18 September 2025
EMA/CHMP/246017/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enzalutamide Viatris

International non-proprietary name: Enzalutamide

Procedure No. EMEA/H/C/006299/X/0003

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List of abbreviations

AES	atomic emission spectroscopy
API	Active Pharmaceutical Ingredient
AR	assessment report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	area under the curve
BDL	Below the limit of detection
CEP	Certificate of Suitability of the EP
CMS	Concerned Member State
CTD	common technical document
CoA	Certificate of Analysis
CRS	Chemical reference substance
DL	Detection Limit
DMF	Dimethylformamide
DOM	Date of manufacture
DSC	Differential scanning Calorimetry
ECD	Electrochemical detection
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ee	enantiomeric excess
EP	European Pharmacopoeia
FDA	US Food and Drug Administration
FID	Flame ionisation detection
FPM	finished product manufacturer
FTIR	Fourier transmission infrared (spectroscopy)
GC	Gas chromatography
GMP	good manufacturing practice
HDPE	high density polyethylene
HPLC	High performance liquid chromatography
ICH	International conference on harmonization
ICP	Inductively coupled plasma
IPA	isopropyl alcohol
IPC	In-process control test
IR	Infra-red
KF	Karl Fischer
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of detection
LoQ	Limit of Quantitation
MA	Marketing Authorisation
MAH	Marketing Authorisation holder
MCC	microcrystalline cellulose
MS	Mass spectroscopy
NfG	Note for Guidance
NIR	Near infra-red
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
PCTFE	Polychlorotrifluoroethene
PDA	Photo diode array
PDE	Permitted Daily Exposure
PVC	Polyvinyl chloride

PVdC	Polyvinyl dichloride
Ph.Eur.	European Pharmacopoeia
QL	Quantitation limit
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference member state
ROI	residue on ignition
RRt	Relative retention time
Rt	Retention time
RT	Room temperature
SAL	Sterility assurance level
SEM	Scanning electron microscopy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TGA	Thermo-Gravimetric Analysis
UV	Ultra violet
XRD	X-Ray Diffraction
XRPD	X-Ray PowderDiffraction

1. Background information on the procedure

1.1. Submission of the dossier

Viatris Limited submitted on 11 November 2024 an extension of the marketing authorisation.

Extension application to add a new strength of 160 mg for solution for film-coated tablets.
The RMP (version 1.0) is updated in accordance.

The MAH applied for an addition of a new strength in all approved indications:

- 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 (see section 5.1).
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) (see section 5.1).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- 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 (see section 5.1).
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

1.2. Legal basis

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP for the current line extension.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Tomas Radimersky

The Rapporteur appointed by the PRAC was Maria del Pilar Rayon

The application was received by the EMA on	11 November 2024
The procedure started on	28 November 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 February 2025
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	NA
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	25 February 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	27 March 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	25 May 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	24 June 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	25 February 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	24 July 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	02 September 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	08 September 2025
The outstanding issues were addressed by the MAH during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Enzalutamide Viatris on	18 September 2025

2. Scientific discussion

2.1. Problem Statement

Enzalutamide Viatris is currently 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 (see section 5.1).
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) (see section 5.1).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- 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 (see section 5.1).
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Enzalutamide Viatris is currently available as 40 mg and 80 mg film-coated tablets. The recommended dose is 160 mg enzalutamide (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose.

This submission is an application for an extension of the marketing authorisation to introduce an additional strengths 160 mg of enzalutamide in addition to the existing 40-mg and 80-mg strengths film-coated tablets formulations.

The objective of the new strengths is to minimize the quantity of dosage units and therefore to reduce the patient "tablet burden".

Two bioequivalence (BE) studies ENZ-0623-60 and ENZ-0623-61 have been performed using the originator Xtandi as a reference product.

2.2. About the product

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as film coated tablets containing 160 mg of enzalutamide as active substance.

Other ingredients are:

Tablet core: methacrylic acid-ethyl acrylate copolymer (1:1) Type A (additionally containing sodium lauryl sulfate and polysorbate 80), colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, magnesium stearate,

Tablet coating: Hypromellose 2910, macrogol MW3350, titanium dioxide (E171), iron oxide yellow (E172), talc; as described in the SmPC section 6.1.

The product is available in aluminium-OPA/Alu/PVC blister pack in a carton, in configurations of blister pack containing 28 film-coated tablets, blister calendar pack containing 28 film-coated tablets or unit-dose blister pack containing 1 x 28 film-coated tablets.

2.3.2. Active Substance

2.3.2.1. General information

The active substance (AS) enzalutamide is supplied by one manufacturer. The ASMF procedure is followed. The applicant's part and restricted part of ASMF have been included in the dossier. Also a satisfactory Letter of access has been provided.

