COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Abirateron Xiromed 500 mg film-coated tablets (abiraterone acetate)

NL/H/5370/001/DC

Date: 12 September 2022

This module reflects the scientific discussion for the approval of Abirateron Xiromed 500 mg film-coated tablets. The procedure was finalised at 7 June 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

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 Xiromed 500 mg film-coated tablets, from Medical Valley Invest AB.

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 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 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 product Zytiga 500 mg, film-coated tablets which has been registered in the EEA by Janssen-Cilag International NV since 9 November 2016 via a centralised procedure (EMEA/H/002321).

The concerned member states (CMS) involved in this procedure were Denmark, Finland, Germany, Iceland, Norway, Poland and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Abirateron Xiromed is a red-beige, oval, film-coated tablet debossed with “500” on one side. Each tablet contains 500 mg of abiraterone acetate.

The film-coated tablets are packed in clear PVC/PE/PVDC/aluminium blisters.

The excipients are:

Tablet core - silicified microcrystalline cellulose (composed of microcrystalline cellulose and silica colloidal anhydrous), croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, colloidal silica sodium and laurilsulfate.

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

II.2 Drug Substance

The active substance is abiraterone acetate. This established active substance is not described in the European Pharmacopoeia (Ph.Eur.). However, a monograph is available in the United States Pharmacopeia (USP). The substance is a white or almost white crystalline powder, practically insoluble in aqueous media over a wide range of pH values and slightly soluble in 0.1N HCl solution. It is soluble in organic solvents. The drug substance shows polymorphism. The selected polymorphic form is produced exclusively by the manufacturing process of both manufacturers. The data provided on polymorphic form are accepted and stability studies have shown no changes in polymorphism.

The Active Substance Master File (ASMF) procedure is used for the active substance from both suppliers. 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 manufacturing process consists of four chemical transformation steps with isolated intermediates, followed by a purification step and a micritisation step. A heavy metal catalyst is used in the process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Manufacturer II - The manufacturing process consists of four chemical transformation steps with isolated intermediates, followed by a purification step. No class 1 solvents are used in the process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

<u>Quality control of drug substance</u>
A single compiled specification for the control of the drug substance from both suppliers has been established in-house by the MAH. The specification is not fully in line with the specification of the respective ASMF holders, with additional drug product specific tests for microbiological quality and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating

compliance with this specification have been provided for three batches from each manufacturer.

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 (6 months) which is in accordance with applicable European guidelines. 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 when the product is stored in a well closed container at controlled room temperature (below 25°C).

Manufacturer II - Stability data on the active substance have been provided for six production scaled batches stored at 30°C/75% RH (up to 12 months) and 40°C/75% RH (6 months) which is in accordance with applicable European guidelines. No clear changes were seen in any of the tested parameters. Based on the data submitted, a retest period could be granted of 12 months. The storage precaution: "Preserve in well closed container, at USP controlled room temperature and avoid direct sunlight exposure." has been accepted.

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 development of the product has been described, the choice of excipients is justified, and their functions have been explained. Development of a quality control dissolution method and the characterisation of the reference product were the primary development studies. The choices made in the development of the dissolution method have been justified and the discriminatory power of the method was demonstrated. A bioequivalence (BE) study was performed against the 500 mg reference product and considered representative. Complementary to the *in vivo* study, comparative dissolution studies between the BE study test and reference product have been provided. The choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process has been 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, including the individual components of silicified microcrystalline cellulose, comply with Ph.Eur. or in-house requirements and 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, identity, assay, uniformity of dosage units, dissolution, related substances 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 from the proposed production site have been provided, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided from three production scaled batches in accordance with applicable European 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 was granted. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the excipients is of human or animal origin except for lactose monohydrate. The milk used to produce lactose monohydrate is derived under the same conditions as milk collected for human consumption and the calf rennet is produced in accordance with the applicable guidelines.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Abirateron Xiromed 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 Xiromed 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 500 mg, film-coated tablets 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 Abirateron Xiromed 500 mg film-coated tablets (Medical Valley Invest AB, Sweden) 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 Zytiga 500 mg. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, full-replicate crossover bioequivalence study was carried out under fasted conditions in 68 healthy male subjects, aged 18-45 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 period of at least 10 hours. There were three dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose (0.0 hours) and at 0.333, 0.667, 1.0, 1.333, 1.667, 2.0, 2.333, 2.667, 3.0, 3.5, 4.0, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

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 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 68 subjects completed the study and 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=68	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	358±234	61.5±37.4	2.33 (0.67 – 5.02)
Reference	314±199	56.2±31.9	2.00 (0.67 – 6.00)
***Ratio (90% CI)**	1.11 (1.02 – 1.17)	1.09 (1.05 – 1.18)	--

$AUC_{0-t\ Area}$ under the plasma concentration curve from administration to last sampling
C_{max} maximum plasma concentration
t_{max} time until C_{max} is reached
****In-transformed values***

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Abirateron Xiromed 500 mg is considered bioequivalent with Zytiga 500 mg.

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 Xiromed.

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 500 mg. 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 based on a bridging report making reference to Zytiga 500 mg, film-coated tablets for content and Losartan 25 mg/ 50 mg/ 100 mg film-coated tablets or the 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 Xiromed 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 follow 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 Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised recognition procedure was finalised with a positive outcome on 7 June 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