COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Abiraterone Zentiva 500 mg film-coated tablets (abiraterone acetate)

NL/H/5242/001/DC

Date: 1 February 2022

This module reflects the scientific discussion for the approval of Abiraterone Zentiva 500 mg film-coated tablets. The procedure was finalised on 27 October 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
mCRPC	Metastatic castration resistant prostate cancer
mHSCP	Metastatic hormone sensitive prostate cancer
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 Abiraterone Zentiva 500 mg film-coated tablets, from Zentiva k.s.

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) (see section 5.1 of the SmPC).
– 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 section 5.1 of the SmPC).
– 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 product Zytiga 500 mg film-coated tablets which has been registered in the EEA by Janssen-Cilag International NV since September 2011 by the procedure EMEA/H/C/002321.

The concerned member states (CMS) involved in this procedure were Austria. Czech Republic, Germany, Denmark, Estonia, France, Italy, Lithuania, Latvia, Norway, Portugal, Sweden and Slovakia.

The marketing authorisation has been granted pursuant to Article 10(1)of Directive

II. QUALITY ASPECTS

II.1 Introduction

Abiraterone Zentiva is a purple to brown film-coated tablets and contains as active substance 500 mg abiraterone acetate.

The film-coated tablets packed in PVC/PVDC/Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium laurilsulfate, Hypromellose, magnesium stearate and colloidal anhydrous silica.
Film-coating - polyvinyl alcohol, macrogol, talc, titanium dioxide, iron oxide red and iron oxide black.

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance described in the United States Pharmacopeia (USP). The active substance is a crystalline powder and is practically insoluble in water. The drug substance shows polymorphism. Polymorphic Form A is used. Abiraterone acetate is a single enantiomer containing eight stereochemical elements. The drug substance is supplied by two different suppliers, both supported by an ASMF.

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.

<u>Manufacturing process</u>
Manufacturer I
The synthesis starts with the starting material. The synthesis covers four chemical transformation steps with isolated intermediates, followed by a purification step and a micronisation step. The second starting material is introduced in the third step of the synthesis. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Manufacturer II
The synthesis starts with starting material to make the intermediate. The second starting material is introduced in the last part of the synthesis. The process from the starting material up to the final abiraterone acetate covers several chemical transformation steps with isolated intermediates. The choice of the regulatory starting materials is justified. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance

A single compiled specification for the control of the drug substance from both suppliers has been established in-house by the applicant. The specification is in line with the specification of the respective ASMF holders, with additional drug product specific tests for microbiological quality, polymorphic identity and particle size. The specification is acceptable.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three drug substance batches from Manufacturer I and two batches from Manufacturer II.

Stability of drug substance

Manufacturer I

Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60% RH (up to 36 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The batches were packed in double PE bags in a fibreboard drum. No clear changes were seen in any of the tested parameters. Based on the data submitted, a retest period could be granted of 36 months without any special storage precaution is justified.

Manufacturer II

Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months; 3 batches) in accordance with applicable European guidelines. The batches were stored in double PE bags (inner transparent, outer black), with desiccant in aluminized bag, inside a HDPE container. The batches were evaluated for description, identity by IR and HPLC, assay, water, loss on drying, organic impurities, XRD and microbiological quality. No clear trends or changes were seen in any of the tested parameters at both storage conditions and all parameters remained well within the specified limits. Based on the data submitted, a retest period could be granted of 60 months with storage precaution 'Preserve in well closed containers and store at controlled room temperature at 20-25°C, with allowed excursions between 15-30°C' is acceptable.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product and the definition of a QTPP and derivation of CQA's thereof, optimization of the formulation and development of a QC dissolution method. The choices made in the development of the dissolution method have been justified and the discriminatory power of the method was demonstrated. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

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

Control of excipients

The excipients comply with Ph.Eur., USP-NF (silicified microcrystalline cellulose) or in-house requirements, with additional control of functionality-related characteristics. 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 appearance, dimensions, average mass, identity of the drug substance and colourants, assay, uniformity of dosage units, dissolution, related substances, microbiological quality, water content, resistance to crushing and disintegration time. Except for related substance, the release and shelf-life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate risk evaluation for nitrosamine impurities has been provided. No risk for nitrosamine impurities was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three full scaled batches 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 four production scaled batches stored at 25°C/60% RH (12-24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable ICH guidelines. The batches were stored in PVC/PVdC-Al blisters. The following parameters were investigated: appearance, average mass, assay, dissolution, related substances, microbiological quality (not all time points), water content, resistance to crushing and disintegration. The stability data show an increase in impurities at all three storage conditions. At accelerated conditions also an increase in water content was seen. No clear trends or changes were seen in the other tested parameters at any of the storage conditions and all results were within the specified limits.

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 was granted of two years. The labelled storage condition ‘This medicinal product does not require any special storage conditions’ is justified.

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

Except for lactose monohydrate, none of the excipients is of human or animal origin. The milk used for the production of lactose monohydrate is sourced from healthy animals in the same conditions as milk collected for human consumption and the calf rennet used is produced in accordance with the Public Statement EMEA/CPMP/571/02 of February 27 2002.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abiraterone Zentiva 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 Abiraterone Zentiva 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

This product is a generic 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 generic 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 Abiraterone Zentiva 500 mg film-coated tablets (Zentiva k.s., Czech Republic) is compared with the pharmacokinetic profile of the reference product Zytiga 500 mg film-coated tablets (Janssen-Cilag International NV, 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 study

Design

A single centre, laboratory-blinded, single-dose, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 46 healthy male subjects, aged 21-67 years. Each subject received a single dose (500 mg) of one of the 2 abiraterone acetate formulations. The tablet was orally administered with water after an overnight fast of at least 10 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, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 9.00, 12.00, 16.00, 24.00, 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

All subjects completed the study. However, one subject did not participate in all 4 study periods. The subject had to leave the clinic before dosing of period 3 for personal reasons and therefore did not participate in period 3. Subject came back for period 4 and completed the study. 46 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=92	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	378.96 ± 177.23	399.12 ± 183.30	68.35 ± 36.02	2.00 (0.67 – 6.00)
Reference	346.75 ± 171.11	363.55 ± 176.41	61.54 ± 33.48	2.33 (0.67 – 9.00)
***Ratio (90% CI)**	1.11 (1.03 – 1.21)	-	1.11 (1.00 – 1.23)	-
CV (%)	33.0	-	42.9	-

$AUC_{0-\infty}$ 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

**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 Abiraterone Zentiva is considered bioequivalent with Zytiga.

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 Abiraterone Zentiva.

Table 2. Summary table 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. No new clinical studies were conducted. 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 generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.

The test consisted of: a pilot test, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Abiraterone Zentiva 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 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 Abiraterone Zentiva with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 27 October 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