The information regarding the AS is satisfactory.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

The *finished* product *(FP)* is film coated tablets containing 160 mg of enzalutamide. The film coated tablets appearance is as follows: yellow, oval, film-coated tablets, debossed with "160" on one side, with dimensions 23.1 mm x 11.1 mm.

The finished product (160 mg film-coated tablets) was developed to complement the range of Enzalutamide Viatris film-coated tablets of the authorised strengths (40 mg, 80 mg) as a hybrid (different strength) of the reference medicinal product Xtandi 40 mg film-coated tablets. Consequently, the objective was to prepare a film-coated tablets being essentially similar to the reference medicinal product.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards except iron oxide yellow. Specification for coating mixture has been presented including analytical methods. Certificates of analysis for the excipients have been submitted. Functionality related characteristics

have been discussed. The composition of the excipient methacrylic acid-ethyl acrylate copolymer was satisfactorily specified. There are no novel excipients used in the finished product formulation. No animal origin excipient has been used. The list of excipients is included in section 6.1 of the SmPC and in paragraph 3.1.1 of this report.

A compatibility study has been performed using AS and excipients used in the finished product formulation. Furthermore, the stability study verified the compatibility of AS with the excipients. No compatibility issues have been identified.

Quality target product profile and critical quality attributes have been identified and discussed.

Bioequivalence under fasted and fed conditions was demonstrated between the reference and test product. In addition dissolution profiles have been compared between FP 160 mg and reference product 40 mg strength. The dissolution profiles have been compared in four different buffers: QC medium, HCl 0.1N, acetate buffer pH 4.5 and phosphate buffer pH 6.8. The dissolution profiles comparison of biobatch and reference product in all media has been adequately discussed.

According to bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) *"in the event that the results of comparative in vitro dissolution of the bio batches do not reflect bioequivalence as demonstrated in vivo the latter prevails."* Since bioequivalence was demonstrated *in vivo* it was concluded that the test product is considered to be bioequivalent to the reference product.

Comparative assay and impurity profile of the test and reference product have been compared and are considered similar.

Enzalutamide AS is classified as Class II compound according to BCS. The conditions for QC method have been satisfactorily selected and justified. The batch-to-batch similarity has been confirmed. The discriminatory power of dissolution method has been confirmed.

Spray-drying approach has been adopted as a manufacturing process.

The choice of container closure system for spray-dried dispersion, bulk and finished product has been justified. The information on primary and secondary materials of container closure system has been stated. The container closure system (primary packaging) is Aluminium-OPA/Alu/PVC blisters and is considered appropriate for this dosage form. The material complies with Ph. Eur. and EC requirements.

2.3.3.2. Manufacture of the product and process controls

The manufacturing sites involved in the manufacture of the FP are stated in the dossier. Satisfactory evidence of GMP compliance of all sites involved the FP manufacturing has been provided.

The FP manufacturing process includes the preparation of the *e*nzalutamide spray-dried dispersion (non-standard manufacturing process - wet granulation step) and manufacture of the final pharmaceutical formula (standard manufacturing process). The FP manufacturing process of enzalutamide spray-dried dispersion consists of five main steps: solution preparation, spray drying, drying, packaging and quality control. The manufacturing process of final pharmaceutical form consists of eight main steps: weighing and sieving, dry mixing, dry granulation and sizing, blending, compression, film-coating, quality control, packaging. Critical steps have been identified. The manufacturing process is considered a non-standard process due to the manufacture of the spray dried dispersion.

The manufacturing process has been described in sufficient detail. Critical steps are clearly stated, and IPC have been stated for each manufacturing step with corresponding specification, which is acceptable.

The calculation of the expiry date of the finished product has been set according to EMA guideline EMA/CHMP/QWP/245074/2015. Information on holding times for bulk products and packaging material of the same have been provided. The proposed holding times are justified.

Process validation and evaluation has been performed for three batches of spray-dried dispersion and finished product. Process validation and evaluation for the manufacturing processes (intermediate and final product) has been performed, validation protocols have been submitted, all results obtained were in the acceptance limit set. It was concluded that this manufacturing process is sufficiently controlled and it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.3.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form.

The FP release and shelf life specifications, include appropriate tests for this kind of dosage form: description (visual), identification of enzalutamide (HPLC, UV), assay (HPLC), related substances (HPLC) residual solvents (GC), dissolution (Ph. Eur., HPLC), uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dimensions (In-house) and microbial examination (Ph. Eur.).

The release and shelf-life specifications are relevant to the dosage form according to the current version Ph. Eur. and requirements of ICH Guideline Q6A. The proposed limits stated in specifications have been discussed and justified.
The tests included in the specifications of the intermediate product are acceptable.

Characterisation of impurities has been submitted. Potential organic impurities included in the active substance specification have been discussed together with limits according to ICH Q3B.
Potential genotoxic impurities have been discussed. Their limits are acceptable.
The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach. No risk has been identified, none of the elemental impurities exceed the PDE as well the control threshold of the 30% of the PDE. No further controls or actions are required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product Enzalutamide 160 mg has been performed considering all suspected and actual root causes.

