25 February 2021
EMA/174959/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abiraterone Accord

International non-proprietary name: abiraterone acetate

Procedure No. EMEA/H/C/005408/0000

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
AR	Androgen receptor
AS	active substance
AUC	The area under the plasma concentration time curve/ total systemic exposure
BSA	Body surface area
CI	Confidence interval
CTC	Circulating tumour cell
C_{max}	The maximum plasma concentration
CPP	critical process parameter
CQA	critical quality attribute
CRPC	Castration-resistant prostate cancer
C.V.	Coefficient of variation
CYP	Cytochrome P450
DHEA	Dehydroepiandrosterone
DLT	Dose limiting toxicity
DSC	differential scanning calorimetry
ECOG PS	Eastern Cooperative Oncology Group performance status
EI	elemental impurities
ESAS	Edmonton Symptom Assessment System
FDA	Food and Drug Administration
FP	finished product
GC	gas chromatography
HDPE	high-density polyethylene
HPLC	high performance chromatography
HR	Hazard ratio
HSPC	Hormone sensitive prostate cancer
IMP	Investigational medicinal product
IPC	in-process control
IR	infra-red spectroscopy
λz	Apparent first-order elimination or terminal rate constant
LHRH	Luteinizing-hormone-releasing hormone
MO	major objection
MS	mass spectrometry
NMR	nuclear magnetic resonance
PDE	permitted daily exposure
PFS	Progression free survival
Ph. Eur.	European Pharmacopoeia

PP	polypropylene
PSA	Prostate specific antigen
PSD	particle size distribution
PVC	Polyvinyl Chloride
PVDC	Polyvinylidene Chloride
QTPP	quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumors
RH	Relative humidity
SULT	Sulfotransferase
T	Test product
t1/2	The elimination half-life associated with the terminal slope of a semi-logarithmic concentration-time curve
TGA	thermogravimetric analysis
Tmax	The time of maximum plasma drug concentration reached
UDP	Uridine diphosphate
UGT	UDP-glucuronosyl transferase
UHPLC	ultra high performance chromatography
UV	ultra-violet spectrometry
Vd	Volume of distribution
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 12 September 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Abiraterone Accord, 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 27 June 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 Accord 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 data 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: Alar Irs

The application was received by the EMA on	12 September 2019
The procedure started on	3 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	03 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	30 January 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	11 July 2020
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	21 September 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to	01 October 2020

CHMP during the meeting on	
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 October 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	22 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	13 January 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	28 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 February 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 Accord on	25 February 2021

2. Scientific discussion

2.1. Introduction

MAAs of Abiraterone Accord 250mg tablets and Abiraterone 500mg film-coated tablets containing abiraterone acetate as an active substance are submitted according to the Article 10.1 of Directive 2001/83/EC, as amended (i.e. generic application) containing the same active substance in the same pharmaceutical form and strengths as the reference product. The reference product Zytiga 250mg tablets and 500mg film-coated tablets, marketed by Janssen-Cilag International N.V was first approved in the European Union on 05/09/2011 via the centralised procedure (EU/1/11/714).

The drug substance is abiraterone on the form of abiraterone acetate. The Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents; ATC code: L02BX03.

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and 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 acetate decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Abiraterone Accord is used to treat cancer of the prostate in adult men when the cancer is metastatic. It 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.

For mHSPC, Abiraterone acetate is used with 5 mg prednisone or prednisolone daily and for mCRPC, Abiraterone acetate is used with 10 mg prednisone or prednisolone daily.

The applied indications for the submitted products are the same as authorised for the reference product.

The products are subject to the medical prescription.

The recommended single daily dose is 1000mg orally that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone. Similar to the recommendations in the SmPC of the reference product, the tablets should be taken at least two hours after eating and no food should be eaten for at least one hour after taking the tablets. The tablets should be swallowed whole with water.

No dose adjustment is necessary for patients with renal impairment according to the SmPC, however, as there is no clinical experience with patients with prostate cancer and severe renal impairment, caution is advised in these patients. Use of Abiraterone acetate should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Abiraterone should not be used in patients with severe hepatic impairment. No dose adjustment is necessary for patients with pre-existing mild hepatic impairment, Child-Pugh Class A.

There is no relevant use of Abiraterone Accord in the paediatric population.

The most common side effects are urinary tract infection, hypokalaemia, high blood pressure, peripheral oedema and increases in liver enzymes. Other important side effects include heart problems, liver problems, fractures and allergic alveolitis.

Important identified risks according to the RMP of the reference product are hepatotoxicity, cardiac disorders, osteoporosis including osteoporosis-related fractures, rhabdomyolysis/myopathy, allergic alveolitis and increased exposure with food.

The important potential risks are anaemia, cataract and drug-drug interaction (CYP2D6).

The application is based on two pivotal bioequivalence studies (fasting).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 250 mg or as film-coated tablets containing 500 mg of abiraterone acetate as active substance.

Other ingredients in the 250 mg tablets are: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulphate, colloidal anhydrous silica, magnesium stearate;

Other ingredients in the 500 mg tablets are:

Tablet cores: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulphate, colloidal anhydrous silica, magnesium stearate;

Film-coating: polyvinyl alcohol, titanium dioxide, macrogol, talc, iron oxide red and iron oxide black.

The 250 mg tablets are available in white high-density polyethylene (HDPE) bottles fitted with a child-resistance tamper-evident polypropylene (PP) closure and the 500 mg film-coated tablets are available in transparent polyvinyl chloride/ polyvinylidene chloride/ aluminium (PVC/PVDC/Al) perforated unit dose blisters.

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. It corresponds to the molecular formula $C_{26}H_{33}NO_2$. Its relative molecular mass is 391.55 g/mol and it has the chemical structure shown in Figure 1.

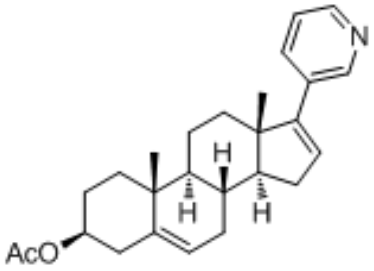

Figure 1. Chemical structure of abiraterone acetate.

The structure of the active substance (AS) was adequately elucidated by a combination of elemental analysis, UV spectroscopy, IR spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry (MS). Physicochemical properties were investigated by differential scanning calorimetry (DSC), X-Ray Powder Diffraction (XRPD) crystallography and thermogravimetric analysis (TGA).

Abiraterone acetate appears as white to off-white, non-hygroscopic, crystalline powder. It is practically insoluble in water and in aqueous media (pH range 2.0 to 12.9), soluble in methanol and freely soluble in chloroform. The active substance pKa is 5.19, and its partition coefficient LogP was found to be 5.12.

Abiraterone acetate is a four-ring androsteroid structure containing eight stereochemical elements, which include six chiral centres: 3*S*, 8*R*, 9*S*, 10*R*, 13*S*, 14*S*, four of which (8*R*, 10*R*, 13*S*, 14*S*) are in the natural

configuration of steroid skeleton, the other two being formed in the synthetic process of the starting material (DHEA). There are also two centres of geometrical isomerism (C5(*Z*), C16(*E*)), the confirmations of which are enforced by the ring structures.

Abiraterone acetate exhibits polymorphism. The selected polymorphic form is the thermodynamically most stable form and is produced exclusively by the manufacturing process of both manufacturers. The data provided on polymorphic form are accepted and stability studies have shown no changes in polymorphism.

Manufacture, characterisation and process controls

Two active substance manufacturers have been stated. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the respective ASMF from each manufacturer and it was considered satisfactory.

Process by ASMF manufacturer #1
The manufacturing process comprises four chemical synthetic steps, followed by a purification and a micronisation step. The proposed starting materials were redefined following a Major Objection (MO) raised by the CHMP. The suitability of the redefined starting materials and their control have been properly justified. Initially a second, slightly different alternative route of synthesis had been proposed in parallel with the one described above but it has been omitted as requested by the CHMP and the ASMF has been updated accordingly.

There are two defined intermediates controlled by acceptable specifications. Critical steps have been identified and adequate in-process controls are in place.

The dossier has also been updated during the procedure in response to a MO with further information on potential impurities and their carry-over. The information with regard to the potentially genotoxic impurities as well as the carry-over investigations performed are accepted taking into account the proposed indication (prostate cancer), hence the ICH M7 guidance is, in general, not applicable and no further questions were raised concerning mutagenicity aspects. The control strategy applied with respect to the residual solvents used has been significantly improved and further control requirements have been included within the specifications of the final AS as well as in the intermediates. The overall control strategy of the active substance synthesis ensures the robustness and consistency of the manufacturing process.

