COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/4967/001-002/DC

Date: 4 August 2021

This module reflects the scientific discussion for the approval of Abirateron DOC 250 mg, tablets and Abirateron DOC 500 mg, film-coated tablets. The procedure was finalised at 10 March 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of 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 DOC 250 mg, tablets and Abirateron DOC 500 mg, film-coated tablets from DOC Generici S.r.l.

Abirateron DOC 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) (see in SmPC section 5.1).
- 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 (see in SmPC section 5.1).
- 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zytiga 250 mg tablets and 500 mg film-coated tablets which has been registered in the European Union by Janssen-Cilag International N.V. since 5 September 2011 (original products) via centralised procedure (EU/1/11/714).

The concerned member state (CMS) involved in the procedure for both the 250 mg tablets and the 500 mg film-coated tablets was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Abirateron DOC 250 mg are white to off-white oval tablets and are debossed with “ATN” on one side and “250” on the other side. Abirateron DOC 500 mg are oval-shaped purple film-coated tablets and are debossed with “A7TN” on one side and “500” on the other side.

Abirateron DOC tablets and film-coated tablets contain as active substance 250 mg and 500 mg of abiraterone acetate, respectively.
Both products are packed in High Density Polyethylene (HDPE) bottles fitted with a polypropylene closure. The 500 mg film-coated tablets can be distributed in PVC/PVdC-aluminium perforated unit dose blisters as well.

The excipients in the 250 mg product are:
- lactose monohydrate
- microcrystalline cellulose
- croscarmellose sodium
- sodium lauryl sulfate
- colloidal anhydrous silica
- magnesium stearate
- povidone

The excipients in the 500 mg product are:
Tablet core
- lactose monohydrate
- microcrystalline cellulose
- croscarmellose sodium
- sodium lauryl sulfate
- colloidal anhydrous silica
- magnesium stearate
- Hypromellose

Film-coating
- polyvinyl alcohol
- titanium dioxide
- macrogol
- iron oxide red and black

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance. There is currently no European Pharmacopoeia (Ph. Eur.) monograph available for abiraterone acetate, however the United States Pharmacopeia (USP) monograph for the active substance is valid since May 2016.
Abiraterone acetate is a white to off-white powder, freely soluble in toluene, soluble in methanol and practically insoluble in aqueous media (pH range 2.0 to 12.9). It is a non-hygroscopic substance. The active substance exists in one crystalline form (form I). Both suppliers of the active substance supply polymorphic form 1.

The active substance abiraterone acetate is an antiandrogen medication used to treat prostate cancer. Abiraterone acetate is a prodrug of abiraterone. It targets the CYP17 enzyme, an enzyme involved in testosterone biosynthesis.

The documentation on the active substance is presented using separate Active Substance Master File (ASMF) procedures from two different manufacturers. 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 products, 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 products.

Manufacturing process

The manufacturing process consists for both manufacturers of several steps of chemical synthesis and purification. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised. The carry-over of residual solvents is sufficiently addressed. Polymorphic form is not relevant since only one stable crystalline form of the active substance is known to exist.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur and of the ICH. Batch analytical data demonstrating compliance with this specification have been provided for three batches per manufacturer.

Stability of drug substance

Stability data on the active substance have been provided in accordance with applicable European guidelines demonstrating the stability of the active substance both at long term as well as at accelerated storage conditions. Based on the data submitted, retest periods could be granted of 24 and 36 months, depending on the manufacturer. No storage restrictions have been indicated.

II.3 Medicinal Products

Pharmaceutical development

The drug products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. Development from early formulations to the commercial formulations has been described. The critical quality attributes have been determined and investigated during the development. The formulation and process development is supported with 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.

To investigate the dissolution profiles of the drug products and reference products a dissolution study was performed. Both the drug products and reference products contain sodium lauryl sulfate (SLS) as a wetting agent due to the poor solubility of the drug substance. Minimum levels of SLS that allowed recoveries of 100% with a suitable dissolution profile were selected. Furthermore, a surfactant was added to the dissolution medium to increase solubility. The use and quantity of surfactants in the formulation and dissolution medium are justified. Also, data provided to prove the discriminatory power of the dissolution study are sufficient. From this dissolution study, it could be concluded that

the drug and reference products show similarity with respect to the major physicochemical parameters, at the media intended for drug product release.

To confirm similarity in bioavailability between the drug products and reference products two bioequivalence study were performed, which will be discussed in section IV.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the products have been presented for three batches per drug product in accordance with the relevant European guidelines. The MAH has committed to perform validation of the manufacturing process to cover the batch size range from the smallest to largest batch size.