An outcome of the nitrosamine impurities evaluation on the currently accepted template has been provided with the conclusion that the risk of nitrosamine formation is low. Therefore, no additional control measures were deemed necessary.

The analytical methods used have been adequately described and mostly satisfactorily validated in accordance with ICH guidelines. Forced degradation study has been carried out to demonstrate the stability-indicating nature of the developed methods.

Certificates of analysis of reference standards of impurities used for analysis of spray dried dispersion and used for analysis of the finished product have been enclosed. Information on used standards of Enzalutamide used for spray dried dispersion and finished product is satisfactory.

Batch analysis results were provided for four FP 160 mg film-coated tablets which were consequently used for validation and stability testing.

Batch analysis results were provided by the FP manufacturer for spray dried dispersion intermediate. In addition, batch analysis results, analysed by intermediate manufacturer, from batches of spray dried dispersion intermediate which are consequently used for FP process validation and stability testing were also provided. Analytical results obtained for spray dried dispersion and film-coated tablets are within the specification limits and confirm both the consistency of production and good performance of the analysis methods.

2.3.3.4. Stability of the product

The proposed shelf-life is 24 months without any special storage conditions.

Stability data for the enzalutamide spray-dried dispersion (SDD) intermediate and the final finished product Enzalutamide Viatris 160 mg film-coated tablets have been provided.

Stability of finished product

Stability data from three commercial scale batches of FP stored for up to 12 months under long term conditions (25°C / 60% RH), and under intermediate (30 °C / 75% RH), and for six months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. Stability data from another smaller scale batch were also presented. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, related substances, dissolution and microbial examination. No significant changes in any of the tested parameters were observed. The stability of the amorphous form of the AS in the finished product has been demonstrated for 6 months under 40 °C/75% RH.

The results of the photostability study in line with ICH Q1B, indicate that upon direct exposure to light the FP is not sensitive to light, hence no special storage conditions with respect to light are required.

Stability of Enzalutamide spray-dried dispersion:

Stability data from batches of intermediate stored for under long-term conditions (25 °C / 60% RH) and under accelerated conditions (40 °C / 75% RH) were provided. The batches of Enzalutamide spray-dried dispersion are identical to those proposed for manufacturing of the final product. No significant changes in the tested parameters have been observed at any timepoint. Results from samples under accelerated condition are available for 6 months. The analytical methods used in the stability testing program were the same as for release and were stability indicating. The proposed shelf-life for SDD can be approved.

Based on the available stability data, the proposed shelf-life of 24 months and without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

2.3.3.5. Adventitious agents

No excipients of human and/or animal origin are used in the manufacture of Enzalutamide Viatris 160 mg film-coated tablets. The suppliers of the excipients have provided declarations confirming their TSE/BSE status.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner. The consolidated version of the ASMF for the active substance is acceptable.

During the procedure a number of issues was raised as other concerns all of which were resolved, and the respective parts of the dossier was updated. No Major Objections were raised.

The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.3.6. Recommendations for future quality development

None.

2.4. Non-clinical aspects

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

2.4.1. Ecotoxicity/environmental risk assessment

The environmental risk assessment was performed following the "Guideline on the environmental risk assessment of medicinal products for human use" ((EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr., 2024). Based on the result obtained following the decision tree for Phase I ERA a tailored ERA was required since enzalutamide is an Endocrine Active Substance (EAS) with an antiandrogen mode of action. The Applicant conducted a comparative assessment to show similarity between the medicinal product at hand and the originator's product Xtandi in terms of indications, market areas, population groups, and strengths. In addition, the Applicant performed the required evaluation of the information available regarding the active substance to show that the scientific conclusions reached via earlier ERA remain applicable for his product. Based on the information available on the EMA website and the available documentation linked to the Marketing Authorisation Approval of the originator's product, Xtandi, is not expected to pose a risk to the environment.

2.4.2. Discussion on non-clinical aspects

The Applicant performed a thorough search of the literature. The new strength introduced has been developed only to serve the daily dose via the intake of lesser tablets therefore the marketing authorization of the new strength will not alter current environmental exposure, and the already available data from procedure EMEA/H/C/006299/0000 are sufficient to support the current application.

The information presented in this application is sufficient to support this conclusion and fulfils the requirements of the CHMP guideline (i.e., EMEA/CHMP/SWP/4447/00 Rev. 1 - Corr., 2024).

The non-clinical sections of the SmPC are in line with the latest version of the originator (Xtandi - EMEA/H/C/002639 - Last updated 09.07.2024)

2.4.3. Conclusion on the non-clinical aspects

The non-clinical data submitted is adequate. The discussion regarding the impurity profile is included and considered sufficient. There are no remaining issues from the non-clinical perspective.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Overview of clinical studies**

To support the application, the applicant has submitted two bioequivalence studies.