A satisfactory summary of manufacturing process development has been provided. Changes introduced have been presented in sufficient detail and have been justified.

Process by ASMF manufacturer #2
The manufacturing process comprises four chemical synthetic steps, followed by a purification and a micronisation step. The proposed designated starting materials are considered acceptable.

The suitability of the starting materials and their control have been properly justified; during the procedure the dossier has been updated with information on all potential impurities including discussions with regard to the carry-over of impurities originating from the defined starting materials. No further questions on potential mutagenicity aspects have been raised taking into account the proposed indication (prostate cancer), hence the ICH M7 guidance is in general not applicable. The carry-over of residual solvents has also been sufficiently addressed. Four isolated intermediates are controlled by acceptable specifications. The overall control strategy of the active substance synthesis ensures the robustness and consistency of the manufacturing process. Critical steps have been identified and adequate in-process controls (IPCs) are in place.

A satisfactory summary of manufacturing process development has been provided. Changes introduced have been presented in sufficient detail and have been justified.

Packaging material
The AS is packaged into double polyethylene bags. The PE bags are placed in PE drum for the AS obtained from ASMF manufacturer #1 and in a fibreboard drum with cap for the AS supplied by ASMF manufacturer #2. The specification of the packaging materials has been presented and is satisfactory. The primary packaging material complies with the requirements of EU Regulation No. 10/2011, Regulation No. 1935/2004, and with Ph. Eur. 3.1.3 "Polyolefins".

Specification, analytical procedures, reference standards, batch analysis and container closure

The AS specification includes appropriate tests and limits for appearance (visual), identification (HPLC, IR), optical rotation (Ph. Eur.), water content (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC-two methods), impurities (HPLC-two methods), assay (HPLC), palladium content (Ph. Eur.), particle size distribution (Ph. Eur.) and microbiological contamination (Ph. Eur.).

The AS specifications have been revised during the procedure to include further test parameters as established by the two AS manufacturers. The methods incorporated in the overall specification are principally the same as those of each supplier. In addition, a test for residual Pd has been introduced in final AS specifications. The proposed limit is below the ICH option 2A limit and it has been shown that it ensures that the Pd content in the finished product will not exceed the permitted daily exposure (PDE) (100 ppm). Therefore, the proposed Pd content limit in the AS specification is considered sufficient. Palladium is the only elemental impurity intentionally introduced in the AS manufacturing process; no further risks for presence of other elemental impurities have been identified.

The AS particle size distribution limits have been set based on the pharmaceutical development of the finished product and is acceptable.

From the provided XRPD diffractograms, it can be concluded that the manufacturing processes consistently produce the same polymorphic form which has been shown to be stable over time. It is therefore considered justified not to include a test for control of polymorphism in the AS specification.

The analytical methods used have been adequately described and validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of the AS has been presented.

Batch data were provided for three pilot batches of AS from ASMF manufacturer #1 and six (three pilot and three commercial scale) of AS batches manufactured by ASMF manufacturer #2 using the proposed synthetic routes for commercial manufacture. All the results comply with the proposed AS specification and demonstrate consistent manufacture and quality of the AS manufactured by both suppliers.

Stability

ASMF manufacturer #1 batches
Stability data has been provided for three pilot scale batches manufactured at the proposed manufacturing site. These stability batches were packaged in the proposed container closure system. Stability data were provided for up to 18 months stored under long term conditions (25°C / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines.

Samples were tested for appearance, identification, water content, Pd content, residue on ignition, assay, impurities and residual solvents. Results met the specifications regardless of the storage condition. No significant trends or variability were observed.

Stress testing was performed to evaluate degradation of the AS. Samples were placed under a variety of stressed conditions to assess the impact of acid, base, oxidation, humidity, heat, and light on the quality of the AS. The analytical methods used in the study were also evaluated for their stability indicating capability. It was concluded from the data generated that the AS is more sensitive to acidic conditions, less so to basic and oxidative conditions, while no degradation was observed to samples exposed to heat and humidity. It was also concluded that the HPLC assay and impurities method are stability indicating.

Photostability testing was carried out as part of the stress testing on a pilot scale batch as per ICH Q1B. No degradation was found in the light-exposed and the control samples after the exposure, indicating that AS is photostable.

Based on the available stability data, the proposed retest period of 2 years without any specific storage restrictions, is acceptable.

ASMF manufacturer #2 batches
Stability data has been provided for seven pilot and three commercial scale batches manufactured at the proposed manufacturing site. These stability batches were packaged in the proposed container closure system. Stability data were provided for up to 36 months stored under long term conditions (25°C / 60% RH) and for up to six months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines.

Samples were tested for appearance, identification, water content, assay, impurities and polymorphic form. Results met the specifications regardless of the storage condition. No significant trends or variability were observed. The XRPD analysis has shown stability of the produced polymorphic form under all testing conditions.

Stress testing of the AS was performed to evaluate degradation of the AS under a variety of stress conditions (acid, base, oxidation, humidity, heat, and light (ICH)). The results of the stress study showed a variable degree of degradation in line with the findings reported above. It was also demonstrated that the HPLC assay and impurities method are stability indicating.

Based on the available stability data, the proposed retest period of 3 years without any specific storage restrictions, is acceptable.

The stability results from both suppliers indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The applicant confirmed that the re-test periods as established in the respective ASMFs are applied; this approach can be accepted.

2.2.3. Finished medicinal product

250 mg tablets

Description of the product and pharmaceutical development

The finished product is presented as a white to off-white oval tablet, approximately 16 mm long by 9.5 mm wide, debossed with "ATN" on one side and "250" on the other side containing 250 mg of abiraterone acetate

as active substance. The qualitative composition of Abiraterone Accord 250 mg tablets is in section 2.2.1 of this report and in SmPC section 6.1.

The formulation contains commonly used excipients for a product manufactured by means of a wet granulation process. All excipients used are well-known and widely used as pharmaceutical ingredients and comply with the current pharmacopoeial monographs and/or directives. Both generic and reference product have the same qualitative composition. The choice of the excipients was justified, and their functions explained. Compatibility between AS and excipients was inferred from stability studies. There is no interaction between the AS and the excipients. In addition, the AS retains its desired polymorphic form during storage of the finished product.

The objective of the development of the 250 mg tablets was to develop a generic product which is bioequivalent and has a similar dissolution and stability profile to the reference product Zytiga 250 mg tablets. Quality by Design principles were applied to develop the generic product.

A Quality Target Product Profile (QTPP) was defined for abiraterone 250 mg tablets taking into account clinical and pharmacokinetic (PK) characteristics, *in vitro* dissolution, physicochemical characteristics of the reference product and intellectual property restrictions.

A risk analysis approach, in accordance with ICH Q9, was used to establish those process parameters that may have the greatest impact on product quality. Experiments were designed based on knowledge of the active substance, the excipients, and the manufacturing process and risk analyses. Risk assessment was carried throughout development to identify potentially high-risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding. Risk Assessment was performed to identify the variables affecting the proposed critical quality attributes (CQAs). The relative risk attributed to each element was ranked as high, medium or low. Subsequently, the risk assessment was updated after formulation and process development to capture the reduced level of risk based on improved process understanding. An updated risk assessment was found to be satisfactory as the high and medium formulation risks were reduced to low.

Development studies from early formulations to the commercial formulations have been described. The CQAs have been determined and investigated during the development. The formulation and process development are supported by satisfactory risk assessment summaries and optimisation studies. The submitted documentation is considered sufficient in order to get an overview of performed development studies and drug specific quality issues.

Abiraterone acetate is classified as a BCS class IV substance (low solubility and low permeability); therefore, the AS particle size is considered a relevant parameter which may have impact on the *in vivo* dissolution. AS with different particle size distributions (PSD) has studied during the development of the finished product and the PSD acceptance criteria have been defined accordingly. The pivotal bioequivalence study demonstrated that test product manufactured with AS with the defined PSD is bioequivalent with the reference product. The AS supplied by the two different suppliers described above is of the same quality; the PSD of the AS is controlled by common acceptance criteria.

Dissolution was investigated in various media in the range of physiological pH between 1.0 and 6.8. The choice of the dissolution method test conditions including the need for a surfactant has been discussed in sufficient detail. The use and quantity of surfactant in the formulation and dissolution medium is justified.

The data provided to prove the discriminatory power of the method is sufficient. The dissolution method has been shown to be discriminatory with regard to relevant formulation and critical material attributes (PSD) changes.

