oral dose of Abiraterone 500mg (n=27)

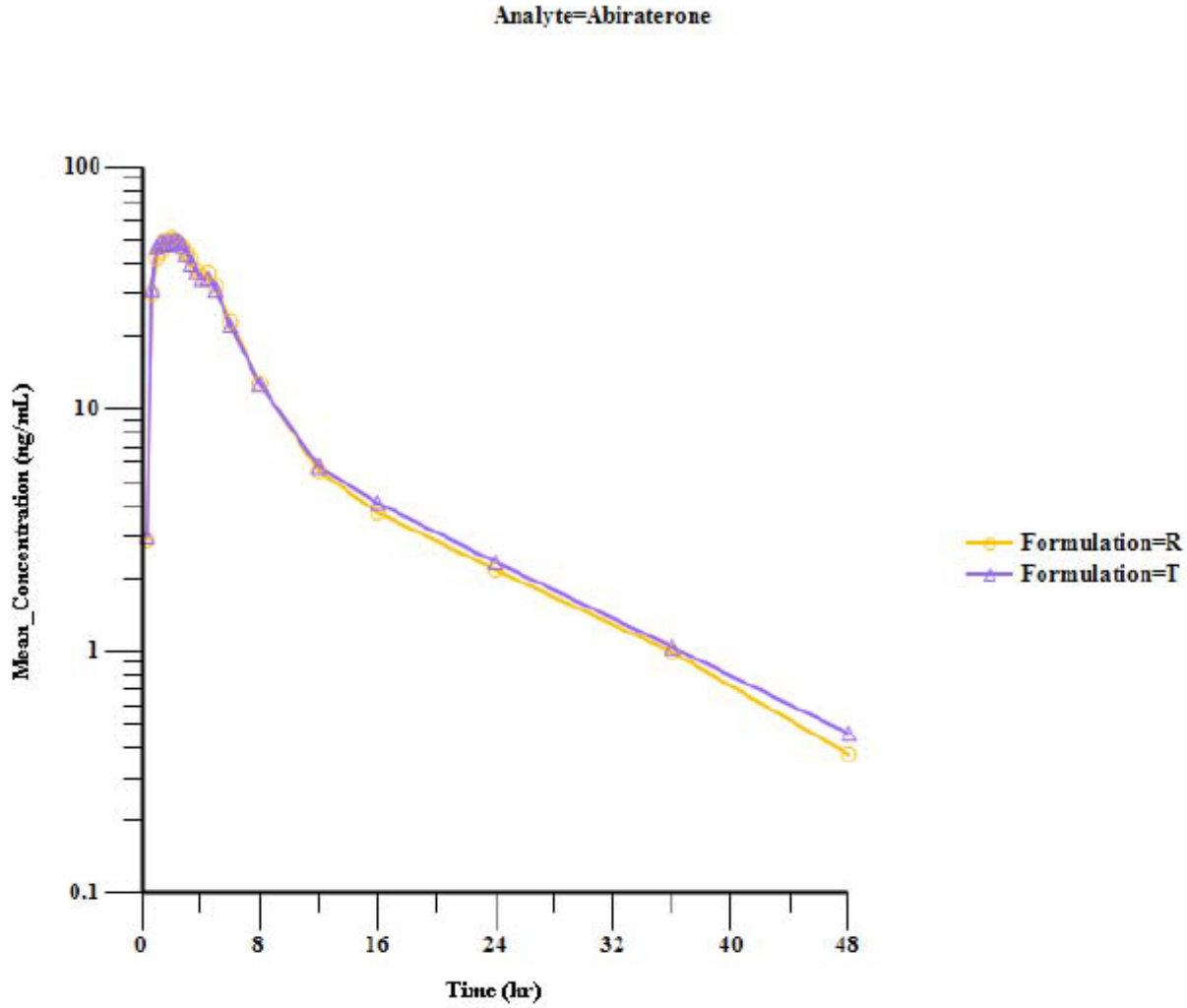
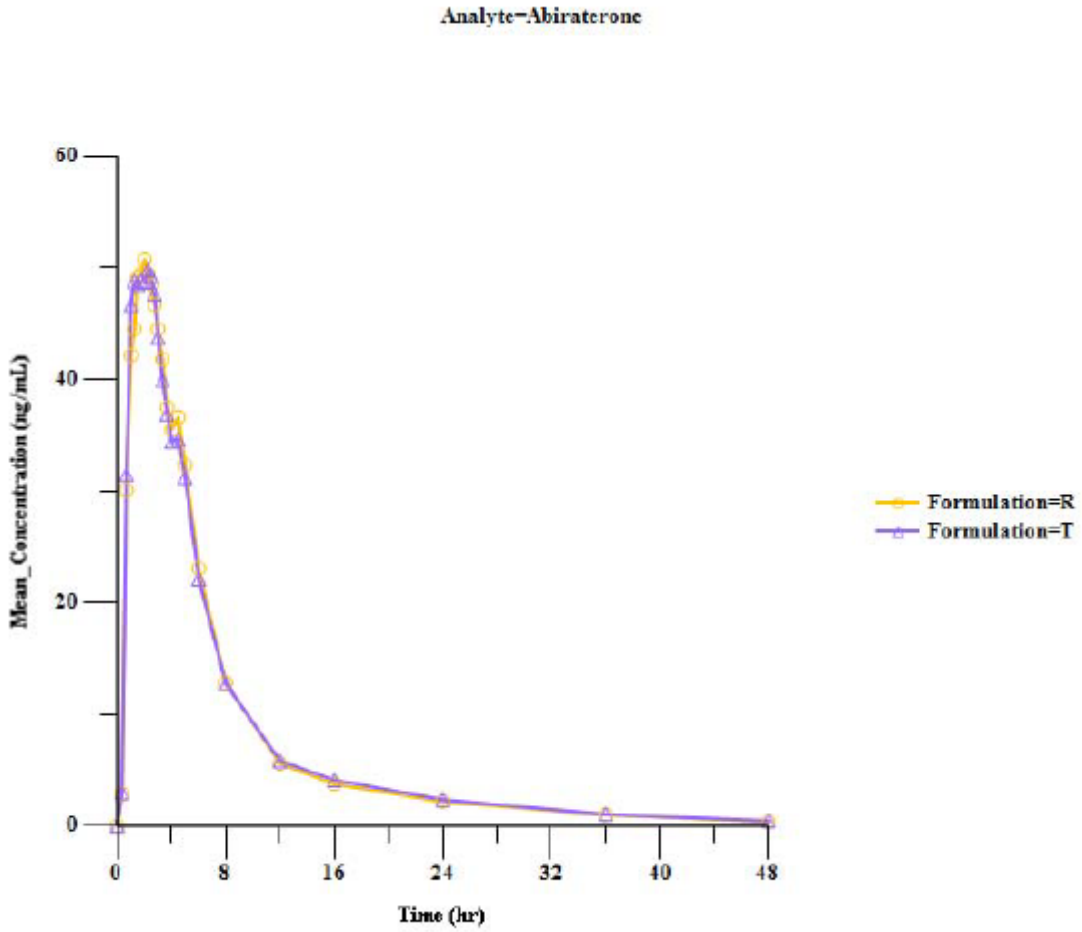


