COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Abirateron 1A Pharma 1000 mg, film-coated tablets
(abiraterone acetate)

NL/H/5166/001/DC

Date: 1 October 2021

This module reflects the scientific discussion for the approval of Abirateron 1A Pharma 1000 mg, film-coated tablets. The procedure was finalised at 12 May 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 1A Pharma 1000 mg, film-coated tablets, from 1A Pharma GmbH.

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 decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Zytiga 250 mg tablets and 500 mg film-coated tablets which has been registered in the EEA by Janssen-Cilag International N.V. since 5 September 2011 by the centralised procedure EU/1/11/714.

The concerned member state (CMS) involved in this procedure was Austria.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Abirateron 1A Pharma is a white to off-white, oval-shaped film-coated tablet, with a break line on one side and plain on the other side. The tablet can be divided into equal halves and contains as active substance 1000 mg abiraterone acetate.

The film-coated tablets are packed in Al-OPA/Al/PVC blisters, HDPE bottles with a child resistant PP cap with oxygen absorbing canister or plain HDPE bottles with a child resistant cap (no canister).
The excipients are:

Tablet core – croscarmellose sodium, sodium laurilsulfate, povidone K 30 (E1201), cellulose microcrystalline (E460), lactose monohydrate, silica colloidal anhydrous (E551) and magnesium stearate (E470b)

Coating – poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521) and talc (E553b)

The 1000 mg tablet is fully dose proportional with regards to the tablet core with the 250 mg and 500 mg products manufactured by the same manufacturer.

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance described in the the US Pharmacopoeia. 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 eight stereochemical elements, i.e. 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 and six chemical reaction steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is in line with the specification of the active substance manufacturer, with additional requirements for particle size distribution and microbiological quality. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three pilot scaled and three production scaled batches manufactured according to the old route of synthesis that were stored at 30°C/65% RH (only full scaled batches; up to 24 months), 30°C/75% RH (up to 60

months) and 40°C/75% RH (six months). Stability data on nine production scaled batches manufactured according to the new (current) route of synthesis have also been provided that were stored at 30°C/65% RH (three-nine months), 30°C/75% RH (three-nine months) and 40°C/75% RH (three-six months). Photostability of the drug substance was investigated under light conditions showing no sensitivity of the drug substance to light exposure. The proposed retest period of 36 months without any special storage conditions is justified.

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 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. The biobatch was manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. The main steps of the process are wet granulation, blending with extragranular components and lubrication, compression, film-coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

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

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, subdivision of tablets, assay, related substances, dissolution, uniformity of mass, uniformity of dosage units, dimensions and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches and on one pilot scale batch from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled and one pilot scaled batch packed in the two different HDPE bottle configurations stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months) and on three production scaled batches packed in OPA/Al/PVC-Al blisters stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months) in accordance with applicable ICH stability guidelines. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life of two years without any special storage conditions is justified.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for the used lactose monohydrate and 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 1A Pharma 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 1A Pharma is intended for hybrid 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

This product is a hybrid formulation of Zytiga which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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 hybrid application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Abirateron 1A Pharma 1000 mg, film-coated tablets (1A Pharma GmbH, Germany) 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 compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A randomized, two-treatment, four-period, two-sequence, single-dose, full-replicate crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 23-44 years. Each subject received a single dose (1000 mg) or two times 500 mg (reference) of one of the two abiraterone acetate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were four 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, 4.5, 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.

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
One subject did not report to the clinical facility for period two-four, and another subject was withdrawn from the study due to positive in alcohol test during period two administration. Since they completed only one period of the study these subjects were not included in pharmacokinetic analyses. 28 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=28	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	462.8±283	479.1±289	118.6±91.5	2.0 (0.67-4.5)
Reference	421.3±206	437.3±479.1	97.7±51.2	1.75 (0.67-4.5)
***Ratio (90% CI)**	1.06 (0.96-1.19)	-	1.10 (0.95-1.27)	-
CV (%)	31.7	-	33.8	-

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
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 study Abirateron 1A Pharma is considered bioequivalent with Zytiga 2 times 500 mg tablets.

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 1A Pharma.

Table 2. Summary table of safety concerns as approved in the 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 a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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 500 mg film-coated tablets for content and key safety message, EMEA/H/C/002321 and Felocord film-coated tablets for design and layout, HU/H/0448/001-002/DC. 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 1A Pharma 1000 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Zytiga 250 mg tablets 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 1A Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 May 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