COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Abirateron MSN 250 mg and 500 mg film-coated tablets (abiraterone acetate)

## NL/H/5915/001-002/DC

## Date: 11 February 2026

**This module reflects the scientific discussion for the approval of Abirateron MSN 250 mg and 500 mg film-coated tablets. The procedure was finalised on 4 December 2024. 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 MSN 250 mg and 500 mg film-coated tablets, from Vivanta Generics s.r.o.

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 250 mg and 500 mg film-coated tablets, which has been registered in the EEA via a centralised procedure (EU/1/11/714) since 5 September 2011.

The concerned member states (CMS) involved in this procedure were Bulgaria, Croatia Czechia, Hungary, Poland, Romania, Slovakia and Slovenia.

# II. QUALITY ASPECTS

## II.1 Introduction

Abirateron MSN 250 mg and 500 mg are film-coated tablets. The two different strengths can be distinguished on their appearance, based on their colour and debossing as follows:

<u>Abirateron MSN 250 mg</u>
Beige coloured, debossed with “MA” on one side and “21” on the other side. Each film-coated tablet contains as active substance 250 mg abiraterone acetate.

<u>Abirateron MSN 500 mg</u>
Purple coloured, debossed with “MA” on one side and “22” on the other side. Each film-coated tablet contains as active substance 500 mg abiraterone acetate.

The excipients are:
*Tablet core* – lactose monohydrate, croscarmellose sodium (E468), hypromellose 2910, 3 mPa.s (E464), sodium laurilsulfate, cellulose microcrystalline (E460), silica, colloidal anhydrous (E551) and magnesium stearate (E470b).
*Film-coating* – polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 3350 (E1521), talc (E553b), iron oxide red (E172), iron oxide yellow (E172; only for 250 mg) and iron oxide black (E172; only for 500 mg).

The two tablet cores are dose proportional.

The film-coated tablets are packed in polyvinyl chloride/polyethylene/polyvinylidene chloride-aluminium (PVC/PE/PVDC-Alu) blisters or perforated unit dose blisters.

## II.2 Drug Substance

The active substance is abiraterone acetate, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). A monograph for abiraterone acetate is available in the US Pharmacopoeia. The active substance is a crystalline powder and is practically insoluble in water and soluble in methanol and chloroform. For this product, one polymorphic form is consistently produced.

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 five steps, four of them are chemical transformation steps and the last step is purification. No class 1 solvents are used during the synthesis. 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 established in-house by the MAH. The parameters for description, solubility, identification by IR and HPLC, water content, melting range, specific optical rotation, residue on ignition, organic impurities, assay, residual solvents, palladium content, polymorphic identification and particle size distribution (PSD) are included.
Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance

Stability data on the active substance have been provided for six full scaled batches and five smaller batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

## 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 choice of excipients is justified and their functions explained. The formulation development studies investigated the wet granulation manufacturing step, the fluid uptake of the drug product, the kneading time of the drug product and the influence of different amounts of excipients used in the product. The choices of the packaging are justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are sifting, dry mixing, wet granulation, drying, milling, pre-lubrication, 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 commercial scale batches of both strengths in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with the Ph.Eur. requirements, except for the coating materials which are controlled according to in-house specifications. Furthermore, additional particle size distribution tests are added for the excipients lactose monohydrate, cellulose, microcrystalline, croscarmellose sodium and magnesium stearate. 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, dimensions, identification, identification of colouring agents, uniformity of dosage units (mass variation), assay, dissolution, related substances, microbiological control, water determination, disintegration time, hardness; resistance to crushing and the residual solvent. The release and shelf-life specification of the drug product is acceptable and 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 production scale batches for each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches for each strength 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. Photostability studies were performed in accordance with ICH recommendations showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. 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 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 MSN 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 MSN 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 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 the 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 MSN 500 mg film-coated tablets (Vivanta Generics s.r.o., Czechia) was 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 study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements are met where the waiver for 250 mg is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the 250 mg and 500 mg strengths is the same,
c. the composition of both strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for both strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule).

Appropriate *in vitro* dissolution data confirms the adequacy of waiving additional *in vivo* bioequivalence testing.
The dissolution was investigated according to the EMA Bioequivalence guideline (with dissolution profiles at pH 1.2, 4.5 and 6.8). The calculated $f_2$ similarity factor values were within criteria (>50%). An $f_2$ value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence study - Study 67722

*Design*

A single-dose, randomised, three-period, two-treatment, three-sequence, crossover, partial replicate bioequivalence study was carried out under fasted conditions in 39 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 240 ml water after a fasting period of at least 10 hours. There were three dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48 and 72 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*
One subject was withdrawn from the study due to not turning up at period 2 and 3. 37 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=37** | **$AUC_{0-t}$ (ng.h/mL)** | **$AUC_{0-\infty}$ (ng.h/mL)** | **$C_{max}$ (ng/mL)** | **$t_{max}$ (h)** |
|---|---|---|---|---|
| **Test** | 397 ± 228 | 409 ± 234 | 80 ± 49 | 1.33 (0.67 – 6.00) |
| **Reference** | 425 ± 232 | 436 ± 236 | 84 ± 45 | 1.67 (0.67 – 6.00) |
| ***Ratio (90% CI)** | 0.95 (0.83 – 1.09) | 0.95 (0.84 – 1.08) | 0.97 (0.82 – 1.16) | - |

| | |
|---|---|
| **$AUC_{0-\infty}$** | 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 = 72 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:
The 90% confidence intervals calculated for $AUC_{0-t}$ and $AUC_{0-\infty}$ are within the bioequivalence acceptance range of 0.80 – 1.25. In addition, as predefined in the protocol, the acceptance range for $C_{max}$ was widened to 69.84 – 143.19%, as the intra-subject variability was ≥50%. Based on the submitted bioequivalence study Abirateron MSN 500 mg is considered bioequivalent with Zytiga 500 mg.

The results of Study 67722 with the 500 mg formulation can be extrapolated to other strength 250 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 MSN. At the time of approval, the most recent version of the RMP was version 1.0 dated 19 November 2024.

**Table 2. Summary table of safety concerns as approved in RMP**

| | |
|---|---|
| Important identified risks | None |
| Important potential risks | None |
| Missing information | None |

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 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 Zytiga 250 mg and 500 mg film-coated tablets (EMEA/H/C/002321) for text and safety and to Rosuvastatin Vivanta 5 mg, 10 mg, 20 mg and 40 mg, film-coated tablets (NL/H/4158/001-004/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

Abirateron MSN 250 mg and 500 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zytiga 250 mg 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 MSN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 December 2024.

## 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 |
|---|---|---|---|---|---|
| - | - | - | - | - | - |