COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Tatica 250 and 500 mg, film-coated tablets (abiraterone acetate)

# NL/H/5263/001-002/DC

# Date: 26 October 2021

**This module reflects the scientific discussion for the approval of Tatica 250 and 500 mg, film-coated tablets. The procedure was finalised at 21 April 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

| | |
|---|---|
| ADT | Androgen Deprivation Therapy |
| 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 |
| mHSPC | 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 Tatica 250 and 500 mg, film-coated tablets, from Pharos Pharmaceutical Oriented Services Ltd.

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 generic application claiming essential similarity with the innovator products Zytiga 250 mg tablets and 500 mg film-coated tablets which have been registered in the EEA by Janssen-Cilag International N.V. since September 2011 via the centralised procedure (EU/1/11/714).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Hungary, Lithuania, Latvia, Poland, Romania and Slovakia.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Tatica are film-coated tablets:

The 250 mg strength tablets are white to off-white, oval-shaped film-coated tablets, debossed with “250” on one side and contain as active substance 250 mg of abiraterone acetate.

The 500 mg strength tablets are purple, oval-shaped film-coated tablets, debossed with “500” on one side, and contain as active substance 500 mg of abiraterone acetate.

The tablets are packed in Aluminium-OPA/Alu/PVC blisters or Aluminium-PVC/PE/PVDC blisters or High density polyethylene (HDPE) bottles with oxygen absorbing canister.

The excipients are:

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

*Film-coating* - poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide red (E172) (500 mg strength) and iron oxide black (E172) (500 mg strength).

The two tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance described in the United States Pharmacopoeia (USP). 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. There are six chemical reaction steps from the starting material to an intermediate which is then purified to produce the final product. The choice of the regulatory starting materials is justified. Adequate specifications have been adopted for starting materials, solvents and reagents. The manufacturing process has been described in sufficient detail, including process parameters, in-process controls, quantities of raw materials and yields. Also sufficient details on the micronisation, use of recovered solvents and reprocessing have been provided. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of in-house specifications established by the MAH, with additional requirements for particle size distribution and microbiological quality. The specification is acceptable in view of the route of synthesis and various European guidelines. 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 to nine months), 30°C/75% RH (three to nine months) and 40°C/75% RH (three to six months) in accordance with applicable European guidelines demonstrating the stability of the active substance. The batches were stored in double LDPE bags, sealed in an aluminium foil bag and placed in a fibre drum. The stability batches were evaluated for description, identification, water content, related substances, assay and polymorphic form. Except for an increase in impurities no clear trends or changes in any of the tested parameters were observed. Results for impurities were variable. The stability data for the batches from the old route of synthesis are considered representative for stability of batches according to the new route of synthesis. Photostability of the drug substance was investigated showing no sensitivity of the drug substance to light exposure. Based on the data submitted, a retest period could be granted of 36 months without special storage conditions.

## II.3 Medicinal Product

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. 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. A bioequivalence (BE) study was performed with the 500 mg product versus the 500 mg reference product. For the 250 mg product a biowaiver was claimed. The biobatch was manufactured according to the finalised composition and manufacturing process. Comparative *in vitro* dissolution testing at three pH's has been successfully studied in support of the bioequivalence study and biowaiver. The pharmaceutical development of the products has been adequately performed.

Manufacturing process

The main steps of the process are wet granulation, blending with extra-granular components and lubrication, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the products have been presented for three pilot scaled batches per strength. The products are manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients

The excipients of the tablet cores 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, 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 the proposed production site have been provided on three full scaled batches per strength and on one pilot scale batch per strength, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scaled batches and one pilot scaled batch per strength packed in Aluminium-OPA/Alu/PVC blisters, three production scaled batches and one pilot scaled batch per strength packed in Aluminium-PVC/PE/PVDC blisters and three production scaled batches per strength packed in High density polyethylene (HDPE) bottles with oxygen absorbing canister stored at 25°C/60% RH (12-18 months) and 40°C/75% RH (six months) in accordance with applicable European guidelines. The conditions used in the stability studies are according to the ICH stability guideline. The following parameters were investigated: description, assay, related substances, dissolution and microbiological quality. No clear trends or changes were seen in any of the tested parameters and all parameters remained 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, without any special storage requirements.

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 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 Tatica have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Tatica are 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 generic formulations of Zytiga 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 product Tatica 500 mg, film-coated tablets (Pharos Pharmaceutical Oriented Services Ltd., the Netherlands) 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 studies 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.