- Bioequivalence study **ENZ-0623-60** is conducted in order to compare the bioavailability of Enzalutamide 160 mg film-coated tablets and Xtandi 40 mg film-coated tablets in healthy, adult, male subjects under fasting conditions.
- Bioequivalence study **ENZ-0623-61** is conducted in order to compare the bioavailability of Enzalutamide 160 mg film-coated tablets and Xtandi 40 mg film-coated tablets in healthy, adult, male subjects under fed conditions.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

Study ENZ-0623-60:

The study is a comparative randomized, single dose, two-arm, parallel, open-label, study to determine the bioequivalence of Enzalutamide 160 mg film-coated tablets of PharOS Ltd, Greece (one tablet) relative to Xtandi 40 mg film-coated tablets (four tablets) of Astellas Pharma Europe B.V., The Netherlands, **under fasting conditions.**

Methods

- **Study design**

This study was a single centre, open-label, laboratory-blinded, randomized, single-dose, two-arm, two treatment, with parallel design comparing the bioequivalence of enzalutamide from Test product and Reference Product given as a single dose of 160 mg enzalutamide **under fasting conditions**, in healthy adult male subjects. To compare the rate and extent of absorption of the test product, Enzalutamide 160 mg film-coated tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of Xtandi 40 mg of Astellas Pharma Europe B.V., The Netherlands under fasting conditions, total of 80 (plus 2 alternates) healthy, adult, male human subjects were enrolled in the study.

- **Objectives**

Primary objective of this study was to investigate the bioequivalence of test product relative to reference product after a single oral dose of 160 mg enzalutamide to healthy male adults under fasting conditions.

Secondary objective of this study was to investigate the safety and tolerability of the test and reference formulation.

- **Dose and mode of administration**

On study day 1, following the overnight fast of at least 10 hours, the study drugs were administered according to a randomization plan. The administration of the study drugs was documented in the drug administration forms. Study drugs were administered as follows:
Test Product (Treatment A): One tablet of Enzalutamide 160 mg film-coated Tablets was given with 240 ml of water. Water was at room temperature and was measured with a graduated cylinder.
Reference Product (Treatment B): Four tablets of Xtandi 40 mg film-coated tablets were given with 240 ml of water. Water was at room temperature and was measured with a graduated cylinder.
The study drugs were given in a sitting posture under the supervision of trained study personnel.

No consumption of beverages or foods containing methylxanthines, (e.g. coffee, tea, cola, energy drinks, chocolate, etc.) or poppy containing foods was permitted for the subjects at least 48 hours prior to the study

drug administration until the end of confinement period. In addition, the consumption of any beverages or foods containing grapefruit, Seville orange or pomelo -containing beverages and food was prohibited at least 30 days prior to the study drug administration until donating the last sample of the study. Also, consumption of alcohol containing beverages and foods was prohibited for at least 30 days before study drug administration and until donating the last sample of the study. Food and fluid-intake was starting from the dinner served at least 11 hours before study drug administration on study day -1 until the end of confinement. The subjects were not allowed to consume any additional beverages or foodstuffs other than those provided throughout the period of confinement.

- **Sampling schedule**

Blood samples (22) were collected before dose (0.00) and 0.167, 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 10.00, 24.00, 36.00, 48.00 and 72.00 hours post dose. The total volume of blood draws did not exceed 420 ml for each subject.

- **Protocol deviations**

All protocol deviations in this study were minor in nature.

- **Randomization**

The study was randomized as a parallel design. Administration was done according to a plan of randomization. Subjects were assigned to one of the two treatments (test or reference).

- **Blinding**

The study was open-label study in terms of the drug and the dose. The randomization plan and dispense records were freely available to all CRO clinical personnel.

None of the laboratory staff in charge of the bioanalysis of plasma samples had access to the randomization, since the bioassay was performed blinded with regard to the randomization.

- **Test and reference products**

Table 1 Test and reference products description

Product Characteristics	**Test product**	**Reference Product**
Name	Enzalutamide 160 mg film-coated tablets	Xtandi™ 40 mg film-coated tablets
Strength	160 mg	40 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufactured for	Manufactured for: PharOS Pharmaceutical Oriented Services Single Member Ltd., Greece	Manufactured for: Astellas Pharma Europe B.V., The Netherlands

Lot No.	Bulk Batch No. CF0579 Packed Batch No. F0579C	22B0818
Batch size (Bio-batch)	22,500 tablets	
Measured content(s) (% of label claim)	101.3%	98.0%
Commercial Batch Size	As defined in 3.2.P.3.2	
Expiry Date/ Retest Date	05/2024	01/2026
Location of Certificate of Analysis	Module 5.3.1.2 – Section 16.1.6	Module 5.3.1.2 – Section 16.1.6
This product was used in the following trials:	Study Code No. ENZ-0623-60 Protocol Code: ENZ-T023	Study Code No. ENZ-0623-60 Protocol Code: ENZ-T023

- **Population(s) studied**

125 healthy subjects were screened to evaluate fulfilment of selection criteria described in the study protocol. 80 subjects plus 2 alternates were enrolled in the study. 80 subjects (100%) were included in PK and statistical analysis.

