COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5454/001-002/DC

Date: 27 June 2023

This module reflects the scientific discussion for the approval of Enzalutamide Sandoz 40 mg and 80 mg, film-coated tablets. The procedure was finalised on 1 December 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
AEs	Adverse Events
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
IMP	Investigational Medicinal Product
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
TEAEs	Treatment-Emergent Adverse Events
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Enzalutamide Sandoz 40 mg and 80 mg, film-coated tablets, from Sandoz B.V.

The product is indicated for:

- the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy.
- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- 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.
- 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 (EMEA/H/C/002639) since 21 June 2013.

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

II. QUALITY ASPECTS

II.1 Introduction

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

- 40 mg: yellow, round, biconvex film-coated tablet with a diameter of 10.5 – 11.3 mm, debossed with “EN” on one side and “40” on the other side.
- 80 mg: yellow, oval, biconvex film-coated tablet with a length of 16.9 – 17.7 mm; width 8.9 – 9.7 mm, debossed with “EN” on one side and “80” on the other side.

The excipients are:
Tablet core - hypromellose acetate succinate, lactose monohydrate, sodium croscarmellose (E468), microcrystalline cellulose (E460) and magnesium stearate (E470b).
Tablet coating - hypromellose (E464), macrogol, talc, titanium oxide (E171), and iron oxide yellow (E172).

The two tablet strengths are fully dose proportional.

The film-coated tablets are packed in Polyvinyl chloride/Polyvinylidene dichloride/Aluminium (PVC/PVdC-Al) blister or High-Density Polyethylene (HDPE) bottle with desiccant, closed with child-resistant polypropylene screw cap with induction heat seal liner.

II.2 Drug Substance

The active substance is enzalutamide, an established active substance. It is not described in any Pharmacopoeia. The active substance is a white to off-white solid. Enzalutamide is freely soluble in acetone and practically insoluble in water. Enzalutamide is achiral; therefore, no stereoisomerism is observed. There are different crystalline forms according to the literature. 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.

Manufacturing process
The manufacturing process consists of a three-stages synthesis involving the reaction of the start materials to form an intermediate product, further reaction of the intermediate with a solvent to form enzalutamide and purification of the drug substance. 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. Information on all possible organic impurities and their carry-over has been discussed. For this product, the ICH M7 (Assessment and control of DNA reactive, mutagenic, impurities in pharmaceuticals to limit potential carcinogenic risk) is not applicable as it is only indicated for advanced cancer.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The specification includes tests and requirements for description, identification, loss on drying, residue on ignition, related substances, assay and residual solvents. The in-house methods for related substances, assay and residual solvents have been adequately validated. The tests and

requirements are 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 six process validation batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 5 years when stored as 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 choice of excipients is justified and their functions explained. During development different technologies were used to improve the apparent solubility and dissolution of the product, also different polymers for solid dispersion preparation were evaluated. The relation between percentage of crystalline active substance in the drug product and the QC dissolution results has been sufficiently addressed.

Manufacturing process

The manufacturing process is a standard process which involves mixing, granulation, milling, mixing, lubrication, compression, coating and packaging. The process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scale batches for both strengths in accordance with the relevant European guidelines.

Control of excipients

The excipients used are of Ph.Eur. quality, except ferric oxide yellow and hypromellose acetate succinate, which comply with the United States Pharmacopoeia/National Formulary (USP/NF) and have tighter limits for several tests. 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 colour, appearance, identification of enzalutamide, identification of titanium dioxide, identification of iron oxides, water activity, assay, uniformity of dosage units, dissolution, degradation products (individual and total impurities), residual solvent and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The methods for assay and degradation products are stability indicating as demonstrated by forced degradation studies. Furthermore, the discriminatory power has been demonstrated for the proposed QC dissolution method and for the crystallisation of the active substance.

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 non-compendial analytical methods have been provided.

Batch analytical data for three production scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been submitted for three production batches per strength, each batch was packed in PVC/PVdC-Al blisters and HDPE bottles and stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with ICH/ European guidelines. An increase in water activity was observed for the product in PVC/PVDC blisters, this is due to the moisture permeability of this packaging. For both packaging, also an increase in impurity A and subsequently also total impurities is observed. These trends are more pronounced at accelerated- than at long-term conditions. Impurity A remains only just within specification over 6 months storage at accelerated conditions. However, all other parameters remained well within specification limits. The same trends are observed in the also performed bulk hold-, transportation- and in-use studies. On basis of the data submitted, a shelf life was granted of 2 years. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data for daily opening have been provided for both strengths packed in HDPE bottle with desiccant. The results comply and no trends are observed. Based on the results, in-use shelf life (after first opening of the bottle) described in the SmPC is 2 months for the 80 mg tablets and 4 months for the 40 mg tablets. These is acceptable; however additional in-use stability data up to minimum 6 months are required. For this, the MAH has submitted a commitment to perform the 6-month study. See section II.4

