COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Enzalutamide PharOS 40 mg and 80 mg, film-coated tablets (enzalutamide)

NL/H/5873/001-002/DC

Date: 28 August 2024

This module reflects the scientific discussion for the approval of Enzalutamide PharOS 40 mg and 80 mg, film-coated tablets. The procedure was finalised on 28 May 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 Enzalutamide PharOS 40 mg and 80 mg, film-coated tablets, from Pharos Pharmaceutical Oriented Services Ltd.

The product is indicated for:

- as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC)
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)
- for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy

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 Xtandi 40 mg and 80 mg film-coated tablets from Astellas Pharma Europe B.V., which has been registered in the EEA via a centralised procedure (EU/1/13/846) since 21 September 2017.

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

II. QUALITY ASPECTS

II.1 Introduction

Enzalutamide PharOS 40 mg and 80 mg are film-coated tablets containing 40 mg and 80 mg enzalutamide as active substance. The tablets are presented in two strengths which can be distinguished by their shape and size.

- 40 mg: yellow, round, film-coated tablets debossed with “40” on one side
- 80 mg: yellow, oval, film-coated tablets, debossed with “80” on one side

The excipients are:
Tablet core - methacrylic acid-ethyl acrylate copolymer (1:1) Type A (contains sodium lauryl sulfate and polysorbate 80); silica, colloidal anhydrous (E551); cellulose, microcrystalline (E460); croscarmellose sodium (E468); and magnesium stearate (E470b).
Tablet coating - hypromellose 2910 (E464); macrogol 3350 (E1521); titanium dioxide (E171); iron oxide yellow; (E172) and talc (E553b).

The two tablet strengths are dose proportional.

The film-coated tablets are either packed in Aluminium-Polyamide/Aluminium/Polyvinyl chloride (Aluminium-OPA/Alu/PVC) blisters or in high density polyethylene (HDPE) bottles with white polypropylene (PP) oxygen absorbing canister, closed with a child resistant polypropylene (PP) closure.

II.2 Drug Substance

The active substance is enzalutamide, an established active substance. It is not described in any Pharmacopoeia. The active substance is white or almost white powder and is practically insoluble in water. For this product, a specific polymorphic form is consistently produced. During the manufacturing process of the finished product, the active substance is dissolved, so initial form and particle size distribution are not relevant.

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>
The manufacturing process consists of four stages of branched process, consisting of six synthetic steps, three isolated intermediates and three starting materials. 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. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. Based on the data submitted, a retest period could be granted of 36 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. During development, the active substance is transferred into an amorphous solid dispersion. As the formulation contains the active substance in an amorphous solid dispersion, the manufacturing process is critical. The development of the formulation, the dissolution method and the manufacturing process have been adequately described.
In order to support the results obtained in the bioequivalence study, dissolution results for the 80 mg test and reference batch were presented. The conditions used during the dissolution studies were in accordance with the requirements in the Guideline on the Investigation of Bioequivalence.

Manufacturing process
The manufacturing process consists of the manufacture of an intermediate, spray-dried dispersion, which is later processed into 40 mg and 80 mg film-coated tablets. As the manufacturing process of the intermediate includes the production of an amorphous solid dispersion, the manufacturing process of the intermediate is considered as non-standard but no complex, while the manufacturing process of the finished product, after the step where the intermediate is produced, is considered as standard. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches for both strengths in accordance with the relevant European guidelines.

Control of excipients
All excipients comply with their respective Ph. Eur. monograph. Only iron oxide yellow, as used in the coating material, is not included in Ph. Eur. Iron oxide yellow complies with Commission Regulation (EU) No. 231/2012. 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 for the intermediate (enzalutamide spray-dried dispersion) adopted by the finished product manufacturer include tests for description, identification of enzalutamide, assay, related substances, residual solvents, loss on drying and microbiological examination. The specification for the film-coated tablets includes tests for description, identification of enzalutamide, identification of titanium dioxide, identification of iron oxide, assay, related substances, residual solvents, dissolution, uniformity of mass, uniformity of dosage units, dimensions, and microbiological examination. It is noted that except for appearance and dimensions, the specifications for release and shelf life are the same for both tablet strengths. 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 batches for the intermediate and three batches for each strength from the production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided for three batches of the intermediate (spray dried dispersion), and three batches per strength for the finished dosage form, stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) 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 was granted of 2 years without any specific storage conditions.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Enzalutamide PharOS 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 Enzalutamide PharOS 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 Xtandi 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