Figure 3: Mean Plasma Concentration Time Curve of Abiraterone in linear scale following single oral dose of Abiraterone 500mg (n=27)



Safety data

During the course of study safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (hematology, biochemistry, immunological tests, urine analysis) and ECG at baseline. Laboratory parameters (hematology and biochemistry) and ECG recording were reassessed at the end of last period of the study.The test and reference products were well tolerated by the subjects. In total, 10 adverse events were reported during the study. Three subjects (Subject No. 05, 06 and 19) reported five adverse events after administration of test product (T); out of them subject no. 05 reported two (02) adverse events, and subject no. 06 reported two (02) adverse events. Two subjects (Subject No. 05 and 06) reported five adverse events after administration of reference product (R). Out of them subject no. 05 reported three (03) adverse events and subject no. 06 reported two (02) adverse events. No clinically significant adverse event and serious adverse event occurred during the conduct of the study.

Study 19-VIN-0187

An open label, balanced, randomised, two-treatment, two-sequence, four-period, fully replicate oral bioequivalence study of Abiraterone Mylan 1000 mg film-coated tablets and Zytiga® (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000 mg (2 tablets of 500 mg) of Janssen-Cilag International NV, Belgium in healthy, adult, male subjects under fasting conditions.

Methods

CRO	**Clinical study site, PK and statistical analysis** Veeda Clinical Research Pvt. Ltd., India Shivalik Plaza, Near I.I.M., Ambawadi Ahmedabad – 380 015, India **Bioanalytical study site** Veeda Clinical Research Pvt. Ltd., India Rev. Sur. No. 12/1, Insignia, Corporate House, Nr. Grand Bhagvati Hotel, Sindhu Bhavan Road, S. G. Highway, Bodakdev, Ahmedabad – 380 054, India
Protocol identification No.	19-VIN-0187
Clinical phase	24 July 2019 to 19 April 2019
Bioanalytical phase	21 August 2019 to 05 September 2019

Study design

This was an open label, balanced, randomised, two-treatment, two-sequence, four-period, fully replicate oral bioavailability study to establish bioequivalence of Abiraterone Mylan 1000 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000mg (2 tablets of 500mg) (MAH: Janssen-Cilag International NV, Belgium and sourced from Germany) in 30 healthy, adult, male subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety of the subjects.

The study was conducted in four periods and in each period; the subjects received either test or Reference products randomly. Randomisation was done in blocks such that the design was balanced. The order of receiving the Reference and test formulations for each subject during the four periods of the study was determined according to randomisation schedule. The dosing (treatment) of Test (T) and Reference (R) product was divided into two sequences (TRTR/RTRT). Subjects who were assigned sequence TRTR received Test product T in period 1 and 3 and reference product R in period 02 and 04. Subjects who were assigned sequence RTRT received Reference product R in Period 01 and 03 and Test product T in period 2 and 4.

Subjects took their assigned formulation, designated by the randomisation scheme, after at least a 10-hour fast. Tablets were administered orally at scheduled dosing time in sitting posture with 240±2mL of water at ambient temperature. Tablets were swallowed as a whole and were not chewed, crushed or divided. A wash out period of 8 days was kept between dosing periods of period 01 to period 02 and period 02 to period 03 and wash out period of 7 days was kept between dosing periods of period 03 to period 04.

Test and reference products

Abiraterone Mylan 1000 mg tablets was compared to Zytiga (abiraterone acetate) 500 mg film-coated tablets of Janssen-Cilag International NV at a dose of 1000m g (2 tablets of 500mg).

Population(s) studied

Thirty (30) healthy adult male human subjects were enrolled as per the protocol to ensure dosing of 24 subjects. A total of 25 subjects completed all the periods of the study. Pharmacokinetic and Statistical analyses were performed on 28 subjects who completed at least two periods, in which the subject received the reference product in both periods, or where a test to reference comparison was possible.

Analytical methods

A validated LC-ESI-MS/MS bioanalytical method developed for the quantification of Abiraterone in Plasma was employed for subjects" sample analysis. The quality control samples showed % Bias (mean accuracy) of -2.28 to 0.58 and % Precision (Coefficient of Variation - CV) of 1.79 to 2.80. At the bioanalytical research facility after completion of analysis.

Incurred Sample Reanalysis

182 samples were identified for incurred sample reanalysis. 99.45% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

Pharmacokinetic variables

Primary parameters: AUC_{0-t} and C_{max}

Secondary parameters: AUC_{0-inf}, AUC_%Extra_obs, Tmax, $t_{1/2}$, λ_Z

Statistical methods

Descriptive statistics: Number of observations (N), mean, standard deviation (SD), minimum, median, maximum, percentage co-efficient of variation (%CY) and geometric mean was calculated for concentration profile at each time points and pharmacokinetic parameters for each formulation.

Statistical analysis: Statistical analyses was performed on In-transformed pharmacokinetic parameters Cmax and AVCo_t of Abiraterone using the SAS® package (SAS Institute Inc., Cary, NC, VSA, Version 9.4 or higher).

Analysis of Variance: In-transformed pharmacokinetic parameters Cmax and AUCo_t was analysed by analysis of variance (ANOVA) using PROC GLM in SAS® Software, Version 9.4 or higher. The model statement of PROC GLM in SAS® Software included the fixed effects of Sequence, Treatment, Period and subject (Sequence).

The Sequence effect was tested using the Subject (Sequence) effect as the error term. The sequence effect was tested at the 0.10 level of significance and other main effects related to treatment and period was tested at the 0.05 level of significance. Each analysis of variance included calculation of least-square means, the difference between the adjusted formulation means and the standard error associated with the difference. *Two One-Sided test for* bioequivalence*:* Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for ln-transformed data of Cmax and AUC0-t.