The dissolution profiles between test and reference product can be considered similar in the media intended for product batch release based on the investigations performed. In addition, comparative dissolution studies with the test biobatch versus the reference product biobatch have been conducted without surfactant as per the Guideline on the Investigation of Bioequivalence and additionally, under the same conditions with surfactant. The test the reference product profiles were shown similar by means of calculating the f2 similarity factor or visually, as appropriate.

Based on the QTPP, the physicochemical properties of the AS, the performed risk assessments and manufacturing experience gained through the development phase of this product, wet granulation was selected as manufacturing process. Initial manufacturing process development studies were performed on a laboratory scale and afterwards, the process was further qualified at a larger scale using equipment resembling that intended for commercial manufacture. The process has been optimised with regard to the granules' flowability properties and tablet hardness. Also, during process development blend and content uniformity, and dissolution profiles were evaluated and found to be within the pre-determined acceptable ranges. Based on the development activities conducted and the batches manufactured, acceptable ranges for critical process parameters (CPPs) of the manufacturing process at commercial scale have been established.

The proposed container closure system is common for this type of dosage form. Tablets are packaged in HDPE bottles fitted with a child-resistance tamper-evident PP closure. The materials comply with relevant directives and regulations on materials intended to come into contact with foodstuffs (i.e. EU No 10/2011, Ph. Eur. 3.2.2, Ph. Eur. 3.1.3). Compliance with ISO 8317 for the child-proof container was confirmed. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing site of Abiraterone Accord 250 mg tablets has been stated. The manufacturing process comprises three main phases: preparation of granulate, preparation of pre-compression blend and tablet compression. The commercial batch size range has been clearly stated and is acceptable. Wet granulation is applied during the manufacturing process. The manufacturing process is a standard process.

The IPCs are considered suitable for the control of the process parameters as defined during the development studies. The applicant has not defined any prolonged bulk holding times despite using many different packaging sites, hence it is assumed that bulk products are not stored over 30 days. It is confirmed and stated in the dossier that the start of shelf-life of the finished product is set in accordance with CPMP/QWP/072/96; this is acceptable.

The manufacturing process validation has been performed on three batches at the lower end of the batch size range. The results demonstrate that the proposed manufacturing process is capable of producing a product with consistent quality that meets the specifications. The process validation data were generated using AS from a single AS source. However, since this is a standard manufacturing process for a conventional product, process validation data covering the second AS supplier are not required to be submitted prior to authorisation. In addition, an acceptable process validation scheme, applicable to tablets produced with AS from either supplier, that will be applied for prospective validation of consecutive full-scale batches at the upper end of the batch size range has been presented.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (UV, UHPLC), assay (UHPLC), impurities (UHPLC), dissolution (Ph. Eur., UV) and uniformity of dosage units (Ph. Eur.).

Identification and uniformity of dosage units are tested only during release. This is acceptable as these are not considered stability indicating parameters. The limits for assay of the active substance have been justified based on the batch analysis and stability study results. The proposed limits for individual impurities have been tightened during the procedure and are in line with the thresholds according to ICH Q3B and also based on the stability results obtained during the stability studies. The shelf life limits stated for the known potential degradation impurities are higher than the ICH qualification threshold but are based on the stability results and have been toxicologically qualified considering a Maximum Daily Dose of 1,000 mg. The initially proposed dissolution limit was not in line with the *Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action* and CHMP requested in a MO that the limit is tightened in line with the reflection paper. The limit was subsequently tightened as requested. The absence of microbial testing at release and during end-of-shelf life is justified, based on the water activity studied during development and the microbial testing batch analysis results.

A satisfactory risk assessment summary on elemental impurities (EI) in accordance with ICH Q3D guideline was provided. The total EI contribution even for Pd (class 2B element) which is intentionally used in the AS production remains well below to the control threshold (defined as 30% of the established PDE) considering the maximum daily dose of 1000 mg. Batch analysis data on 14 AS batches have been presented; this data indicates that Pd levels in the finished product cannot exceed 30% of the respective PDE. Therefore, according to the ICH Q3D, no additional control is necessary for the finished product.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was submitted considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, no risk was identified and no additional control measures are deemed necessary.

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 data have been provided on three commercial scale batches of the finished product (including the biobatch) manufactured with AS from ASMF manufacturer #1. All the test results remain within the proposed specification limits. Batch results from an additional lab scale batch manufactured with a process equivalent to commercial manufacturing process using AS from ASMF manufacturer #2 were also presented. It is noted that the 500 mg film-coated tablets (see below in this report) were developed at production scale with AS from ASMF manufacture #2 while the 250mg tablets were developed using AS from ASMF manufacturer #1. Although lab scale batches may not present adequate information by themselves due to their small size, considering the simplicity of the manufacturing process and the similar excipients used, the

presented additional information is considered sufficient. It can be further accepted that both AS suppliers can be used to manufacture the 250 mg tablets.

Stability of the product

Stability data from three commercial scale batches, stored for up to 24 months under long term conditions (25±2°C / 60±5% RH), and for up to 6 months under accelerated conditions (40±2ºC / 75±5% RH), according to the ICH guidelines, were provided. These primary stability batches were manufactured at the proposed manufacturing site and were packaged in the proposed commercial container closure system.

Stability samples were tested for appearance, dissolution, assay, impurities and microbial contamination. For the microbial contamination the samples were tested using the relevant Ph. Eur. method. Regardless of the storage conditions, results comply with the specification limits at the time of testing. No trends were observed under all conditions.

Stability data from a lab scale batch made with active substance from one manufacturer stored for 12 months under long term conditions, and for 6 months under accelerated conditions has also been presented and compared with the stability results of the test product biobatch. With the exception of the out of specification (OOS) level of a degradation product, all other parameters were within the specification limits and comparable with those of the biobatch. The OOS results at release were attributed to the fact that the sample was analysed 3 months after production and not at release. The observed subsequent increase of some impurities in the product was similar compared to finished product batches with AS from one manufacturer and the reported result is within the acceptance criteria for end-of-shelf life (NMT 0.70%). It is therefore considered that the stability profiles of finished product batches manufactured with AS from either supplier are comparable.

A photostability study as per ICH Q1B guidance was conducted on a commercial scale batch. The results indicate that the product is stable when exposed to light.

An in-use stability study was designed to simulate daily use and was conducted on two commercial scale batches to support an in-use period of 60 days. This 60-day period was based on the labelling information. This study was performed with product packaged in the proposed container closure stored at 30ºC/ 75% RH. All tested samples complied with the acceptance criteria. No significant changes were observed. Hence, it is not necessary to lay down a separate in-use shelf-life in the product information.

A forced degradation study was also performed on a single batch exposing samples to light, thermal (humid and dry) degradation, oxidation by an oxidative agent, presence of metal ions, basic and acidic hydrolysis conditions. No significant degradation was observed under humid thermal, dry thermal and photolytic treatments. The degradation was significant under oxidative and acidic hydrolysis conditions and less prominent in the presence of metal ions and under basic hydrolysis conditions. This study also demonstrated that the analytical method for impurities is stability indicating.

Based on the overall submitted stability data, the proposed shelf-life of 2 years without any special storage condition, as stated in SmPC 6.3 and 6.4, is acceptable.

Adventitious agents

Lactose monohydrate used in Abiraterone Accord 250 mg tablets is of animal origin. 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.

500 mg film-coated tablets

Description of the product and pharmaceutical development

The finished product is presented as immediate-release oval-shaped purple film-coated tablets, approximately 19 mm long by 11 mm wide and debossed with "A7TN" on one side and "500" on the other side containing 500 mg of abiraterone acetate as active substance. The qualitative composition of Abiraterone Accord 500 mg tablets is in section 2.2.1 of this report and in SmPC section 6.1.

The formulation contains commonly used excipients for a product manufactured by means of a wet granulation process. All excipients used are well-known and widely used as pharmaceutical ingredients and comply with the current pharmacopoeial monographs and/or directives. Both generic and reference products have the same qualitative composition. The choice of the excipients was justified, and their functions explained. Compatibility between AS and excipients was assessed in binary mixtures of each excipient with AS stored at elevated temperatures and under refrigerated conditions. There was no observed interaction between the AS and the excipients. In addition, the AS retains its desired polymorphic form during storage of the finished product. These results were confirmed by accelerated stability data of the final drug product.

PSD was considered an important parameter because of possible influence on dissolution and bioavailability. Finished product containing ASs with different PSDs was tested for dissolution. Based on these studies, limits for PSD were defined, which were later confirmed by the pivotal bioequivalence study. The outcome of this bioequivalence study demonstrated that test product is bioequivalent to the reference product (Zytiga 500 mg).