Demographic characteristics - subjects who were administered treatment A (N=40)

Table 2 Study ENZ-0623-60: Demographic characteristics

Variable			**Profile**		**Percentage**
Sex			Males		100.00%
Race			Middle Eastern		100.00%
Smoking status			Non-smokers		100.00%
	N	**Mean**	**SD**	**Min**	**Max**
Age (Years)	40	28	6.71	18	46
Height (cm)	40	174	5.74	165	188
Weight (Kg)	40	71	9.65	55	90
BMI (Kg/m^2)	40	23.6	2.86	18.8	28.7

Demographic characteristics - subjects who were administered treatment B (N=40)

Variable			**Profile**		**Percentage**
Sex			Males		100.00%
Race			Middle Eastern		100.00%
Smoking status			Non-smokers		100.00%
	N	**Mean**	**SD**	**Min**	**Max**
Age (Years)	40	30	8.47	19	49
Height (cm)	40	174	6.34	160	189
Weight (Kg)	40	71	11.02	55	90
BMI (Kg/m^2)	40	23.4	3.09	18.6	29.4

- **Determination of Sample size**

Sample size calculation was based on the power of Schuirmann's two one-sided tests procedure for interval hypotheses using the ± 20 rule for the assessment of average bioequivalence.

For Enzalutamide, considering total variability of 26% and a T/R ratio of 92.4%, power of 80%, 80 subjects were considered sufficient to establish bioequivalence between formulations.

- **Analytical methods**

Enzalutamide was determined by a LC/MS/MS method.

Study samples handling, processing and storage conditions were described in the Bioanalytical Report and in the Final Clinical Study Report.

Each run contained 16 QC samples (four samples at each of four levels) – more than 5 % of the total number of unknown samples in the run.

Unexpired certificates of Analysis for enzalutamide and enzalutamide-D6 were attached to the Bioanalytical Report. Isotopic enrichment of internal standard was 98.5 %. Stock solutions were stored at -20°C within the validated stability period. The preparation of calibration standards and quality control samples was from two separate stock solutions.

One sample was repeated under code A due to obvious problem arising during analysis (it means e.g. technical error, sample processing error, equipment failure). This reason for re-assay was predefined in the SOP and was acceptable.

The pre-dose concentrations higher than LLOQ were not observed.

Incurred sample reproducibility was evaluated with enough samples around cmax and at 72 h. At least 2/3 of the total samples selected for ISR evaluation have met the percent difference criteria of ≤ 20.0% of the mean between original and re-assayed concentrations.

All chromatograms (of 100 % of study subjects) and chromatograms of failed analytical run were attached to the Bioanalytical Report. The chromatography data acquisition and analysis were accomplished using SCIEX OS 2.1.0. No re-integration or manual integration was performed during the analysis of study samples.

The method was validated for the calibration range of 10 to 8000 ng/mL.

In line with the ICH guideline M10, 100 % chromatograms were submitted for all validation and partial validation tests.

- **Pharmacokinetic variables**

The pharmacokinetic parameters of enzalutamide were calculated from the drug concentration vs time profile by non-compartmental model using WinNonlin statistical software, version 8.4.

Primary pharmacokinetic variables:

C_{max}	Maximum measured plasma concentration over the time span specified.
Truncated AUC_{0-72}	The area under the plasma concentration versus time curve, from time (0) hour to the last measurable concentration time (72) hour, as calculated by the linear trapezoidal method via partial AUC.

Secondary pharmacokinetic variables:

$AUC_{0-\infty}$ The area under the plasma concentration versus time curve from time (0) to infinity. $AUC_{0-\infty}$ was calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant.

t_{max} Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, t_{max} was defined as the first time point with this value.

$t_{1/2el}$ The elimination or terminal half-life was calculated as 0.693/ K_{el}.

K_{el} Apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations and excluding C_{max}.

$AUC_{\%Extrap\_obs}$ Percent of $AUC_{0-\infty}$ extrapolated, represented as

$$[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100.$$

The secondary pharmacokinetic parameters $AUC_{0-\infty}$, K_{el}, $t_{1/2el}$ and $AUC_{\%Extrap\_obs}$ were calculated for information purposes only.

- **Statistical methods**

The pharmacokinetic calculations were performed by WinNonlin statistical software, version 8.4.