Power: The power of the ANOVA test to detect a 20% mean difference between test and reference formulations was reported.

If the intra-subject co-efficient of variation of the reference formulation for Cmax was less than or equal to 30%, the conventional acceptance range of 80.00% - 125.00% for bioequivalence would

apply to Cmax. The 90% confidence interval of the relative mean Cmax and AUC_{0-t} of the test to reference formulation for ln-transformed data was to be within 80.00% to 125.00% for Abiraterone. For Cmax, the intra-subject co-efficient of variation for the reference formulation was evaluated.

If the intra-subject co-efficient of variation of Cmax for the reference formulation was greater than 30%, the acceptance range for 90% confidence interval is widened to a maximum of 69.84 – 143.19%, which was applied with an intra-subject variability of ≥50% for the reference formulation. This is in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **) applicable for highly variable drugs.

Results

Table 4: Pharmacokinetic parameters for Abiraterone 1000 mg (n=28) (non-transformed values)

Pharmacokinetic Parameter	Arithmetic Means (±SD)[1]	
	Test Product	Reference Product
$AUC_{(0-t)}$ [2] (ng.hr/mL)	462.840 ± 282.6857	421.288 ± 206.6397
$AUC_{(0-\infty)}$ [3] (ng.hr/mL)	479.144 ± 288.5069	437.312 ± 210.1137
Cmax (ng/mL)	118.598 ± 91.5071	97.650 ± 51.2448
tmax[4](hr)	2.000 (0.67 - 4.50)	1.750 (0.67 - 4.50)

Table 5: Statistical analysis for Abiraterone 1000 mg (n=28) (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals (%)	CV %[7]
$AUC^{8}_{(0-t)}$	106.89	96.01% -119.01%	31.73
C_{max}	110.00	95.65% -126.50%	33.80

Figure 4: Mean Plasma Concentration Time Curve of Abiraterone in linear scale following single oral dose of Abiraterone 1000 mg (n=28)