The objective of the development of Abiraterone Accord 500 mg film-coated tablets was to develop a generic product which is bioequivalent and has a similar dissolution and stability profile with the reference product Zytiga 500 mg. Quality by Design was applied to develop the generic product.

A QTPP was defined for the 500 mg film-coated tablets taking into account clinical and PK characteristics, *in vitro* dissolution, physicochemical characteristics of the reference product and intellectual property restrictions.

A risk assessment (RA) was performed to identify critical formulation variables and their influence on CQAs. The AS attributes of abiraterone ranked as high/medium risk in the initial AS RA were included in the initial RA of the formulation. Based on that, the different formulation variables and their influence on the high/medium risked CQAs were studied.

The formulation development has been clearly presented. The impact of filler type, glidant, amount of surfactant, disintegrant, amount of binder, AS PSD and coating on the relevant product quality attributes and on the manufacturing process were investigated by purposely designed studies. Based on the outcome of the formulation development studies, the RA was updated. The final proposed commercial formulation as presented above was defined.

Dissolution was investigated in various media in the range of physiological pH between 1.0 and 6.8. The choice of the dissolution method test conditions including the need for a surfactant and its quantity has been discussed in sufficient detail and are justified. The data provided to prove the discriminatory power of the

method is sufficient. The dissolution method has been shown to be discriminatory with regard to relevant meaningful formulation changes.

The dissolution profiles between test and reference products can be considered similar in the medium intended for product batch release based on the investigations performed. In addition, comparative dissolution studies with the test biobatch versus the reference product biobatch have been conducted without surfactant as per the Guideline on the Investigation of Bioequivalence. The test the reference product profiles were shown to be similar by means of calculating the f2 similarity factor or visually, as appropriate.

Based on the QTPP, the physicochemical properties of the AS, the performed risk assessments and manufacturing experience gained through the development phase of this product, wet granulation was selected as was the case for the 250 mg tablets. Potentially CPPs were studied in all the steps of the manufacturing process. Based on the development activities conducted and the batches manufactured, acceptable ranges for CPPs for the manufacturing process at commercial scale have been established.

The finished product is packaged into transparent Polyvinyl Chloride (PVC) / Polyvinylidene Chloride (PVDC) / Aluminium (Al) blisters. The materials comply with relevant directives and regulations on materials intended to come into contact with foodstuffs (i.e. EU No 10/2011, Ph. Eur. 3.2.2, Ph. Eur. 3.1.3). The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing site for Abiraterone Accord 500 mg film-coated tablets has been stated. The manufacturing process comprises 6 main steps: preparation of blend 1, granulation, preparation of blend 2, preparation of final blend, tablet compression and film-coating. The commercial batch size range has been clearly stated and is acceptable. Wet granulation is applied during the manufacturing process. The manufacturing process is a standard process.

The IPCs are considered suitable for the control of the process parameters as defined during the development studies. Bulk holding times have not been defined; it is confirmed and stated in the dossier that the start of shelf-life of the finished product is set in accordance with CPMP/QWP/072/96; this is acceptable.

The manufacturing process validation has been performed on three batches at the lower end of the batch size range. The results demonstrate that the proposed manufacturing process is capable of producing a product with consistent quality that meets the specifications. The process validation data generated using AS from a single AS source. However, since this is a standard manufacturing process for a conventional product, process validation data covering the second AS supplier are not required to be submitted prior to authorisation. In addition, an acceptable process validation scheme, applicable to film-coated tablets produced with AS from either supplier, that will be applied for prospective validation of consecutive full-scale batches at the upper end of the batch size range has been presented.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), identification (UV, UHPLC), assay (UHPLC), impurities (UHPLC), dissolution (Ph. Eur., UV) and uniformity of dosage units (Ph. Eur.).

Identification and uniformity of dosage units are tested only during release, which is acceptable as these are not considered stability indicating parameters. The limits for assay of active substance are the same as for

the 250 mg tablets; they have been tightened during the procedure and have been justified based on the batch analysis and stability study results.

The proposed limits for individual impurities are the same as for the 250 mg tablets; they have been tightened during the procedure and are in line with the thresholds according to ICH Q3B and also based on the stability results obtained during the stability studies. The shelf life limits stated for the known potential degradation impurities are higher than the ICH qualification threshold but are based on the stability results and have been toxicologically qualified considering a Maximum Daily Dose of 1,000 mg.

The dissolution limit was set in accordance with the *Reflection paper on the dissolution specification for generic* solid oral immediate release products with systemic action.

As for the 250 mg, the absence of microbial testing at release and during end-of-shelf life was justified, based on the water activity studied during development and the microbial testing batch analysis results.

A satisfactory risk assessment summary on EI in accordance with ICH Q3D guideline was provided. The total EI contribution even for Pd (class 2B element) which is intentionally used in the AS production remains well below to the control threshold (defined as 30% of the established PDE) considering the maximum daily dose of 1000 mg. Batch analysis data on 14 AS batches have been presented; this data indicates that Pd levels in the finished product cannot exceed 30% of the respective PDE. Therefore, according to the ICH Q3D, no additional control is necessary for the finished product.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product was submitted considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, no risk was identified, and no additional control measures are deemed necessary.

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 on the market based on the above release specifications, through traditional final product release testing.

Batch analysis data have been provided on three commercial scale batches of the finished product (including the biobatch) manufactured with AS from ASMF manufacturer #2. All the test results remain within the proposed specification limits. Batch results from an additional lab scale batch manufactured with a process equivalent to commercial manufacturing process using AS from ASMF manufacturer #1 were also presented. It is noted that the 250 mg tablets (see above in this report) were developed at production scale with AS from manufacturer #1 while the 500 mg tablets were developed using AS from ASMF manufacturer #2. Although lab scale batches may not present adequate information by themselves due to their small size, considering the simplicity of the manufacturing process and the similar excipients used, the presented additional information is considered sufficient. It can be further accepted that both AS suppliers can be used to manufacture the 500 mg film-coated tablets.

Stability of the product

Stability data from three commercial scale batches, stored for up to 18 months under long term conditions (25±2°C / 60±5% RH), and for up to 6 months under accelerated conditions (40±2ºC / 75±5% RH), according to the ICH guidelines, were provided. These primary stability batches were manufactured at the proposed manufacturing site and were packaged in the proposed commercial container closure system and in addition, in HDPE bottles (as supportive data).

Stability samples were tested for appearance, dissolution, assay, impurities, water activity and microbial contamination. For the microbial contamination, the samples were tested using the relevant Ph. Eur. method; the methodology for the water activity study was presented in the pharmaceutical development section. Regardless of the storage conditions, results complied with the specification limits at the time of testing. No trends were observed under all conditions.

Stability data from a lab scale batch made with active substance from ASMF manufacturer #1 stored for 12 months under long term conditions, and for 6 months under accelerated conditions has also been presented and compared with the stability results of the 500 mg test product biobatch. All parameters were within the specification limits and comparable with those of the biobatch. It is therefore considered that the stability profiles of finished product batches manufactured with AS from either supplier are comparable.

A photostability study as per ICH Q1B guidance was conducted on a commercial scale batch. The results indicate that the product is stable when exposed to light.

Supportive data from an in-use stability study designed to simulate worst-case scenario and conducted on one commercial scale batch in an open container (HDPE bottle container) over 90 days, stored at 25ºC / 60% RH was provided too. The evaluation of data demonstrates that no significant change is observed. Since the HDPE bottle container is not intended for marketing, it is not necessary to lay down an in-use shelf-life in the product information.

A forced degradation study was also performed on a single batch exposing samples to light, thermal (humid and dry) degradation, oxidation by an oxidative agent, presence of metal ions, basic and acidic hydrolysis conditions. No significant degradation was observed under photolytic, humid thermal or dry thermal treatments. The degradation was significant in the presence of metal ions, and under acidic hydrolysis, basic hydrolysis and oxidative conditions. This study also demonstrated that the analytical method for impurities is stability indicating.

Based on the overall submitted stability data, the proposed shelf-life of 2 years without any special storage condition, as stated in SmPC 6.3 and 6.4, is acceptable.

Adventitious agents

Lactose monohydrate used in Abiraterone Accord 500 mg film-coated tablets is of animal origin. 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.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance has been presented in a satisfactory manner. The active substance is supplied by two manufacturers. A MO was raised in relation to a starting material (SM) and the initial proposal for alternative synthetic processes by ASMF manufacturer #1; it has been resolved by redefining the SM and clearly define a single process. Another MO, linked with the redefinition of the SM, concerning the information on all potential impurities related to AS from ASMF manufacturer #1, has also been resolved by the provision of updated discussion and the relevant dossier updating. The active substance is controlled by the same set of specification for both sources. The overall control strategy applied by both AS manufacturers and the applicant is adequately justified and is acceptable.

