COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Enzalutamide SDZ 160 mg, film-coated tablets (enzalutamide)

NL/H/5851/003/DC

Date: 16 January 2026

This module reflects the scientific discussion for the approval of Enzalutamide SDZ 160 mg, film-coated tablets. The procedure was finalised on 24 September 2025. 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
BCR	Biochemical Recurrent
CRPC	Castration-Resistant Prostate Cancer
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
mHSPC	metastatic Hormone-Sensitive Prostate Cancer
nmHSPC	non-metastatic Hormone-Sensitive Prostate Cancer
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 SDZ 160 mg, film-coated tablets, from Sandoz B.V.

The product is indicated:

- 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.

This decentralised procedure concerns a line extension (as defined under Regulation 1234/2009, Annex II) of the current marketing authorisation of Enzalutamide SDZ 40 mg and 80 mg, film-coated tablets with procedure number NL/H/5851/001-002/DC, which have been registered in the Netherlands by Sandoz B.V. since 28 May 2024 (original product). The current product from the same MAH, Enzalutamide SDZ 160 mg, concerns a new strength.

In this decentralised procedure, bioequivalence is proven between the new product and the innovator product Xtandi 40 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 marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application. Enzalutamide SDZ 160 mg and Xtandi 40 mg differ in quantitative composition in terms of strength. The legal base of this application is therefore acceptable.

The concerned member states (CMS) involved in this procedure were Austria, Czechia, Germany, Greece, France, Hungary, Latvia, Lithuania, Poland, Romania, Slovenia and Slovakia.

II. QUALITY ASPECTS

II.1 Introduction

Enzalutamide SDZ is a film-coated tablet. Each tablet contains 160 mg of enzalutamide as active substance. The film-coated tablets are yellow, oval, debossed with “160” on one side.

The excipients are:
Tablet core - methacrylic acid-ethyl acrylate copolymer (1:1) Type A (contains sodium lauryl sulfate and polysorbate 80), colloidal anhydrous silica (E551), microcrystalline PH 102 cellulose (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 film-coated tablets are packed in aluminium-oriented polyamide/aluminium/polyvinyl chloride (Aluminium-OPA/Alu/PVC) (perforated unit dose) blisters.

II.2 Drug Substance

The active substance is enzalutamide, an established active substance not described in any Pharmacopoeia. The active substance is white or almost white powder and is practically insoluble in water. For this product, one 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 several stages of branched process, consisting of multiple synthetic steps, isolated intermediates and 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 36 months. Based on the data submitted, a retest period could be granted of 48 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 are explained. During development, the active substance is transferred into an amorphous solid dispersion.

To support the results obtained in the bioequivalence study, comparative dissolution results for the 160 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.

The development of the formulation, the dissolution method and the manufacturing process have been adequately described.

Manufacturing process

The manufacturing process consists of the manufacture of an intermediate, spray-dried dispersion. This spray-dried dispersion is mixed with some excipients followed by dried granulation, mixing with the other excipients and compression of the tablets. The tablets are film-coated and packaged. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with their relative Ph. Eur. monograph. Only iron oxide yellow, as used in the coating material, is not included in Ph. Eur. Iron oxide yellow complies with EU 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) includes 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, assay, related substances, residual solvents, dissolution, uniformity of mass, uniformity of dosage units, dimensions and microbiological examination. The release and shelf life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The nitrosamines risk evaluation report was not complete. However, considering the already registered 40 mg and 80 mg strengths, the risk on nitrosamines is not considered different.