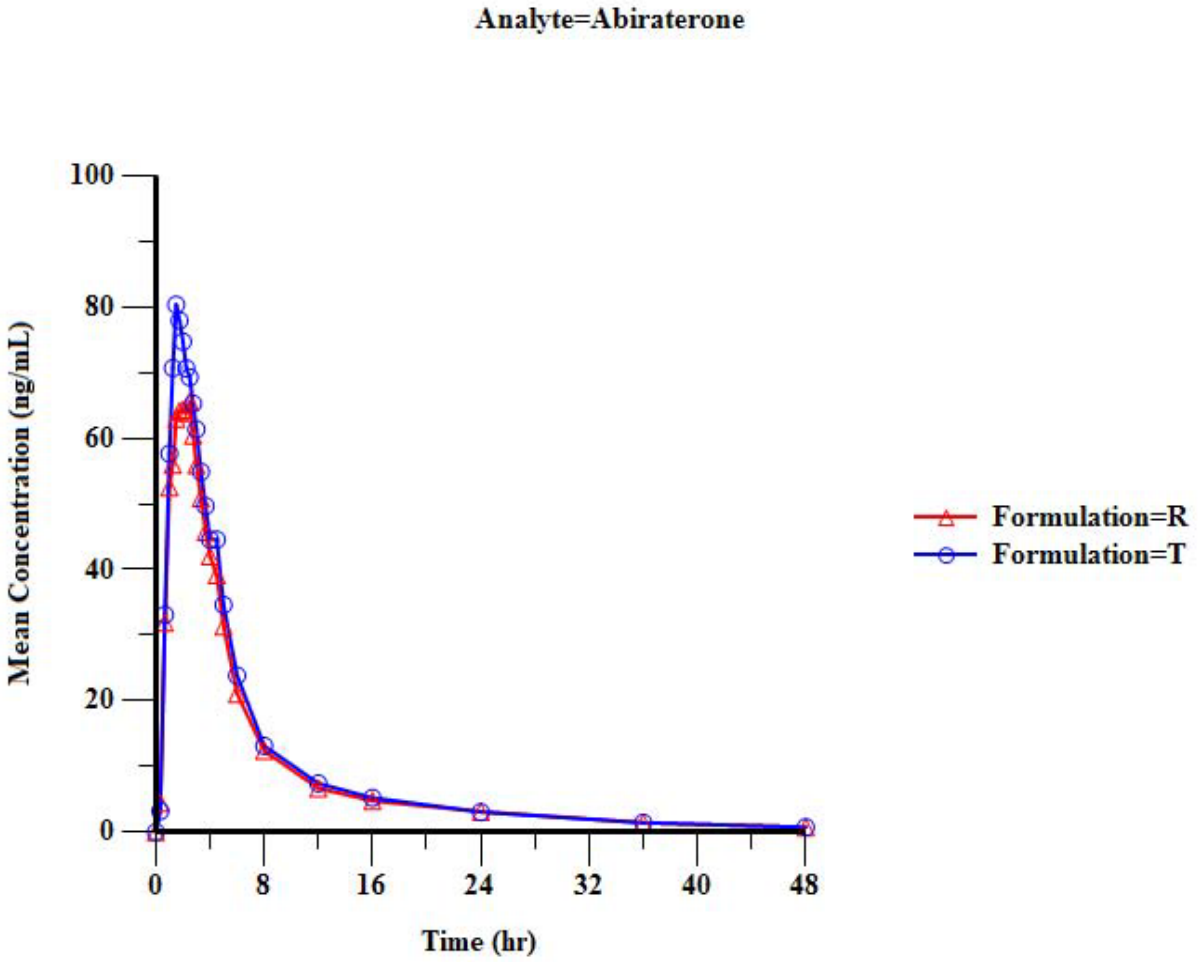