The finished product is a 250 mg tablet and a 500 mg film-coated tablet generic of Zytiga. Information on development, manufacture and control of the finished product has also been presented in a satisfactory manner. A MO raised regarding the initially proposed dissolution test limits for the 250 mg tablet has been resolved by tightening the limit in line with existing guidance. The manufacturing process for both the tablets and the film-coated tablets is a standard manufacturing process and sufficient process validation data has been provided. Active substance from both suppliers can be used to manufacture both the 250 mg tablet and the 500 mg film-coated tablets of comparable quality. Bioequivalence of both the tablets and the film-coated tablets with the reference product has been demonstrated.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. 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. Pharmacodynamic, pharmacokinetic and toxicological properties of abiraterone are well known. As abiraterone is a widely used, well-known active substance. 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.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Abiraterone Accord manufactured by Accord Healthcare S.L.U. 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.

The applicant presented data on the environmental exposure of the active substance in line with the question 1 in 'Questions and answers' in 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010 Rev. 1).

In 2019, abiraterone sales in the EU (including the UK) totalled 11,779 kg. In the EU no generic abiraterone containing product is available yet. In the USA, generic abiraterone products are available since 2017, and market data indicate that a 15% increase could occur in 2020 compared to 2018 sales volumes. The impact on the sales volumes of abiraterone products has been assessed assuming a market volume increase of 20% in the European market as a worst-case estimate. This will amount in 14,134 kg abiraterone being used (including UK and when using 2019 as the reference year).

Based on 2019 total actual API sales, the PEC value for abiraterone is 0,036 µg/L (the worst-case estimate, no removal in WWTP or refinement used, EU population 447,7 million). The PNEC value for abiraterone is 0.0013 µg/L, which results in PEC/PNEC value of 27,72. Assuming a market volume increase of 20%, the calculated PEC is 0,0432, and PEC/PNEC value is 33,27.

The PNEC value used is available in the public domain, i.e. in the Swedish FASS.

The environmental risk for use of Abiraterone acetate was concluded for the originator product: Based on daily dose 1000 mg/day, the initial PEC was 5 µg/L. Considering refinement due to waste water treatment plant removal (removal rate of 87,2%) and market penetration (based on 2019 sales), the refined PEC was 0,0046 µg/L, and PEC/PNEC was 3,56 for fish (modified partial life-cycle exposure test to identify endocrine disrupting properties). Abiraterone is metabolised into two inactive metabolites (abiraterone sulfate and N-oxide abiraterone sulfate), excreted in faeces (~88%) and urine (~5%), but the major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively), the substance largely not being biodegradable but shifting to the sediment. No risk was identified in the Tier IIB studies of the originator for sediment dwelling organisms (lowest NOEC was 100 mg/kg). Refinement considerations for abiraterone PECwater show Koc values that indicate most of abiraterone remains or has a significant retention time in the sludge in WWTPs. Abiraterone will degrade in the aquatic environment with an aerobic degradation half-life in water of 2.3 days and of 3.3 days in aquatic sediment systems, and potential impacts for sediment/soil organisms are much lower than in aquatic compartment (data not shown).

2.3.3. Discussion on non-clinical aspects

The non-clinical overview is based on published literature data. This is acceptable since abiraterone is well known active substance and essential similarity is claimed to the reference product. There are no new non-clinical studies performed in support of the proposed application hence the presented Non-clinical Overview is considered sufficient for this type of MAA.

The applicant has provided brief comparative assessment of PEC/PNEC calculations before and after generic introduction. A market volume increase of 20% in the European market is a reasonable worst-case estimate,

thus, it can be agreed that the increase of the PEC/PNEC is not expected to significantly alter the environmental impact of abiraterone.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Abiraterone Accord 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. Information provided on the ERA is sufficient.

2.4. Clinical aspects

2.4.1. Introduction

This application concerns a generic application of a centrally authorised medicinal product according to Art. 10 (1) of Directive 2001/83/EC.

The reference product for the application is Zytiga 250 mg tablets and Zytiga 500 mg film-coated tablets by Janssen-Cilag International NV, Belgium. The community granted first marketing authorisation of the reference product Zytiga® on 07/09/2011 under number EMEA/H/C/002321.

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).

To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting conditions.

The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

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, as the application concerns two different formulations:

2.4.2. Pharmacokinetics

Study No. ARL/15/277 A randomized, two-treatment, four-period, two-sequence, single-dose, full-replicate crossover, bioequivalence study comparing abiraterone acetate **250 mg tablets** and Zytiga 250 mg

tablets, in healthy, adult, male volunteers under fasting conditions.

Methods

Study design

Study ARL/15/277 was a randomized, two-treatment, four-period, two-sequence, single-dose, full-replicate crossover bioequivalence study in healthy, adult, male volunteers under fasting conditions with a wash out period of 7 days between two administrations. In each period single oral dose of either test or reference product of abiraterone acetate **uncoated 250 mg tablets** was administered.

Administrative data

CRO: Accutest Research Laboratories India (I) Pvt. Ltd., A-31, M.I.D.C, TTC Industrial Area, Khairane, Navi Mumbai – 400 709, Maharashtra, India.

Sponsor: Synthon B.V., The Netherlands

Site and dates of clinical and analytical part of the study: Accutest Research Lab (I) Pvt. Ltd., India. Clinical part: Oct 15 to Nov 09, 2015. Analytical part: Nov 19, 2015 to Apr 06, 2016

Study Protocol version 02 dated Aug 05, 2015 and the informed consent forms were approved by Independent Ethics Committee on Aug 19, 2015. The Amendment to protocol and other related documents were reviewed and approved by the members of Independent Ethics Committee on Oct 01, 2015.

Food and fluid intake

The subjects were confined within the facility from at least 10.50 hours before dosing until 24.00 hrs post-dose in each study period. Blood samples at 36, 48 and 72 hrs post-dose were collected on ambulatory basis. After an overnight fast of at least 10 hours, subjects were administered a single 250 mg dose of a tablet of either the test or the reference product in sitting posture with 240 mL of drinking water. Subjects received lunch at least 4 hours after dosing in each period and further meals were served at appropriate intervals from then on. Water was not permitted 1 hour before dosing until 1 hours post-dosing. At all other times drinking water was given ad libitum.

Sampling schedule

A total of 18 blood samples (5 mL each) were collected from the subjects in K_2EDTA vacutainers during each study period at pre-dose (collected within 1 hr prior to dosing), 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hrs post-dose. There was a 7-day washout period between each of the four study periods. The total blood volume collected per subject was 401 mL.

Test and reference products

Test Product: Abiraterone acetate 250 mg tablets by Synthon Hispania S.L., Spain/Synthon BV, The Netherlands; batch No. 150047; batch size: 100,000 tablets (commercial batch size); manufacturing date: Sept 03, 2015, expiry date: Sept 2016.

Reference Product: ZYTIGA 250 mg tablets by Janssen-Cilag International NV, Belgia; Lot No.: EFZS200 from German market; expiry date: May 2016.

Population(s) studied

A total of 50 healthy male subjects (Asian race, aged 20 – 43 years, BMI 18.71 – 29.76 kg/m^2) were enrolled in the study. Only non-smokers were allowed in this study.

49 subjects completed the clinical phase of the study and received twice test and reference product. The plasma samples of the 50 subjects were analysed and considered for pharmacokinetic and statistical analysis. Data of 49 subjects was considered for within subject CV calculations.

Dropouts:

Subject No.44 was withdrawn due to adverse event (fever) after dosing in period IV. Subject No. 44 completed first three study periods (Period I, II and III) successfully and hence was considered for pharmacokinetic analysis. Data of subject no. 44 was not considered for calculation of within subject CV as he did not complete at least two reference treatment periods.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method over a concentration range of 0.201 ng/mL to 100.018 ng/mL for abiraterone. Study drug was extracted from 200 µl of plasma using solid phase extraction. Abiraterone-D4 was used as internal standard. Further partial method validation was done on additional instrument with lower limit of quantification 0.202 ng/mL with linearity range 0.202 ng/mL to 99.957 ng/mL.

Blood samples were collected into K_2EDTA tubes and centrifuged within 60 minutes after the last blood draw at 3500 RPM for 10 minutes at 5°C ± 3°C. In each 1 mL plasma aliquot (analytical and control), 0.2 mL of 1M Ascorbic acid solution was added immediately and mixed. All plasma samples were stored at -20°C ± 5ºC until the analysis. The bioanalyses were carried out between Nov 19, 2015 and Apr 06, 2016.