Control of excipients

The choice of the excipients is justified and their functions explained. Drug-excipient compatibility studies and also stability studies with the drug products indicate that the selected excipients are compatible with the drug substance. The quality requirements of excipients refer to the current Ph. Eur. monographs, except for the colouring agent of the 500 mg tablets. It is confirmed that each component used in the Opadry mixture is tested to comply with the Ph. Eur. quality requirements. The functionality-related characteristics of the excipients are controlled by the excipients suppliers to ensure particles properties and batch-to-batch consistency.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification of abiraterone acetate, assay of abiraterone acetate, impurities, dissolution and uniformity of dosage units. Limits in the specification have been justified and are considered appropriate for adequate quality control of the products. Satisfactory validation data for the analytical methods have been provided. Batch analytical data have been provided from three batches where the active substance from one of the production sites has been used. Additional batch analytical data and stability results have been provided for a single batch using the active substance from the second production site. Both data demonstrate compliance with the specification.

Stability of drug products

Stability data on both products have been provided for three batches stored at 25°C/60%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are in accordance with applicable European guidelines demonstrating the stability of both products for 24 months. In the case of the 250 mg tablets, an in-use stability study was conducted covering 60 days at 30°C/75% RH based on the dosing recommendations of the drug product. All tested samples complied with the acceptance criterion. A photostability study was performed and showed that the drug products are stable when exposed to light.
On basis of the data submitted, a shelf life was granted of 24 months. These medicinal products do not require any special storage conditions.

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

There are no substances of ruminant animal origin present in the products nor have any been used in the manufacturing of these products, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abirateron DOC tablets and film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

The following post-approval commitments were made:

- To perform validation of the manufacturing process to cover the batch size range from the smallest to largest batch size.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

These products are a generic formulation of Zytiga 250 mg and 500 mg which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are 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

overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test products Abirateron DOC 250 mg, tablets and Abirateron DOC 500 mg, film-coated tablets (DOC Generici S.r.l., Italy) are compared with the pharmacokinetic profile of the reference products Zytiga 250 mg tablets and 500 mg film-coated tablets (Janssen-Cilag International NV, Belgium).

The choice of the reference products in the bioequivalence studies has been justified by comparison of dissolution results and composition of the EU reference products.
The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

Bioequivalence studies
Design
For each drug product, a randomised, single-dose, two-treatment, four-period, two-sequence, full-replicate crossover bioequivalence study was carried out under fasted conditions in 50 healthy male subjects, aged 20 – 43 years. Each subject received a single dose (250 mg tablet or 500 mg film-coated tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected within 1 hour prior to dosing, and 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 hours after administration of the products. The design of the studies 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
250 mg drug product
All 50 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of abiraterone acetate 250 mg under fasted conditions.

Treatment N=50	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	246.14±149.77	252.9±151.1	45.8±35.6	2.0 (0.5 – 12.0)
Reference	233.7±136.71	240.1±136.8	44.4±29.6	2.0 (0.5 – 5.0)
***Ratio (90% CI)**	1.03 (0.95 – 1.12)	1.03 (0.95 – 1.11)	0.99 (0.90 – 1.10)	-
Intra-subject variability of the reference product (%)	29.6	-	36.1	-

$AUC_{0-\infty}$ 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 t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

<u>500 mg drug product</u>

Two subjects withdrew from the study on their own accord and one subject was withdrawn due to an adverse event. 48 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of abiraterone acetate 500 mg under fasted conditions.

Treatment N=48	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	471.8±283	484.7±286	90.3±69.8	2.0 (0.5-5.0)
Reference	488.2±334	501.6±338	94.1±73	2.0 (1.0-5.0)
***Ratio (90% CI)**	1.0 (0.92 – 1.08)	-	0.97 (0.88 – 1.08)	-
Intra-subject variability of the reference product (%)	-	-	40.3	-

$AUC_{0-\infty}$ 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 t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Abirateron DOC is considered bioequivalent with Zytiga.

The MEB has been assured that the bioequivalence studies have 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 DOC.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatotoxicity • Cardiac disorders • Osteoporosis including osteoporosis-related fractures • Rhabdomyolysis/Myopathy • Alveolitis allergic • 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 products Zytiga 250 mg and 500 mg. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the products is similar to the pharmacokinetic profile of these reference products. Risk management is adequately addressed. The 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 and 500 mg film-coated tablets (for content) and Clozapine 12.5 mg orodispersible tablets (for 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 DOC 250 mg, tablets and Abirateron DOC 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 250 mg tablets and 500 mg film-coated tablets. Zytiga 250 mg and 500 mg are well-known medicinal products with established favourable efficacy and safety profiles.

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 DOC with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 March 2021.

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