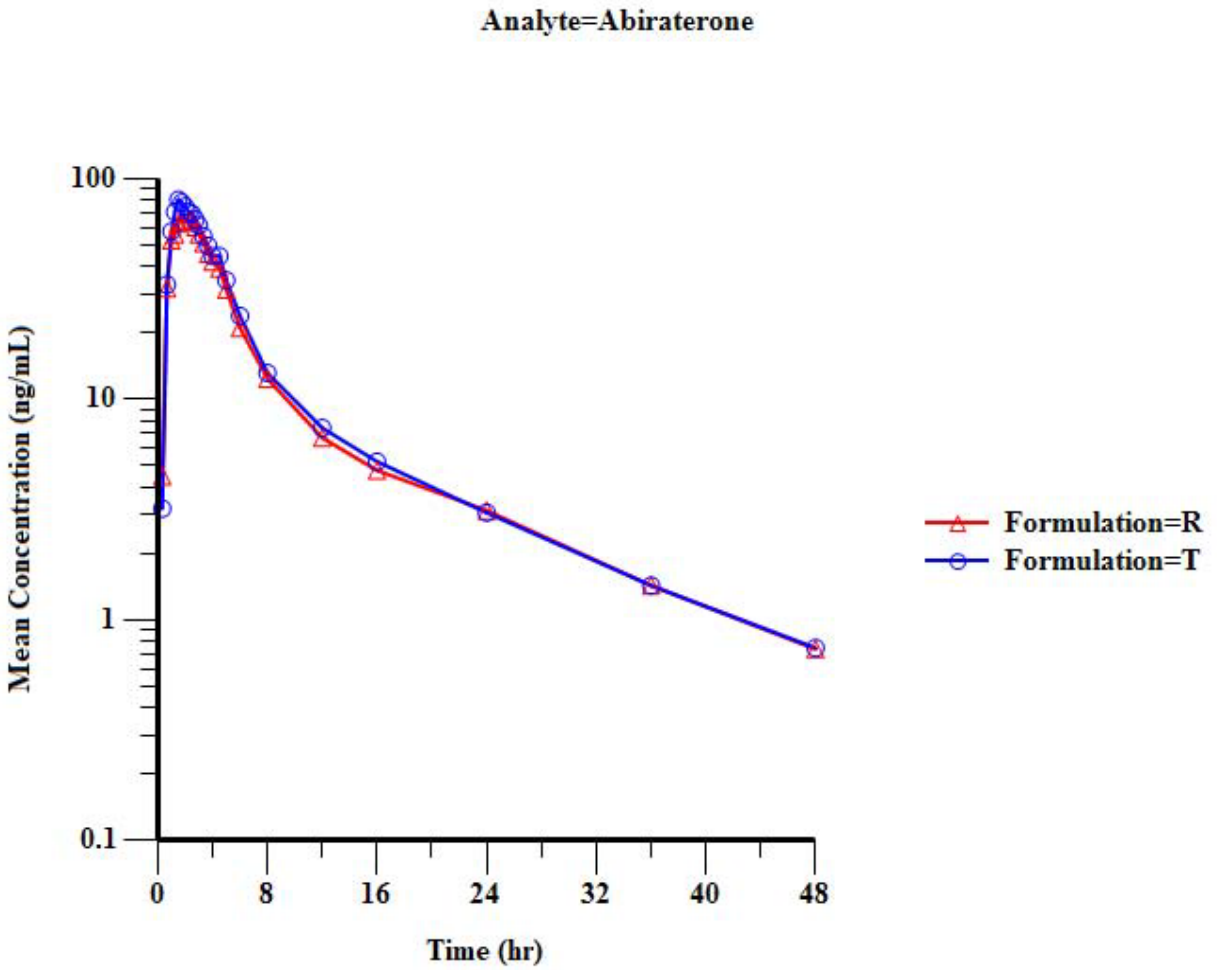