9 non-zero calibrates and 4 levels of QC samples were used. LOQ was 0.201 ng/mL. The quality control (QC) concentrations were 0.201 (LOQ QC), 0.601 (low), 12.015 (low medium), 35.044 (medium), 80.099 (high) and 160.199 (dilution) ng/mL. Four QC samples with concentrations 0.602 (LQC), 12.041 (M1QC), 35.120 (MQC) and 80.275 (HQC) ng/mL were used for study sample analysis.

The linear calibration curve calculated by weighted linear regression (weight = $1/x^2$) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report are provided. The method selectivity and sensitivity were demonstrated. Stability of analytes at various conditions during storage, sample preparation and analysis was shown according to the requirements for bio-analytical method validation. Dilution integrity, carryover and matrix effect were tested. The mean recovery from plasma was 71.3% for abiraterone.

Study sample analysis: Accuracy and precision of the back-calculated concentrations of the calibration curve standard points during the study were 98.6 to 101.4% and 1.6 to 3.3%, respectively. The between run precision and accuracy of quality control samples were 2.3 to 4.6% and 98.2 to 101.0 %, respectively. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 400 samples (11.15% of 3587 samples). 93.75% (25/400) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

The maximum study sample storage period from first blood draw (Oct 16, 2015) to last sample analysis (Apr 06, 2016) was 173 days. The long-term stability data of abiraterone in human plasma covers 186 days at -20±5°C.

All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 3587 study samples were received and analysed in 59 accepted analytical runs. 31 (0.86%) samples were re-assayed for analytical reasons (sample outside assay range, inconsistent internal standard area response).

Pharmacokinetic variables

Primary variables were C_{max} and AUC_{0-72}.

Secondary pharmacokinetic parameters determined were $AUC_{0-\infty}$, T_{max}, residual area, K_{el}, and $t_{½}$.

Statistical methods

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile. Statistical comparison of the PK of the two formulations was carried out using PROC GLM of SAS® Version 9.2 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

PK parameters for each individual were tabulated and graphically presented. Actual time-points of the sample collection are used for the calculation of PK parameters. All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-72} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. ANOVA model included sequences, subjects nested within sequence, period and treatment as fixed factors.

Criteria for conclusion of bioequivalence:

For AUC_{0-72} and if for C_{max} the within-subject variability of reference product (S_{WR}) was <= 30%, the acceptance range is 80.00-125.00% for Abiraterone.

If it was demonstrated that the within-subject variability of reference product (S_{WR}) for C_{max} is >30% as assessed using replicate design, then widened acceptance criteria for C_{max} would be considered.

Results

Table 1. Pharmacokinetic parameters for abiraterone (non-transformed values; 250 mg dosage strength)

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean **geometric mean**	**SD**	**arithmetic mean** **geometric mean**	**SD**
$AUC_{(0-72h)}$ (ng*hr/mL)	**246.14** 204.53	± 149.77	**233.70** 197.65	± 136.71

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean geometric mean	**SD**	**arithmetic mean geometric mean**	**SD**
$AUC_{(0-\infty)}$ (ng*hr/mL)	**252.90** 211.93	±151.06	**240.05** 205.53	±136.78
C_{max} (ng/mL)	**45.79** 35.40	±35.63	**44.44** 35.52	±29.62
T_{max}* (hrs)	2.00	0.50 - 12.00	2.00	0.50- 5.00
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2. Statistical analysis for abiraterone (ln-transformed values), N=50

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*	Within subject variability of reference product (%)
$AUC_{(0-72h)}$	103.48	95.95 - 111.61	33.04	**29.58**
C_{max}	99.66	90.66 - 109.56	42.01	**36.08 (N=49)**
* estimated from the Residual Mean Squares				

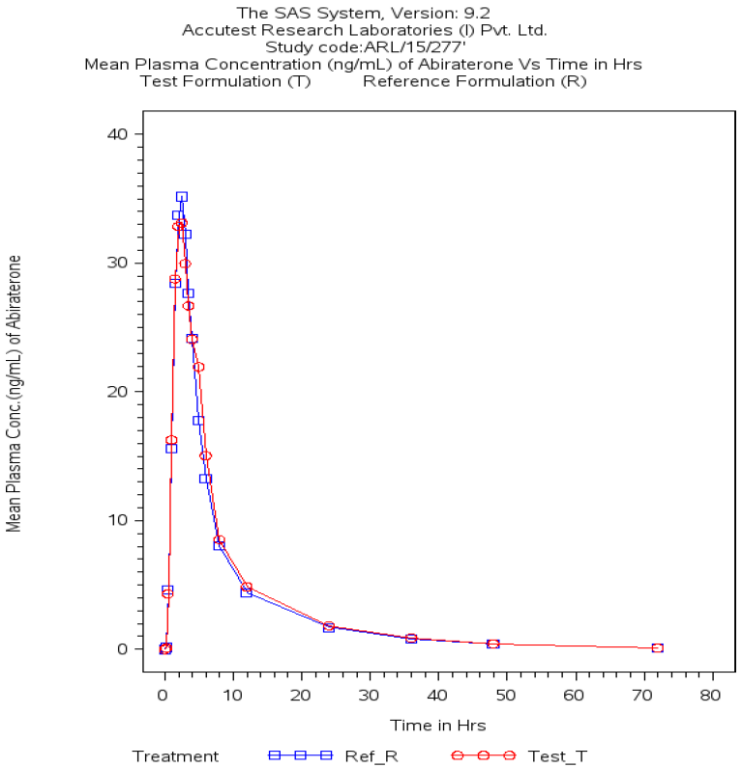

Figure 2. Mean plasma concentration vs. time curve for abiraterone after administration of Test and Reference formulations (250 mg) to healthy subjects (N=50).

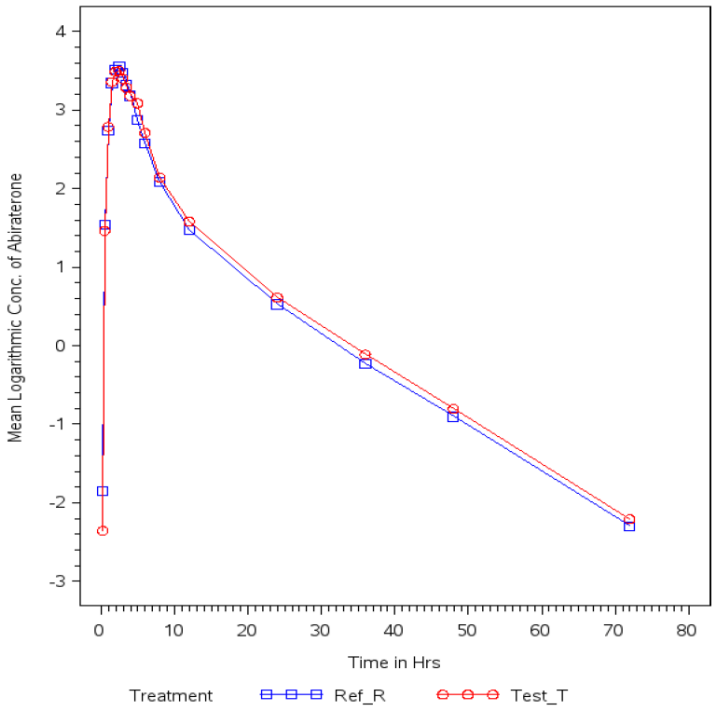

Figure 3. Semi-logarithmic plot of mean plasma concentration vs. time curve for abiraterone after administration of Test and Reference formulations (250 mg) to healthy subjects (N=50).

Safety data

A total of four AEs were reported during the clinical phase of the study of which, three AEs (bradycardia) were possibly related to study drug and one AE (fever) was not related to study drug. The AEs were mild to moderate in severity and were resolved.

No serious AEs were observed during the clinical phase.

Study No. ARL/18/135 A randomized, blinded, balanced, two-treatment, four-period, two sequence, single dose, full replicate, crossover, bioequivalence study of test product abiraterone acetate **500 mg film-coated tablets** with reference product Zytiga 500 mg film-coated tablets in healthy, adult, male volunteers under fasting conditions.

Methods

Study design

Study ARL/18/135 was designed as a single centre, randomized, open label, two-treatment, four-period, two sequence, single dose, full replicate crossover bioequivalence study in healthy, adult, male volunteers under fasting conditions with a wash out period of 7 days between two administrations. In each period single oral dose of either test or reference product of abiraterone acetate **500 mg film-coated tablets** was administered.

Administrative data

CRO: Accutest Research Laboratories India (I) Pvt. Ltd., India.

