COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Abirateron Devatis 500 mg, film-coated tablets (abiraterone acetate)

NL/H/5549/001/DC

Date: 8 July 2024

This module reflects the scientific discussion for the approval of Abirateron Devatis 500 mg, film-coated tablets. The procedure was finalised on 29 March 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Devatis 500 mg, film-coated tablets, from Devatis 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Zytiga 500 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EMEA/H/C/002321) by Janssen-Cilag International N.V., since 5 September 2011.

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

II. QUALITY ASPECTS

II.1 Introduction

Abirateron Devatis 500 mg is a purple coloured, oval, biconvex film-coated tablet and contains as active substance 500 mg of abiraterone acetate.

The excipients are:
Tablet core - lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulphate, hypromellose type 2910 6cP, silica colloidal anhydrous and magnesium stearate.

Film-coat - polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide red (E172) and iron oxide black (E172).

The film-coated tablets are packed in transparent polyvinylidene dichloride/polyethylene/ polyvinyl chloride (PVdC/PE/PVC) aluminium blister.

II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance, which is not described in the European Pharmacopoeia (Ph.Eur.). A monograph for abiraterone acetate is available in the USP. The active substance is a crystalline, white to off white powder and is practically insoluble in water. The drug substance exhibits polymorphism. For this product a specific polymorphic form is consistently manufactured. Abiraterone acetate is a single enantiomer containing eight stereochemical elements.

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 the synthesis of the drug substance. The synthesis starts with one starting material and covers four chemical transformation steps with isolated intermediates, followed by a purification step and a micronisation step. A second starting material is introduced in the third step of the synthesis, for this a heavy metal catalyst is used. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the Ph.Eur. and in-house specifications. The manufacturer adopts the active substance specification of the ASMF with additional requirements for particle size distribution and microbiological purity (Ph.Eur.). Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance have been provided for six production scaled batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 36 months when stored under the conditions stated in the ASMF.

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 were the characterisation of the reference product and the definition of a development of the quality target product profile (QTPP) and derivation of CQA's thereof, optimisation of the formulation and development of a QC dissolution method. The choice of

excipients is justified and their functions explained. The excipients are selected based on the composition of the reference product and the drug excipients compatibility study performed during development. The study results demonstrated compatibility of abiraterone acetate with the chosen excipients. 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.

A bioequivalence (BE) study was performed against the 500 mg reference product. *In vitro* dissolution tests were performed complementary to the bioequivalence studies. Dissolution was tested at pH 1.2 HCl 0.1N, pH 4.5 phosphate buffer, pH 6.8 phosphate buffer and pH 6.8 QC medium. The results show similar dissolution profiles for the test and reference product at the tested pH solutions.

Manufacturing process

The manufacturing process is considered a standard process. The main steps of the manufacturing process are wet granulation, drying, sieving, blending with extra granular components, 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. The product is manufactured using conventional manufacturing techniques. The manufacturing process is described in sufficient detail and applied process parameters and in-process control acceptance criteria are adequate.

Control of excipients

The excipients comply with Ph.Eur. or in-house requirements. 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 (description and dimensions), identification, water content, hardness, assay, dissolution, uniformity of dosage units (mass variation), degradation products and microbiological quality. The release and shelf-life specification are identical except for the impurity limits which is sufficiently justified. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product 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 three production scaled batches stored at 25°C/ 60% RH (18 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. The batches were stored in polyvinylidene dichloride/ polyethylene / polyvinyl chloride (PVdC/PE/PVC) aluminium blisters. The following parameters were investigated: appearance, assay, dissolution, related substances, microbial contamination. Photostability studies have been performed in accordance with ICH recommendations and demonstrate photosensitivity of the tablets. The stability data show no significant trends at any parameter at both conditions. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM for the excipient lactose monohydrate have been provided 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 Devatis 500 mg 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 Devatis 500 mg 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 500 mg film-coated tablets 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 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 member states agreed that no further clinical studies are required, besides 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 Devatis 500 mg, film-coated tablets (Devatis GmbH., Germany) was compared with the pharmacokinetic profile of the reference product Zytiga 500 mg film-coated tablets by Janssen-Cilag International N.V. (Belgium).

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

Bioequivalence studies

Design

A single-dose, balanced, open-label, randomised, two-treatment, two-sequence, four-period, fully replicate, crossover, bioequivalence study was carried out under fasted conditions in 39 healthy male subjects, aged 20-42 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 an overnight fasting of at least 8 hours. There were four dosing periods, separated by a washout period of 4 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75,1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 18, 24 and 36 hours after administration of the products.

The design of the study is acceptable. According to the SmPC, the medicinal product must not be taken with food. It is recommended to take the tablets on an empty stomach, at least two hours after eating, and food must not be eaten for at least one hour after taking the tablets. Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety when given with food have not been established, therefore this medicinal product must not be taken with food. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** Note for Guidance on the investigation of bioavailability and bioequivalence.

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 40 subjects were enrolled for the study, one subject was withdrawn from the study in period 4 due to safety reasons. No serious adverse events were reported during the conduct of this study. 39 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of abiraterone acetate, 500 mg under fasted conditions.

Treatment N=39	AUC_{0-t} (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	262 ± 142	50.3 ± 30.1	2.00 (0.75 – 5.50)
Reference	267 ± 140	53.1 ± 33.7	2.50 (0.75 – 6.13)
***Ratio (90% CI)**	0.98 (0.90 – 1.07)	0.98 (0.87– 1.11)	--

AUC_{0-t} Area under the plasma concentration-time curve from time zero to the last measurable plasma concentration / to t = 36 hours
C_{max} Maximum plasma concentration
t_{max} Time after administration when maximum plasma concentration occurs
CI Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
In general, an acceptance range of 80.00% – 125.00% (0.80 – 1.25) is described in the protocol but widening is proposed for C_{max} in case the intra-subject CV (ISCV) of the reference product is higher than 30%. The ISCV of C_{max} for reference product was 58.50%. and therefore 90% CI limit was widened using scaled-average-bioequivalence of 69.84% to 143.19%. The study showed that the 90% CI for the AUC_{0-t} and C_{max} mean ratios between the test and reference product are within the defined acceptance range of 80.00 – 125.00% and 69.84% to 143.19%, respectively. Bioequivalence between Abiraterone Devatis and the reference product under fasting condition is considered demonstrated.

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 Devatis.

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 interactions (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

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 Lenalidomide Devatis hard capsules NL/H/4989/001-007/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 Devatis 500 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form 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 Abirateron Devatis with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 29 March 2023.

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/5549/ 001/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	27-9-2023	Approved	N.A.
NL/H/5549/ 001/IB/002	Change in pack size of the finished product: - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.	Yes	2-4-2024	Approved	N.A.