Therefore, the information on nitrosamines is considered sufficient, no risk is expected and confirmatory testing is not required.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites has been provided for three full scaled batches of the intermediate (spray-dried dispersion), and three full scaled batches plus one pilot scaled batch for the finished dosage form, demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product have been provided for three batches of the intermediate (spray-dried dispersion), and four batches, of which one pilot scaled, for the film-coated tablets. The batches for the intermediate were stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The batches for the tablets were 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 on the tablets 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 2 years was granted for the film-coated tablets. 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

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 SDZ 160 mg 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 Pharmacology, pharmacokinetics and toxicology

The pharmacodynamic, pharmacokinetic and toxicological properties of enzalutamide are well known. As enzalutamide is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Upon request, the MAH has provided an updated ERA and states that it has been carried out according to the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr.*, Aug 2024). The MAH refers (in the initial, first round ERA but also in the updated ERA) to the statement that the marketing authorisation of this generic product will not lead to an increase in the environmental exposure of the substance. The RMS agrees that further ERA studies can be waived.

III.3 Discussion on the non-clinical aspects

This product is a hybrid 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 overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required, besides 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 SDZ 160 mg, film-coated tablets (Sandoz B.V., the Netherlands) was compared with the pharmacokinetic profile of (four tablets of) the reference product Xtandi 40 mg, film-coated tablets (Astellas Pharma Europe B.V., the Netherlands).

According to 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 (QC-medium, pH 1.2, pH 4.5 and pH 6.8). 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.

Bioequivalence studies

Study 1 (ENZ-0623-60), 160 mg under fasted conditions

Design

A single-dose, comparative randomised, two-arm, two-treatment, parallel open label bioequivalence study was carried out under fasted conditions in 80 healthy male subjects, aged 18-49 years. Each subject received a single dose (160 mg) of one of the two enzalutamide formulations (one test tablet of 160 mg or four reference tablets of 40 mg). The tablets were orally administered with 240 ml water after an overnight fast of at least 10 hours.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.667, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 10, 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

80 Subjects enrolled in the study; all 80 were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of enzalutamide, 160 mg under fasted conditions.

Treatment N=80	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	187759 ± 54269	54802 ± 233673	5062 ± 1354	2.00 (0.67-4.00)
Reference	186706 ± 62439	545137 ± 252541	4942 ± 1074	2.33 (1.00-4.50)
***Ratio (90% CI)**	1.02 (0.90 – 1.14)	--	1.01 (0.92 – 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 t = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

*Study 2 (**ENZ-0623-61), 160 mg under fed conditions***

Design

A single-dose, comparative randomised, two-arm, two-treatment, parallel open bioequivalence study was carried out under fed conditions in 80 healthy male subjects, aged 18-41 years. Each subject received a single dose (160 mg) of one of the two enzalutamide formulations (one test tablet of 160 mg or four reference tablets of 40 mg). The tablets were

orally administered with 240 mL water after an overnight fast of at least 10 hours, followed by a standardised, high-fat, high calorie breakfast of around 927 kcal.

Blood samples were collected pre-dose and at 0.167, 0.333, 0.667, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 10, 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
80 Subjects enrolled in the study. One subject reported hypotension before study drug administration (treatment A). The adverse event (AE) was assessed as mild in intensity and it was resolved during the study. All 80 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of enzalutamide, 160 under fed conditions.

Treatment N=80	**AUC_{0-t} (ng.h/mL)**	**$AUC_{0-\infty}$ (ng.h/mL)**	**C_{max} (ng/mL)**	**t_{max} (h)**
Test	186955 ± 62914	701132 ± 399685	3987 ± 1032	3.33 (0.67-24.00)
Reference	170929 ± 50134	628466 ± 393636	4145 ± 1133	2.00 (0.67-6.00)
***Ratio (90% CI)**	1.08 (0.96 – 1.22)	--	0.96 (0.87 – 1.07)	--

$AUC_{0-\infty}$	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 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 SDZ is considered bioequivalent with Xtandi under fasting and fed conditions.

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 SDZ. At* the time of approval, the most recent version of the RMP was version 2.1 dated of sign-off 4 August 2025.

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 hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

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 Enzalutamide SDZ 40 mg and 80 mg, NL/H/5851/001-002/DC. 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 SDZ 160 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Xtandi 40 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 bioequivalence has been demonstrated for Enzalutamide SDZ with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 September 2025.

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
-	-	-	-	-	-