Sponsor: Synthon B.V., The Netherlands

Site and dates of clinical and analytical part of the study: Accutest Research Lab (I) Pvt. Ltd., India. Clinical part: Nov 19, 2018 to Jan 02, 2019. Analytical part: Dec 24, 2018 to Jan 19, 2019

Study Protocol version 01 dated Aug 27, 2018 and the informed consent forms were approved by Independent Ethics Committee on Sept 09, 2018.

The final report version 01 is dated July 02, 2019.

Food and fluid intake

Following an overnight fast of at least 10 hours, a single oral dose 500 mg film-coated tablet of either the test or the reference product was administered to the trial subjects with 240 mL of water. Plasma samples were taken at regular intervals during 72 hours after dose administration. There was a washout period of at least 7 days between each of the four study periods.

Sampling schedule

A total of 18 blood samples (5 mL each) were collected from the subjects in K_2EDTA vacutainers during each study period at pre-dose (collected within 1 hr prior to dosing), 0.25, 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hrs post-dose.

Test and reference products

Test Product: Abiraterone acetate 500 mg film-coated tablets by Synthon Hispania S.L., Spain/Synthon BV, The Netherlands; batch No. 180025A; batch size: 100,000 tablets (commercial batch size); manufacturing date: July 04, 2018, expiry date: Jan 2019.

Reference Product: ZYTIGA® 500 mg film-coated tablets by Janssen-Cilag International NV, Belgia; Lot No.: IDZT100; expiry date: Mar 2020.

Population(s) studied

A total of 50 healthy male subjects (Asian race, aged 22 – 43 years, BMI 19.43 – 29.09 kg/m^2) were enrolled in the study. Only non-smokers were allowed.

47 subjects completed all four study periods, one subject completed the first 3 study periods, and two subjects completed only one study period. The plasma samples of all 50 subjects were analysed. 48 subjects were included for pharmacokinetic and statistical analyses. Data of 47 subjects were considered for calculation of within-subject variability of the reference product.

Dropouts:

Three dropouts: Subject No.01 and No.43 were withdrawn due to personal reason on check-in day of period II. Subject No. 07 was withdrawn due to adverse event (high serum potassium) noted in pre enrolment health check-up for period IV.

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method over a concentration range of 0.401 ng/mL to 200.381 ng/mL for abiraterone. Study drug was extracted from 200 µl of plasma using solid phase extraction. Abiraterone-D4 was used as internal standard.

Blood samples were collected into K_2EDTA tubes and centrifuged within 60 minutes after the last blood draw at 3500 RPM for 10 minutes at 5°C ± 3°C. In each 1 mL plasma aliquot (analytical and control), 0.2 mL of 1M Ascorbic acid solution was added immediately and mixed. All plasma samples were stored at -20°C ± 5ºC until the analysis. The bioanalyses were carried out between Dec 24, 2018 and Jan 19, 2019.

9 non-zero calibrates and 5 levels of QC samples were used. LOQ was 0.401 ng/mL. The quality control (QC) concentrations were 0.401 (LOQ QC), 1.203 (low), 24.06 (low medium), 70.175 (medium), 160.399 (high) and 801.996 (dilution) ng/mL.

The linear calibration curve calculated by weighted linear regression (weight = 1/x^2) was used for calculation of sample concentration.

Pre-study validation and bio-analytical report are provided.

Study sample analysis: Accuracy and precision of the back-calculated concentrations of the calibration curve standard points during the study were 98.75 to 100.74% and 1.23 to 2.33%, respectively. The between run precision and accuracy of quality control samples were 1.01 to 3.72% and 98.25 to 104.12 %, respectively. Composition of analytical runs has been described.

Incurred sample reanalysis was conducted on 386 samples (11.14% of 3466 samples). 96.89% (374/386) of concentrations obtained by reanalysis were found within 20% of their mean initial value.

The maximum study sample storage period from first blood draw (Nov 20, 2018) to last sample analysis (Jan 19, 2019) was 60 days. The long-term stability data of abiraterone in human plasma covers 62 days at -20±5°C and at -70±10°C.

All concentration values below limit of quantification were set as zero for PK analysis.

Reanalysis of study samples: A total of 3466 study samples were received and analysed in 53 valid analytical runs. 116 samples (3.35%) were haemolysed. 44 (1.27%) samples were re-assayed for analytical reasons (sample outside assay range, inconsistent internal standard area response, poor chromatography).

Pharmacokinetic variables

Primary variables were C_{max} and AUC_{0-72}.

Secondary pharmacokinetic parameters determined were $AUC_{0-\infty}$, T_{max}, residual area, K_{el}, and $t_{½}$.

Statistical methods

The pharmacokinetic parameters were calculated from the plasma concentration vs. time profile. Statistical comparison of the PK of the two formulations was carried out using PROC GLM of SAS® Version 9.2 (SAS Institute Inc., USA) to assess the bioequivalence between test and reference formulations.

PK parameters for each individual were tabulated and graphically presented. Actual time-points of the sample collection are used for the calculation of PK parameters. All concentration values below the lower limit of quantification are set to zero for the pharmacokinetic and statistical calculations. Individual AUC parameters were calculated using the linear trapezoidal rule. ANOVA was performed on the ln-transformed C_{max}, AUC_{0-72} and $AUC_{0-\infty}$. Non-parametric analysis of t_{max} was performed on untransformed data. ANOVA model included sequences, subjects nested within sequence, period and treatment as fixed factors.

Criteria for conclusion of bioequivalence:

For AUC_{0-72} and if for C_{max} the within-subject variability of reference product was <= 30%, the acceptance range is 80.00-125.00% for Abiraterone.

If it was demonstrated that the within-subject variability of reference product for C_{max} is >30% as assessed using replicate design, then widened acceptance criteria for C_{max} would be considered.

Results

Table 3. Pharmacokinetic parameters for abiraterone (non-transformed values; 500 mg dosage strength), N=48

Pharmacokinetic parameter	**Test**		**Reference**	
	arithmetic mean **geometric mean**	**SD** **CV%**	**arithmetic mean** **geometric mean**	**SD** **CV%**
$AUC_{(0-72h)}$ (ng*hr/mL)	**484.71** 401.20	± 285.51 60.0%	**501.63** 400.04	± 334.31 68.5%

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean geometric mean	**SD CV%**	**arithmetic mean geometric mean**	**SD CV%**
$AUC_{(0-\infty)}$ (ng*hr/mL)	**471.75** 414.78	±283.21 58.9%	**488.14** 413.80	±337.97 67.4%
C_{max} (ng/mL)	**90.33** 71.49	±69.76 77.2%	**94.15** 73.53	±73.03 77.6%
T_{max}* (hrs)	2.00	0.50 - 5.00	2.00	1.00- 5.00
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4. Statistical analysis for abiraterone (ln-transformed values, 500 mg dosage strength), N=48

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals (%)	CV%*	Within subject variability of reference product (%)
$AUC_{(0-72h)}$	100.29	92.95 - 108.20	32.48	n.a
$AUC_{(0-\infty)}$	100.24	93.06 – 107.96	31.71	n.a.
C_{max}	97.22	88.02 - 107.39	43.30	**40.36 (N=47)**
* estimated from the Residual Mean Squares				