Descriptive statistics were calculated for plasma concentrations at each individual time point and for all PK parameters.

The statistical evaluation of bioequivalence included analysis of variance (ANOVA) in the logarithmically transformed data of C_{max} and truncated AUC_{0-72} calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed C_{max} and truncated AUC_{0-72} parameters.

An analysis of variance (ANOVA) tested for treatment effect was used. ANOVA was performed on ln truncated AUC_{0-72} and ln C_{max} for enzalutamide. Fixed effects model was used.

Treatment effect was tested at the 0.05 level of significance for C_{max} and truncated AUC_{0-72}. Intersubject variability was calculated using residual variance of ANOVA for ln-transformed analysis of C_{max} and truncated AUC_{0-72}.

A logarithmic transformation of the original data was used. Under the assumption of a logarithmic normal distribution, a parametric approach recommended by Steinijans and Diletti based on the inclusion of the shortest 90% confidence interval in the bioequivalence range was adopted.

For the parametric analysis of bioequivalence for ln-transformed data, the 90% confidence interval for the ratio of (Test /Reference) was to be contained within the acceptance boundaries of 80.00 - 125.00% for truncated AUC_{0-72} (that defines the extent of absorption) and for C_{max} (parameter that reflects rate of absorption) to conclude bioequivalence between formulations.

- ***Results***

Table 3 Pharmacokinetic parameters for enzalutamide (non-transformed values)

Pharmacokinetic parameter	Test (N=40)		Reference (N=40)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	187759.2	54268.54	186705.6	62438.59
$AUC_{(0-\infty)}$	548202.3	233672.67	545137.3	252541.32
C_{max}	5061.63	1353.58	4941.57	1074.04
T_{max}*	2.00	(0.67-4.00)	2.33	(1.00-4.50)
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 4 Statistical analysis for enzalutamide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-72h)}$	101.63	90.44 - 114.20	32.11
C_{max}	101.15	91.66 - 111.61	26.92
* estimated from the Residual Mean Squares			

Treatment effect was tested at the 0.05 level of significance for C_{max} and truncated AUC_{0-72}. There was no significant treatment effect for both parameters.

- **Safety data**

No adverse events were reported during the study.

Study ENZ-0623-61:

The study is a comparative randomized, single dose, two-arm, parallel, open-label, study to determine the bioequivalence of Enzalutamide 160 mg film-coated tablets of PharOS Ltd, Greece (one tablet) relative to Xtandi 40 mg film-coated tablets (four tablets) of Astellas Pharma Europe B.V., The Netherlands, under fed conditions.

Methods

- **Study design**

This study was a single centre, open-label, laboratory-blinded, randomized, single-dose, two-arm, two treatment, with parallel design comparing the bioequivalence of enzalutamide from Test product Enzalutamide 160 mg film-coated tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of the Reference Product, Xtandi (Enzalutamide), 40 mg of Astellas Pharma Europe B.V., The Netherlands

(Enzalutamide) given as a single dose of 160 mg enzalutamide under fed conditions, in healthy adult male subjects. A total of 80 (plus 2 alternates) healthy, adult, male human subjects were enrolled in the study.

- **Objectives**

Primary objective of this study is to investigate the bioequivalence of test product relative to reference product after a single oral dose of 160 mg enzalutamide to healthy male adults under fed conditions.

Secondary objective of this study is to investigate the safety and tolerability of the test and reference formulation.

- **Dose and mode of administration**

On study day 1, following the overnight fast of at least 10 hours, a standardized high fat, high caloric breakfast was served 30 minutes before dosing. Thereafter, the study drugs were administered according to a randomization plan. The administration of the study drugs was documented in the drug administration forms. Study drugs were administered by the clinical staff of IPRC as follows:

Test Product (Treatment A): One tablet of Enzalutamide 160 mg film-coated Tablets was given with 240 ml of water. Water was at room temperature and was measured with a graduated cylinder.
Reference Product (Treatment B): Four tablets of Xtandi 40 mg film-coated tablets were given with 240 ml of water. Water was at room temperature and was measured with a graduated cylinder.
The study drugs were given in a sitting posture under the supervision of trained study personnel.

No consumption of beverages or foods containing methylxanthines, (e.g. coffee, tea, cola, energy drinks, chocolate, etc.) or poppy containing foods was permitted for the subjects at least 48 hours prior to the study drug administration until the end of confinement period. In addition, the consumption of any beverages or foods containing grapefruit, Seville orange or pomelo -containing beverages and food was prohibited at least 30 days prior to the study drug administration until donating the last sample of the study. Also, consumption of alcohol containing beverages and foods was prohibited for at least 30 days before study drug administration and until donating the last sample of the study. Food and fluid-intake was starting from the dinner served at least 11 hours before study drug administration on study day -1 until the end of confinement. The subjects were not allowed to consume any additional beverages or foodstuffs other than those provided throughout the period of confinement.