Biowaiver

The MAH has requested a biowaiver for the lower strength Tatica 250 mg film-coated tablets based on the provided bioequivalence study with the 500 mg formulation. The biowaiver was based on the following conditions: The qualitative and quantitative composition of the different strengths are dose proportional and only differs in the film-coating. Both strengths of Tatica are manufactured by the same process. Dissolution studies supporting the biowaiver are acceptable. The results of study I with 500 mg formulation can be extrapolated to the 250 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Bioequivalence studies

**Study I**

*Design*

A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with water after at least ten hours of fasting. There were two 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, 4.50, 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*
A total of 27 subjects completed at least two periods in the study, all of these subjects were included in the pharmacokinetics (PK)- and statistical analysis. 25 subjects completed all study periods. One subject completed only one period of the study and was therefore excluded from the analysis. Another subject completed three periods, two periods with reference and one period with test formulation. The third subject also completed 3 periods, two periods with test and one period with reference formulation.

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

| Treatment N=27 | $AUC_{0-t}$ (ng/h/ml) | $AUC_{0-\infty}$ (ng/h/ml) | $C_{max}$ (ng/ml) | $t_{max}$ (h) |
|---|---|---|---|---|
| **Test** | 358.82 ± 240.93 | 373.48 ± 245.51 | 71.34 ± 44.35 | 1.50 (0.67 – 5.00) |
| **Reference** | 355.22 ± 258.12 | 369.84 ± 260.72 | 74.13 ± 51.95 | 2.00 (0.67 – 5.00) |
| ***Ratio (90% CI)** | 0.98 (0.87 – 1.11) | - | 0.99 (0.85 – 1.15) | - |
| **CV (%)** | 24.62 | - | 34.01 | - |

**$AUC_{0-\infty}$** 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*

**Study II – Pilot study**
*Design*
A randomised, open label, balanced, two-treatment, four-period, two sequence, single dose, crossover fully replicate, oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 22-44 years. Each subject received a single dose (500 mg) of one of the two abiraterone acetate formulations. The tablet was orally administered with water after at least ten hours of fasting. There were two 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, 4.50, 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.

*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 27 subjects completed at least two periods in the study, all of these subjects were included in the PK- and statistical analysis. 25 subjects completed all study periods. One subject completed only one period of the study and was therefore excluded from the analysis. Another subject completed 3 periods, two periods with reference and one period with test formulation. The third subject also completed three periods, two periods with test and one period with reference formulation.

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

| **Treatment N=27** | **$AUC_{0-t}$ (ng/h/ml)** | **$AUC_{0-\infty}$ (ng/h/ml)** | **$C_{max}$ (ng/ml)** | **$t_{max}$ (h)** |
|---|---|---|---|---|
| **Test** | 288.64 ± 195.92 | 302.09 ± 197.81 | 68.18 ± 53.05 | 2.00 (0.67 – 5.00) |
| **Reference** | 280.37 ± 197.50 | 292.77 ± 198.18 | 64.18 ± 48.00 | 1.60 (0.67 – 5.00) |
| ***Ratio (90% CI)** | 1.00 (0.84 – 1.20) | - | 1.04 (0.86 – 1.25) | - |
| **CV (%)** | 39.14 | - | 41.39 | - |

**$AUC_{0-\infty}$** 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 studies:
The 90% confidence intervals calculated for $AUC_{0-t}$ and $C_{max}$ are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Tatica 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 Tatica.

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

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|---|---|
| Important identified risks | - Hepatotoxicity<br>- Cardiac disorders<br>- Osteoporosis including osteoporosis-related fractures<br>- Rhabdomyolysis/myopathy<br>- Allergic alveolitis<br>- Increased exposure with food |
| Important potential risks | - Anaemia<br>- Cataract<br>- Drug-drug interaction (CYP2D6) |
| Missing information | - Use in patients with active or symptomatic viral hepatitis<br>- Use in patients with moderate/severe hepatic impairment and chronic liver disease<br>- Use in patients with severe renal impairment<br>- 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. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the 500 mg product is

similar to the pharmacokinetic profile of the 500 mg reference product. A biowaiver has been granted for the 250 mg strength. Risk management is adequately addressed. These 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 500 mg film-coated tablets, EMEA/H/C/002321 for content and key safety message, and Felocord film-coated tablets, HU/H/0448/001-002/DC for design and 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

Tatica 250 and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 250 and 500 mg, film-coated tablets. Zytiga 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 Tatica with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 April 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 |
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