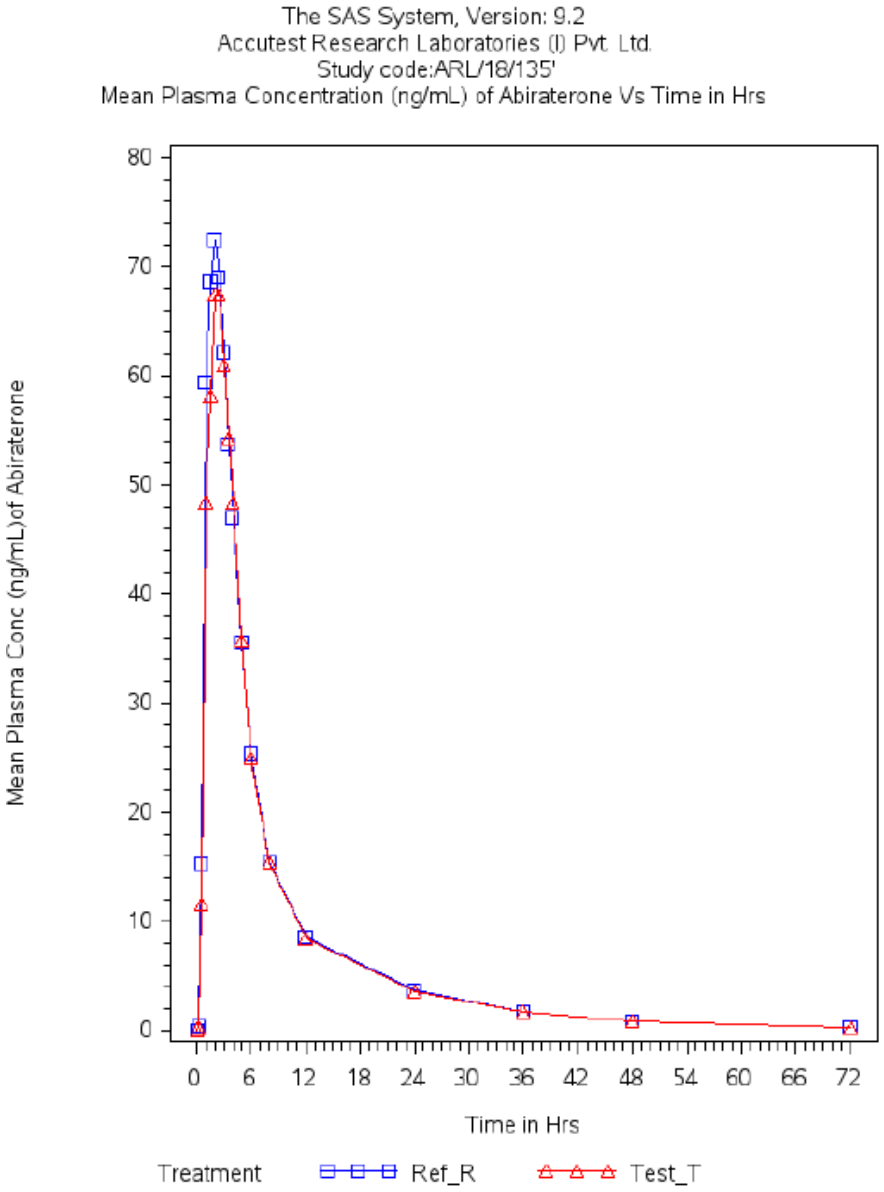

Figure 4. Mean plasma concentration vs. time curve for abiraterone after administration of Test and Reference formulations (500 mg) to healthy subjects (N=48).

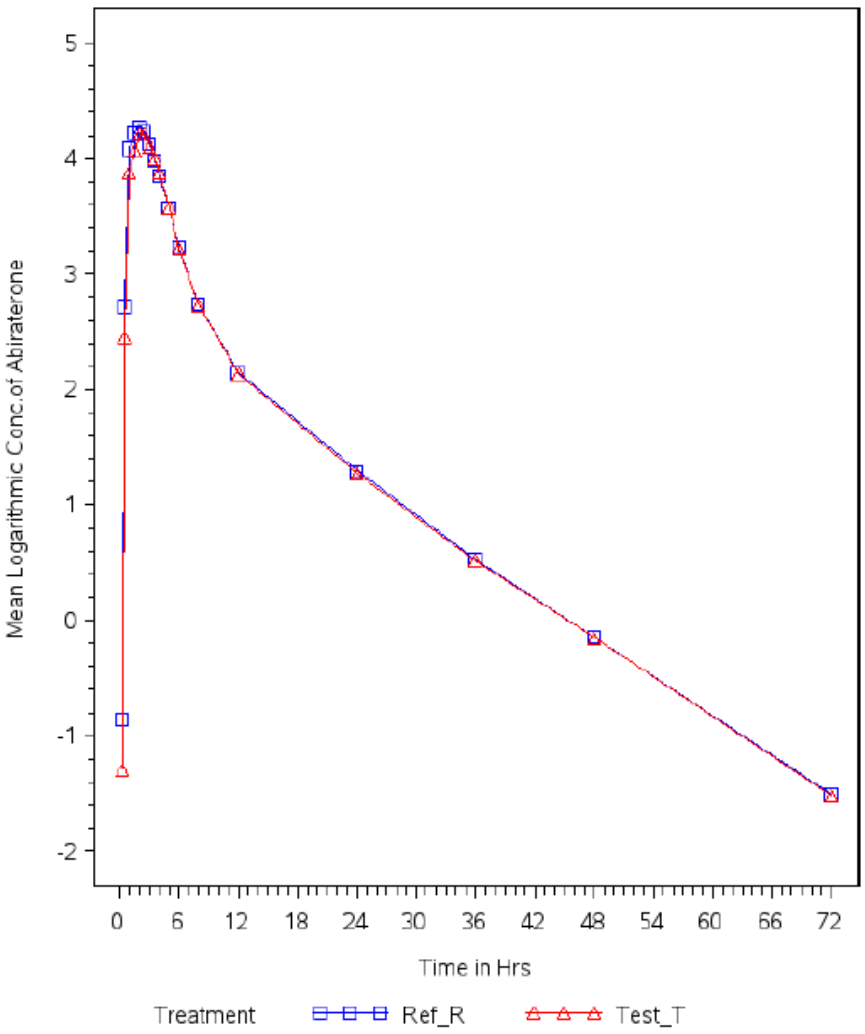

Figure 5. Semi-logarithmic plot of mean plasma concentration vs. time curve for abiraterone after administration of Test and Reference formulations (500 mg) to healthy subjects (N=48).

Safety data

A total of thirteen AEs were reported during the clinical phase of the study which were mild in severity. Nine (headache, bradycardia, high serum alkaline phosphatase, low haemoglobin, high SGPT, throat pain) AEs were related to study drug and four (neck pain, high eosinophil count, high WBC count, high serum potassium) AEs were unrelated to study drug. All AEs were resolved except the AEs high WBC count, high SGPT and high serum alkaline phosphatase. Three subjects with one AE each (high WBC count, high SGPT and high serum alkaline phosphatase) were considered as lost to follow up.

No serious AEs were observed during the entire clinical phase of the study.

Conclusions

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

2.4.3. Pharmacodynamics

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

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

To support the application, the applicant has submitted two single dose four-period replicate crossover design bioequivalence studies under fasting conditions to demonstrate essential similarity with Zytiga 250 mg uncoated tablets and Zytiga 500 mg film-coated tablets by Janssen-Cilag International NV, Belgium.

The recommended dose of Abiraterone acetate is 1000 mg as a single daily dose that must not be taken with food, therefore, the conduct of bioequivalence study under fasting conditions is justified. One bioequivalence study was performed for each strength applied in order to demonstrate equivalence directly between respective test and reference dosage strength and formulations *in vivo*. The applicant had suspected high intra-subject variability in abiraterone absorption and therefore proposed widened BE acceptance range for C_{max}. As the request for wider acceptance interval is prospectively specified in the study protocols and studies designed accordingly (i.e. replicate 4-period crossover design), the widening of acceptance criteria is considered acceptable.

Overall design of BE studies is acceptable and in line with pharmacokinetic properties of abiraterone. Both studies were conducted under standardised conditions. The study populations were chosen according to the guidelines. 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 sampling period was sufficient, the sampling time schedule and wash-out period were adequate taking into account the t_{max} and elimination half-life of abiraterone. The sampling schedule was sufficient for immediate release formulation and reached up to 72 hours. Data regarding the test and reference products were generally adequate, the country of origin for purchasing the reference batches and the information about the county of origin of the reference product batches provided.

Bioanalytical methods had satisfactory performance and were adequately validated. The pharmacokinetic and statistical methods applied were appropriate for single-dose studies.

In both studies, the 90% confidence intervals for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-72} and $AUC_{0-\infty}$ were within the conventional bioequivalence range of 80.00% to 125.00%. The pharmacokinetic variables determined for abiraterone were comparable between test and reference products. Both formulations were relatively well tolerated.

2.4.6. Conclusions on clinical aspects

Based on the presented bioequivalence studies, Abiraterone Accord 250mg tablets and 500mg film-coated tablets are considered bioequivalent with Zytiga 250 mg tablets and Zytiga 500 mg film-coated tablets by Janssen-Cilag International NV, Belgium. The application is approvable from the clinical perspective.

2.5. Risk management plan

Safety concerns

List 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.

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Conclusion

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

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 Solifenacin succinate 5/10mg film-coated tablets and ZYTIGA 250/500 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 250 and 500 mg 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 form the pivotal basis with a randomized, two-treatment, four-period, two-sequence, single-dose, crossover design in healthy, adult, male volunteers under fasting conditions. 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 Accord met the protocol-defined criteria for bioequivalence when compared with Zytiga in both studies. The point estimates and their 90% confidence intervals for the parameters AUC_{0-72}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. 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 Accord is favourable in the following indication:

Abiraterone Accord 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.