Subjects received a standardized, high-fat high-calorie breakfast 30 minutes prior to administration of the study drug. The subjects were asked to finish breakfast within 30 minutes before the scheduled dosing time. High fat, high calories meal was served in the study.

- **Sampling schedule**

Blood samples (22) were collected before dose (0.00) and 0.167, 0.333, 0.667, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 10.00, 24.00, 36.00, 48.00 and 72.00 hours post dose. The total volume of blood draws did not exceed 420 ml for each subject.

- **Protocol deviations**

All protocol deviations in this study were minor in nature.

- **Randomization**

The study was randomized as a parallel design. Administration was done according to a plan of randomization. Subjects were assigned to one of the two treatments (Test or Reference).

- **Blinding**

The study was open-label study in terms of the drug and the dose. The randomization plan and dispense records were freely available to all CRO clinical personnel.

None of the laboratory staff in charge of the bioanalysis of plasma samples had access to the randomization, since the bioassay was performed blinded with regard to the randomization.

- **Test and reference products**

Table 5 *Test and reference products description*

Product Characteristics	**Test product**	**Reference Product**
Name	Enzalutamide 160 mg film-coated tablets	Xtandi™ 40 mg film-coated tablets
Strength	160 mg	40 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufactured for	Manufactured for: PharOS Pharmaceutical Oriented Services Single Member Ltd., Greece	Manufactured for: Astellas Pharma Europe B.V., The Netherlands
Lot No.	Bulk Batch No. CF0579 Packed Batch No. F0579C	22B0818
Batch size (Bio-batch)	22,500 tablets	
Measured content(s) (% of label claim)	101.3%	98.0%
Commercial Batch Size	As defined in 3.2.P.3.2	
Expiry Date/ Retest Date	05/2024	01/2026
Location of Certificate of Analysis	Module 5.3.1.2 – Section 16.1.6	Module 5.3.1.2 – Section 16.1.6
This product was used in the following trials:	Study Code No. ENZ-0623-61 Protocol Code: ENZ-T024	Study Code No. ENZ-0623-61 Protocol Code: ENZ-T024

- **Population(s) studied**

110 healthy subjects were screened to evaluate fulfilment of selection criteria described in the study protocol. 80 subjects plus 2 alternates were enrolled in the study. 80 subjects (100%) were included in PK and statistical analysis.

Table 6 Demographic characteristics - subjects who were administered treatment A (N=40)

Variable			Profile		Percentage
Sex			Males		100.00%
Race			Middle Eastern		100.00%
Smoking status			Non-smokers		100.00%
	N	Mean	SD	Min	Max
Age (Years)	40	28	7.45	18	41
Height (cm)	40	174	3.66	167	178
Weight (Kg)	40	71	10.44	55	93
BMI (Kg/m^2)	40	23.6	3.16	18.6	29.8

Table 7 Demographic characteristics - subjects who were administered treatment B (N=40)

Variable			Profile		Percentage
Sex			Males		100.00%
Race			Middle Eastern		100.00%
Smoking status			Non-smokers		100.00%
	N	Mean	SD	Min	Max
Age (Years)	40	30	7.62	19	45
Height (cm)	40	174	6.58	160	189
Weight (Kg)	40	74	11.96	57	94
BMI (Kg/m^2)	40	24.2	3.24	19.2	29.7

- **Determination of Sample size**

Sample size calculation was based on the power of Schuirmann's two one-sided tests procedure for interval hypotheses using the ± 20 rule for the assessment of average bioequivalence.
For Enzalutamide, considering total variability of 26% and a T/R ratio of 92.4%, power of 80%, 80 subjects were considered sufficient to establish bioequivalence between formulations.

- **Analytical methods**

Enzalutamide was determined by the same validated LC/MS/MS method as in the study ENZ-0623-60 over the same calibration range of 10 to 8000 ng/mL. The validation parameters have already been summarized and assessed for the study ENZ-0623-60 (see above). In addition, the long-term stability of enzalutamide in human plasma was proved also in presence of N-Desmethyl Enzalutamide up to 22 days at -20 °C (Attachment 05 to the Validation Report).

The compliance with SOPs and GLP principles was declared and the QAU statement was enclosed in the Bioanalytical Report.

Study samples handling, processing and storage conditions were described in the Bioanalytical Report and in the Final Clinical Study Report.

All acceptance criteria for calibrators and QC samples followed the ICH guideline M10. Each run contained 16 QC samples (four samples at each of four levels) – more than 5 % of the total number of unknown samples in the run. All runs passed the acceptance criteria. The results of between-run QC samples accuracy and precision demonstrated reliable performance of the method. QCs graphs trend analysis and internal standard plots were provided as outlined in the updated ICH M10 guideline. All runs passed the acceptance criteria.

