COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Abirateron Stada 250 mg and 500 mg, film-coated tablets (abiraterone acetate)

NL/H/5602/001-002/MR

Date: 22 February 2023

This module reflects the scientific discussion for the approval of Abirateron Stada 250 and 500 mg, film-coated tablets. The procedure was finalised on 13 July 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADT	Androgen Deprivation Therapy
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration Resistant Prostate Cancer
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
MRP	Mutual recognition procedure
Ph.Eur.	European Pharmacopoeia
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Abirateron Stada 250 and 500 mg, film-coated tablets, from Stada Arzneimittel AG.

The product 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.

A comprehensive description of the indications and posology is given in the SmPC.

This is a MRP originating from a duplex of procedure NL/H/5220/001-002/DC, which was finalised on 21 April 2021. The original decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zytiga 250 mg tablets and 500 mg film-coated tablets which have been registered in the EEA by Janssen-Cilag International N.V. since September 2011 via the centralised procedure (EU/1/11/714). These are the reference products for this mutual recognitions procedure for Abirateron Stada.

The concerned member states (CMS) involved in this procedure were Estonia, Latvia and Lithuania.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Abirateron Stada are film-coated tablets:

- The 250 mg strength tablets are white to off-white, oval-shaped film-coated tablets, debossed with “250” on one side and contain as active substance 250 mg of abiraterone acetate.
- The 500 mg strength tablets are purple, oval-shaped film-coated tablets, debossed with “500” on one side, and contain as active substance 500 mg of abiraterone acetate.

The tablets are packed in Aluminium (Al)-OPA/Al/PVC blisters or Al-PVC/PE/PVDC blisters.

The excipients are:

- *Tablet core* - croscarmellose sodium, sodium lauryl sulphate, povidone (E1201), microcrystalline cellulose (E460), lactose monohydrate, colloidal anhydrous silica (E551), magnesium stearate (E470b).
- *Film-coating* - polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol (E1521) and talc (E553b), and for the 500 mg strength: red iron oxide (E172) and black iron oxide (E172).

The two tablet strength cores are dose proportional.

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance described in the United States Pharmacopoeia (USP). The active substance is a crystalline powder and is practically insoluble in water. The active substance shows polymorphism and is consistently manufactured as polymorphic form A. Abiraterone acetate is a single enantiomer containing six chiral centres and two centres of geometrical isomerism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of four stages. There are six chemical reaction steps from the starting material to an intermediate which is then purified to produce the substance. The choice of the regulatory starting materials is justified. The manufacturing process has been described in sufficient detail. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of in-house specifications established by the MAH, with additional requirements for particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scale batches and three production scale batches, manufactured according to the old route of synthesis that were stored at 30°C/65% RH (only full scale batches; up to 24 months), 30°C/75% RH (up to

60 months) and 40°C/75% RH (6 months). Stability data on nine production scaled batches manufactured according to the NEW route of synthesis have also been provided that were stored at 30°C/65% RH (3 to 9 months), 30°C/75% RH (3 to 9 months) and 40°C/75% RH (3 to 6 months) in accordance with applicable European guidelines demonstrating the stability of the active substance. The stability batches were evaluated for description, identification, water content, related substances, assay and polymorphic form. Except for an increase in impurities no clear trends or changes in any of the tested parameters were observed. Results for impurities were variable. The stability data for the batches from the old route of synthesis are considered representative for stability of batches according to the new route of synthesis. Photostability of the drug substance was investigated by ICH standards, showing no sensitivity of the drug substance to light exposure. Based on the data submitted, a retest period could be granted of 36 months without special storage conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies performed were the dissolution method development, formulation optimization studies, where the impact of different levels of excipients, particle size of the drug substance and polymorphic stability were investigated, and scale-up studies. A bioequivalence study was performed with the 500 mg product versus the 500 mg reference product. For the 250 mg product, a biowaiver was claimed. The bio-batch was manufactured according to the finalised composition and manufacturing process. The pharmaceutical development of the products has been adequately performed.

Manufacturing process

The main steps of the process are wet granulation, blending with extra-granular components and lubrication, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients of the tablet cores comply with Ph.Eur. requirements and the film-coating materials comply with in-house requirements. Where relevant, additional functionality-related characteristics have been specified. These specifications are acceptable.