Figure 4: Mean Plasma Concentration Time Curve of Abiraterone in semi-log scale following single oral dose of Abiraterone 1000 mg (n=28)



Safety data

During the course of study safety parameters assessed were vital signs, physical examination, medical history, clinical laboratory safety tests (haematology, biochemistry, immunological tests, urine analysis) and ECG at baseline. Laboratory parameters (haematology and biochemistry) and ECG recording were reassessed at the end of last period of the study. The test and reference products were well tolerated by the subjects. A total of 17 adverse events were reported by 13 subjects during entire course of study. Out of these, subject no. 01 and 12 reported two adverse events and subject no. 07 reported three adverse events.

Four (04) subjects (Subject no. 10, 15, 24 and 27) reported adverse events after administration of test product (T) and seven (07) subjects (Subject no. 01, 03, 04, 07, 12, 16, and 25) reported ten (10) adverse events after administration of reference product (R). Subject no. 19 reported clinically significant abnormal lab value at 2 hours post dose safety assessment after administration of reference product (R). Subject no. 07 and 13 reported clinically significant abnormal lab value during post study safety assessment after administration of reference product (R) and test (T) product respectively. There were no deaths, serious adverse event occurred during the conduct of the study.

Conclusions

Based on the presented bioequivalence studies Abiraterone Mylan is considered bioequivalent with Zytiga.

2.3.3. Pharmacodynamics

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

2.3.4. Post marketing experience

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

2.3.5. Discussion on clinical aspects

BE Study: 18-VIN-0695

This study was submitted to establish bioequivalence of Abiraterone Mylan 500 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets (MAH: Janssen-Cilag International NV, Belgium and sourced from Germany). The study was designed as an open label, balanced, randomised, two-treatment, two-sequence, four-period, single-dose, crossover fully replicate study under fasting conditions. According to the SmPC of the originator, when abiraterone is administered with food, there is an increase in the systemic exposure of abiraterone. Hence, abiraterone tablets should not be taken with food. The design of a fasting bioequivalence study is considered appropriate. The sampling periods are acceptable upon review of the graphs with ample time points around Tmax (approximately 2 hours) and with an adequate wash-out period at greater than five times the half-life (approximately 15 hours). The sampling frequency enabled an adequate estimation of Cmax. Both the clinical study and the bioanalytical site have been inspected by an EU competent authority.

Certificates of analysis for both the test and reference products have been provided. The batch control results appear satisfactory and the batch size (10% of the proposed commercial batch) and manufacturing date of the test product have been declared and are acceptable. The assay ranges are well within the 5% limit of each other in accordance with the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).

The population studied is also 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). The subjects as per inclusion criteria were all male since in the absence of data, abiraterone is contraindicated in women due to safety concerns. The number of subjects not completing the study does not have an effect on the results, as 24 patients are enough to power the study. Protocol deviations listed in the report are considered minor and do not have a negative effect of the study results. The concomitant medication taken by subject 19 is accounted for in the bioanalytical method.

The analytical methods used are acceptable and appropriate. The chromatograms presented are acceptable and the 19 re-analysed samples have been adequately justified. The calibration curve is appropriate (9 points) and the stability testing supports the conditions the samples were exposed to during collection and testing. The applicant has also provided all the validation reports and relevant supportive data together with certificates of analysis for the analyte standard and internal standards

used in the analytical method validation. The relevant SOPs have been provided and deemed valid. The Incurred sample reanalysis was provided as well as information on the partial revalidation of the method. These are deemed acceptable. Co-administered drug effect was carried out including the concomitant medication administered during the clinical phase. The bioanalytical method was audited and a signed quality assurance statement dated 05 April 2019 was provided.