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 Enzalutamide Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- For the proposed in-use shelf life, an in-use stability study was conducted for 2 months. However, in line with the Quality Working Party (QWP, EMA), 6 months in-use stability data should be provided. The MAH has submitted a commitment to provide the 6-month stability study data and update the patient information accordingly if necessary.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Enzalutamide Sandoz 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 in which the pharmacokinetic profile of the test product Enzalutamide Sandoz 80 mg, film-coated tablets (Sandoz B.V., manufactured in Slovenia) 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 applicable. 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 must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline CPMP/EWP/QWP/1401/98Rev.1/Corr**:

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 is 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,
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution profiles of the bio batch test 80 mg and the additional 40 mg strength were studied at pH 1.2 simulated gastric fluid, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and QC medium. 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. Therefore, a waiver for the lower 40 mg strength is acceptable and bioequivalence studies with only the 80 mg (highest strength) is justified.

Bioequivalence studies, fasted conditions

Design

An open label, single-dose, randomised, one-period, two-treatment, parallel, bioequivalence study was carried out under fasted conditions with 100 healthy non-smoking male subjects, aged between 18 and 55 years. After an overnight fast of at least 10 hours, the subjects received either one film-coated tablet of the test product (80 mg) or two film-coated tablets of the reference product (2x40 mg= 80 mg total). The tablets were orally administered with 240±5 mL water. 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 4 hours after dosing.

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, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

A total of 100 subjects were enrolled and completed the study. 50 subjects received the test product and the other 50 subjects received the reference product. All subjects were eligible for pharmacokinetic analysis. There were eight treatment emergent adverse events (AEs). Six AEs were detected after administration of the test product, these included tachycardia (1x), flatulence (1x), neutrophil count decreased (1x) and headache (3x). Two AEs were detected after administration of the reference and included headache (1x) and hot flush (1x).

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

Treatment N=50	**$AUC_{0-72\ hrs}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	58859.2 ± 11776.9	2183.4 ± 499.8	2.00 (0.50 – 5.00)
Reference	56862.8 ± 14032.1	2142.8 ± 581.5	2.00 (0.75 – 4.50)
***Ratio (90% CI)**	1.05 (0.97 – 1.12)	1.03 (0.95-1.12)	-

$AUC_{0-\infty}$	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

An open label, single-dose, randomised, one-period, two-treatment, parallel, bioequivalence study was carried out under fasted conditions with 130 healthy non-smoking male subjects, aged between 18 and 55 years. After an overnight fast of at least 10 hours, subjects consumed a standardised high fat, high calorie breakfast (907 kcal) starting 30 minutes prior to drug administration. The subjects received either one film-coated tablet of the test product (80 mg) or two film-coated tablets of the reference product (2x40 mg= 80 mg total). The tablets were orally administered with 240±5 mL water. 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 4 hours after dosing.

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, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Results

A total of 130 subjects were enrolled for the study. 65 subjects received the test product and the other 65 subjects received the reference product. One subject who received the reference product withdrew from the study due to personal reasons. A total of 129 subjects completed the study and were eligible for pharmacokinetic analysis. Ten subjects reported a total of 11 treatment-emergent adverse event, TEAEs. Six subjects reported 7 TEAEs after administration of the test product and 4 subjects reported 4 TEAEs after administration of the reference. Six TEAEs affecting 5 subjects were assessed as drug-related (suspected relationship to the investigational medicinal product, IMP). Four subjects reported 5 drug-related AEs after administration of the test product and 1 subject reported 1 drug-related AE after administration of the reference.

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

Treatment N=65	**AUC_{0-t} (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	56835.3 ± 13132.5	1525.9 ± 383.4	4.50 (0.75-24.0)
Reference	56778.8 ± 13729.7**	1647.3 ± 407.7	4.50 (0.50-16.1)
***Ratio (90% CI)**	1.01 (0.94 – 1.08)	0.92 (0.86-0.99)	-

$AUC_{0-\infty}$	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*
*** N= 64*

According the SmPC, enzalutamide may be taken with or without food. Therefore, the design of the studies under fed and fasted conditions 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 for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Conclusion on bioequivalence studies:
For the bioequivalence studies, two tablets of the reference product were administered, instead of one 80 mg tablet. This is considered acceptable as the 40 mg and 80 mg tablets can be interchanged according the SmPC. The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25 for both studies.

Based on the submitted bioequivalence studies under fasted and fed conditions, Enzalutamide Sandoz 80 mg is considered bioequivalent with Xtandi. The results of 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 studies have 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 Sandoz.

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

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 EMEA/H/C/002639 for content, and for design and layout reference was made to several approved products from Sandoz (EMEA/H/C/1181-1183, AT/H/0350/DC, DE/H/1354-1356, DK/H/300/01-02/II/18, SE/357,359,361/01-04/R01 and UK/H/2385-2387/001-004). 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 Sandoz 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 December 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
-	-	-	-	-	-