Quality control of drug product

The finished product specifications were adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, assay, related substances, dissolution, uniformity of mass, uniformity of dosage units, dimensions and microbiological quality. The release and shelf-life requirements are identical, except for the limits for related substances. Limits in the specification have been justified and were considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three pilot scale batches per strength at the maximum acceptable production scale and on one smaller batch per strength, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production scaled batches and one pilot scaled batch per strength stored at 25°C/60% RH (12-18 months) and 40°C/75% RH (6 months). The batches were packed in packed in Al-OPA/Al/PVC blisters, Al-PVC/PE/PVDC blisters and HDPE bottles with oxygen absorbing canister. The conditions used in the stability studies are according to the ICH stability guideline. The following parameters were investigated: description, assay, related substances, dissolution and microbiological quality. No clear trends or changes were seen in any of the tested parameters and all parameters remained within the specified limits. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The stability data support the claimed shelf-life of 2 years without any special storage requirements.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Certificates of suitability issued by the EDQM have been provided for lactose monohydrate. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abirateron Stada has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Abirateron Stada is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zytiga, which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there was no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies were required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Abiraterone acetate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Abirateron Stada 500 mg, film-coated tablets (Stada Arzneimittel AG, the Netherlands) is compared with the pharmacokinetic profile of the reference product Zytiga 500 mg, film-coated tablets (Janssen-Cilag International N.V., Belgium).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

<u>Biowaiver</u>
The MAH has requested a biowaiver for the lower strength Abirateron Stada 250 mg film-coated tablets based on the provided bioequivalence study with the 500 mg formulation. The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

These requirements were met for the 250 mg strength, as both strengths of Abirateron Stada are manufactured by the same process, the qualitative and quantitative composition of the different strengths are dose proportional and only differ in the film-coating, and the dissolution studies are acceptable. The bioequivalence results for the 500 mg strength can be extrapolated to the 250 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Bioequivalence studies

Study 1 – single dose, 500 mg, fasted

Design

A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with 240 mL water after at least ten hours of overnight fasting. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products. The design of the study is acceptable.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a ten-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone with meals has the potential to result in highly variable exposures. Therefore, abiraterone must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking abiraterone. The tablets should be swallowed whole with water.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 27 subjects completed at least two periods in the study, all of these subjects were included in the statistical analysis (25 subjects completed all study periods).

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of abiraterone acetate under fasted conditions.

Treatment N=27	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	358.82 ± 240.93	373.48 ± 245.51	71.34 ± 44.35	1.50 (0.67 – 5.00)
Reference	355.22 ± 258.12	369.84 ± 260.72	74.13 ± 51.95	2.00 (0.67 – 5.00)
***Ratio (90% CI)**	0.98 (0.87 – 1.11)	--	0.99 (0.85 – 1.15)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Ln-transformed values

Study 2 – single dose, 500 mg, fasted, pilot study

Design

A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with water after at least ten hours of fasting. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products. The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

A total of 27 subjects completed at least two periods in the study, all of these subjects were included in the PK- and statistical analysis (25 subjects completed all study periods).

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of abiraterone under fasted conditions.

Treatment N=27	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	288.64 ± 195.92	302.09 ± 197.81	68.18 ± 53.05	2.00 (0.67 – 5.00)

Reference	280.37 ± 197.50	292.77 ± 198.18	64.18 ± 48.00	1.60 (0.67 – 5.00)
***Ratio (90% CI)**	1.00 (0.84 – 1.20)	--	1.04 (0.86 – 1.25)	--

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*****	Ln-transformed values

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies, Abirateron Stada is considered bioequivalent with Zytiga. The results for the 500 mg strength can be extrapolated to the 250 mg strength.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Abirateron Stada.

Table 3. Summary of safety concerns as approved in RMP

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%

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zytiga. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the 500 mg product is similar to the pharmacokinetic profile of the 500 mg reference product. A biowaiver has been granted for the 250 mg strength. Risk management was adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Zytiga 250 mg tablets, EMEA/H/C/002321 for content and key safety message, and Felocord 5 mg and 7.5 mg film-coated tablets, HU/H/0448/001-002/DC for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Abirateron Stada 250 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 250 mg and 500 mg, film-coated tablets. Zytiga is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Abirateron Stada with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 13 July 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5602/1-2/ IA/003	Change to importer, batch release arrangements and quality control testing of the finished product – Replacement or addition of a manufacturer responsible for importation and/or batch release	Yes	15-8-2022	Approved	N/A
NL/H/5602/1-2/ IB/001	Changes in the manufacturing process of the active substance – Minor change to the restricted part of an Active Substance Master File	No	12-9-2022	Approved	N/A
NL/H/5602/1-2/ IB/002	Change in the shelf-life or storage conditions of the finished product – Extension of the shelf life of the finished product – As packaged for sale (supported by real time data)	Yes	12-9-2022	Approved	N/A