The pharmacokinetic variables chosen for the study are adequate. The appropriate variables were measured and the statistical methodology is accepted. The sampling schedule provides adequate estimation of Cmax. Statistical data and a graphical representation to cover the plasma concentration time curve, long enough to provide an estimate of the extent of absorption, have been provided.

The intra-subject variability of Reference formulation for Cmax of Abiraterone was 34.01%. Intra-subject variability of Reference formulation for Cmax is greater than 30%, hence the bioequivalence acceptance range of Cmax was widened to 77.77% - 128.59% based on the intra-subject variability of reference formulation for Abiraterone. Even though there was a widening in the acceptance bioequivalence range for Cmax pre-specified in the protocol, the 90% confidence intervals for geometric least square mean ratio of (T/R) for ln-transformed Cmax was found to be 85.19% - 115.31%, which falls within the acceptance bioequivalence range of 80.00 – 125.00%. The 90% confidence intervals for the ratios of test and reference product (least-squares means) derived from the analysis of log transformed pharmacokinetic parameter AUC0-t was within 80-125% acceptance range for Abiraterone. These are in line with the requirements of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **). No statistically significant treatment or sequence differences were observed for any of the pharmacokinetic parameters involved in the assessment of bioequivalence. Bioequivalence with the reference product has been shown.

The two treatments were also well tolerated by the subjects enrolled in the study. The adverse events seen during the study were all included in the SmPC and there are no new concerns arising from the study. The two products had similar safety profiles.

BE Study: 19-VIN-0187

This study was submitted to establish bioequivalence of Abiraterone Mylan 1000 mg tablets and Zytiga (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000mg (2 tablets of 500mg) (MAH: Janssen-Cilag International NV, Belgium and sourced from Germany). The study was designed as an open label, balanced, randomised, two-treatment, two-sequence, four-period, fully replicate under fasting conditions. According to the SmPC of the originator when abiraterone is administered with food, there is an increase in the systemic exposure of abiraterone. Hence, abiraterone tablets should not be taken with food. The design of a fasting bioequivalence study is considered appropriate. The sampling periods are acceptable upon review of the graphs with ample time points around Tmax (approximately 2 hours) and with an adequate wash-out period at greater than five times the half-life (approximately 15 hours). The sampling frequency enabled an adequate estimation of Cmax. Both the clinical study site and the bioanalytical site have been inspected by an EU competent authority.

Certificates of analysis for both the test and reference products have been provided. The batch control results appear satisfactory and the batch size (10% of the proposed commercial batch) and manufacturing date of the test product have been declared and are acceptable. The assay ranges are well within the 5% limit of each other in accordance with the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01 Corr**).

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). The subjects as per inclusion criteria were all male since in the absence of data, abiraterone is contraindicated in women due to safety concerns. The number of

subjects not completing the study will not have an effect on the results as 24 patients are enough to power the study. Protocol deviations are considered minor and will not have a negative effect on the study results. The concomitant medications taken by subjects 01, 04, 12 and 15 are accounted for, in the bioanalytical method.

The analytical methods used are acceptable and appropriate. The chromatograms presented are acceptable and the 3 re-analysed samples have been adequately justified. The calibration curve is appropriate (10 points) and the stability testing supports the conditions the samples were exposed to during collection and testing. The applicant has also provided all the validation reports and relevant supportive data together with certificates of analysis for the analyte standard and internal standards used in the analytical method validation. The relevant SOPs have been provided and deemed valid. The Incurred sample reanalysis was provided as well as information on the partial revalidations of the method. These are deemed acceptable. Co-administered drug effect was carried out including the concomitant medications administered during the clinical phase. The method was audited and the report is dated 25 October 2019.

The pharmacokinetic variables chosen for the study are adequate. The appropriate variables were measured and statistical methodology is accepted. The sampling schedule provides adequate estimation of Cmax. Statistical data and a graphical representation to cover the plasma concentration time curve long enough to provide an estimate of the extent of absorption, have been provided.