Enzalutamide 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies, one under fasted and one under fed conditions, in which the pharmacokinetic profile of the test product Enzalutamide PharOS 80 mg, film-coated tablets (Pharos Pharmaceutical Oriented Services Ltd, Greece) was compared with the pharmacokinetic profile of the reference product Xtandi 40 mg, film-coated tablets (Astellas Pharma Europe B.V., the Netherlands). For the lower product strength, 40 mg, a biowaiver was requested.

According the SmPC, enzalutamide may be taken with or without food. Therefore, the design of the studies under fed and fasted conditions is acceptable.

Dissolution studies were conducted in different pH conditions (pH 1, pH 4.5 and pH 6.8). The choice of the reference product in the bioequivalence study has been justified by comparison of the dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula for marketing.

Biowaiver

The following general requirements must be met where a waiver for an additional strength 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 different strengths is the same,
c. the composition of the 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 all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. 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.
All criteria were met.

Bioequivalence studies, fasted conditions

Design

A comparative randomised, single-dose, two-arm, parallel, open-label bioequivalence study was carried out under fasted conditions in 160 healthy male subjects, aged 19-49 years. Each subject received a single dose (80 mg) of one of the two enzalutamide formulations (one 80 mg film-coated tablet of the test product or two 40 mg film-coated tablets of the reference product). The tablet(s) were orally administered with 240 mL water after an overnight fast of at least 10 hours.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 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

A total of 160 subjects completed the study. All 160 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of enzalutamide, 80 mg under fasted conditions.

Treatment N=80	**AUC_{0-72h} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	64743 ± 19206	210836 ± 113576	1809 ± 474	1.67 (0.67 – 47.13)
Reference	64940 ± 23890	245563 ± 174607	1841 ± 494	2.00 (0.33 – 5.00)
***Ratio (90% CI)**	1.01 (0.93 – 1.1)	-	0.98 (0.92 – 1.05)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / 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*

Bioequivalence studies, fed conditions

Design

A comparative randomised, single-dose, two-arm, open-label, parallel bioequivalence study was carried out under fasted conditions in 160 healthy male subjects, aged 18-48 years. After an overnight fast of at least 10 hours, subjects consumed a standardised high fat, high calorie breakfast (927 kcal) starting 30 minutes prior to drug administration. Each subject received a single dose (80 mg) of one of the two enzalutamide formulations (one 80 mg film-coated tablet of the test product or two 40 mg film-coated tablets of the reference product).The tablet(s) were orally administered with 240 mL water after. Except for the water administered with the dose, water consumption was restricted from 1 hour prior to drug administration until 1 hour post dose. Food consumption was not allowed up to at least 5 hours after dosing.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 12, 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

A total of 160 subjects completed the study. All 160 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of enzalutamide, 80 mg under fed conditions.

Treatment N=80	AUC_{0-72h} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	75254 ± 23150	270369±170416	1654 ± 417	4.50 (0.33 – 35.47)
Reference	73776 ± 25532	309620±347212	1730 ± 544	2.67 (0.33 – 8.00)
***Ratio (90% CI)**	1.03 (0.95 – 1.11)	-	0.97 (0.90 – 1.04)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / 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 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 Enzalutamide PharOS 80 mg is considered bioequivalent with Xtandi.

The results of both studies with the 80 mg formulation can be extrapolated to the strength 40 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 Enzalutamide PharOS.

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

Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
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 Xtandi. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies 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.

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 Xtandi, EU/1/13/846. 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

Enzalutamide PharOS 40 mg and 80 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Xtandi 40 mg and 80 mg, film-coated tablets. Xtandi 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 Enzalutamide PharOS with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 May 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
-	-	-	-	-	-