As per protocol, subjects who have completed at least 2 periods where both are the reference products or where a test to reference comparison is possible, were included in the pharmacokinetic and statistical analysis. A total of 24 subjects completed all four periods of the study, 2 subjects completed three periods of the study, 2 subjects completed two periods of the study, and 2 subjects were withdrawn/dropped out from the study. Hence, a total of 28 subjects were included in the pharmacokinetic and statistical analysis in line with the protocol.

The intra-subject variability of Reference formulation for Cmax of Abiraterone evaluated on 28 subjects was 33.80%. Intra-subject variability of Reference formulation for Cmax is greater than 30%, hence the bioequivalence acceptance range of Cmax was widened to 77.88% - 128.40% based on the intra-subject variability of reference formulation for Abiraterone. The 90% confidence interval for geometric least square mean ratio of (T/R) was 95.65% - 126.50% for pharmacokinetic parameter Cmax, which was within the acceptance range of 77.88% - 128.40%.

The widening of the pharmacokinetic criteria 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 study is of a replicate design and the within-subject variability for Cmax of the reference compound has been demonstrated to be more than 30%. The request for widened interval was prospectively specified in the protocol.

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 01/Corr **) section 4.1.10 Highly variable drugs, the applicant was requested to discuss with supporting documentation that a wider difference in Cmax is not considered clinically relevant. The applicant conducted additional statistical analysis of the results of the BE study to assess whether the calculated intra-subject variability is a reliable estimate and not the result of outliers (data not shown). Analysis did not identify any outlying value; therefore, the calculated intra-subject variability of Cmax is a reliable estimate and it is not the result of outliers. Given that the intra-subject variability of the Reference product for Cmax is > 30%, the acceptance criteria for Cmax can be widened.

The geometric least square mean ratio (T/R) was found 110.00% for pharmacokinetic parameter Cmax, which was within the conventional acceptance range of 80.00% to 125.00%. The 90%

confidence intervals calculated for AUC0-t for abiraterone 1000 mg fall within the 80.00%-125.00% acceptance range after single dose administration under fasting conditions.

The two treatments were also well tolerated by the subjects enrolled in the study. The adverse events seen during the study were all included in the SmPC and there are no new concerns arising from the study. The two products had similar safety profiles.

2.3.6. Conclusions on clinical aspects

Based on the bioequivalence study 18-VIN-0695 presented Abiraterone Mylan 500 mg film-coated tablets is considered bioequivalent with Zytiga 500 mg film-coated tablets manufactured by Janssen-Cilag NV, Belgium.

Based on the bioequivalence study 19-VIN-0187 presented, Abiraterone Mylan 1000 mg film-coated tablets is considered bioequivalent with Zytiga (abiraterone acetate) 500 mg film-coated tablets at a dose of 1000 mg (2 tablets of 500 mg) of Janssen-Cilag International NV, Belgium.

2.4. Risk Management Plan

Safety concerns

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

No additional pharmacovigilance activities.

Risk minimisation measures

Safety concern	Risk minimisation measures
Hepatotoxicity	Routine risk minimisation measures
Cardiac disorders	Routine risk minimisation measures
Osteoporosis including osteoporosis-related fractures	Routine risk minimisation measures
Rhabdomyolysis/Myopathy	Routine risk minimisation measures
Allergic alveolitis	Routine risk minimisation measures
Increased exposure with food	Routine risk minimisation measures
Anaemia	Routine risk minimisation measures
Cataract	Routine risk minimisation measures
Drug-drug interaction (CYP2D6)	Routine risk minimisation measures
Use in patients with active or symptomatic viral hepatitis	Routine risk minimisation measures
Use in patients with moderate/severe hepatic impairment and chronic liver disease	Routine risk minimisation measures
Use in patients with severe renal impairment	Routine risk minimisation measures
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%	Routine risk minimisation measures

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.5. 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.

2.6. Product information

2.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Duloxetine Mylan 30 mg hard gastro-resistant capsules and to Zytiga 250 mg tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of abiraterone acetate 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.

Two bioequivalence studies were submitted. The study designs were considered adequate to evaluate bioequivalence and were in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out periods were adequate. The analytical methods were validated. Pharmacokinetic and statistical methods applied were adequate.

Both studies met the protocol-defined criteria for bioequivalence when compared with the reference product. Bioequivalence was demonstrated.

4. Recommendation

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

Abiraterone Mylan 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.

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.