No sample was repeated. There was no pre-dose sample with quantifiable concentration.

Incurred sample reproducibility was evaluated with enough samples around cmax and at 72 h. At least 2/3 of the total samples selected for ISR evaluation have met the percent difference criteria of ≤ 20.0% of the mean between original and re-assayed concentrations as outlined in the guidelines.

All chromatograms (100 % of study subjects) as well as all validation chromatograms were attached to the Bioanalytical Report. The chromatography data acquisition and analysis were accomplished using SCIEX OS 2.1.0 software. No re-integration or manual integration was done.

- **Pharmacokinetic variables**

The pharmacokinetic parameters of enzalutamide were calculated from the drug concentration vs time profile by non-compartmental model using WinNonlin statistical software, version 8.4.

Primary pharmacokinetic variables:

C_{max} Maximum measured plasma concentration over the time span specified.

Truncated AUC_{0-72} The area under the plasma concentration versus time curve, from time (0) hour to the last measurable concentration time (72) hour, as calculated by the linear trapezoidal method via partial AUC.

Secondary pharmacokinetic variables:

$AUC_{0-\infty}$ The area under the plasma concentration versus time curve from time (0) to infinity. $AUC_{0-\infty}$ was calculated as the sum of the AUC_{0-t} plus the ratio of the last measurable plasma concentration to the elimination rate constant.

t_{max} Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, t_{max} was defined as the first time point with this value.

$t_{1/2el}$ The elimination or terminal half-life was calculated as 0.693/ K_{el}.

K_{el} Apparent first-order elimination or terminal rate constant calculated from a semi-log plot of the plasma concentration versus time curve. The parameter was calculated by linear least-squares regression analysis using the last three (or more) non-zero plasma concentrations and excluding C_{max}.

$AUC_{\%Extrap\_obs}$ Percent of $AUC_{0-\infty}$ extrapolated, represented as

$$[(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}] \times 100.$$

The secondary pharmacokinetic parameters $AUC_{0-\infty}$, K_{el}, $t_{1/2el}$ and $AUC_{\%Extrap\_obs}$ were calculated for information purposes only.

- **Statistical methods**

The pharmacokinetic calculations were performed by WinNonlin statistical software, version 8.4.

Descriptive statistics were calculated for plasma concentrations at each individual time point and for all PK parameters.

The statistical evaluation of bioequivalence included analysis of variance (ANOVA) in the logarithmically transformed data of C_{max} and truncated AUC_{0-72} calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed C_{max} and truncated AUC_{0-72} parameters.

An analysis of variance (ANOVA) tested for treatment effect was used. ANOVA was performed on ln truncated AUC_{0-72} and ln C_{max} for enzalutamide. Fixed effects model was used.

Treatment effect was tested at the 0.05 level of significance for C_{max} and truncated AUC_{0-72}. Intersubject variability was calculated using residual variance of ANOVA for ln-transformed analysis of C_{max} and truncated AUC_{0-72}.

A logarithmic transformation of the original data was used. Under the assumption of a logarithmic normal distribution, a parametric approach recommended by Steinijans and Diletti based on the inclusion of the shortest 90% confidence interval in the bioequivalence range was adopted.

For the parametric analysis of bioequivalence for ln-transformed data, the 90% confidence interval for the ratio of (Test /Reference) was to be contained within the acceptance boundaries of 80.00 - 125.00% for truncated AUC_{0-72} (that defines the extent of absorption) and for C_{max} (parameter that reflects rate of absorption) to conclude bioequivalence between formulations.

- ***Results***

Table 8 Pharmacokinetic parameters for enzalutamide (non-transformed values)

Pharmacokinetic parameter	**Test (N=40)**		**Reference (N=40)**	
	arithmetic mean	**SD**	**arithmetic mean**	**SD**
$AUC_{(0-72h)}$	186955.4	62914.37	170928.8	50134.34
$AUC_{(0-\infty)}$	701132.1	399684.94	628466.0	393636.05
C_{max}	3987.39	1031.87	4145.02	1133.31
T_{max}*	3.33	(0.67-24.00)	2.00	(0.67-6.00)
AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours				
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity				
C_{max} maximum plasma concentration				
T_{max} time for maximum concentration (* median, range)				

Table 9 Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**CV%***
$AUC_{(0-72h)}$	107.87	95.76 - 121.53	32.85
C_{max}	96.26	86.69 - 106.89	28.70
* estimated from the Residual Mean Squares			

Treatment effect was tested at the 0.05 level of significance for C_{max} and truncated AUC_{0-72}. There was no significant treatment effect for both parameters.

- ***Safety data***

One subject reported hypotension during the study on 07/03/24, blood pressure test was performed at 07:30 and found below 90/60 mm Hg then blood pressure test was repeated at 07:56 and found to be within normal range. The AE was resolved prior to study drug administration.

No severe, serious or life-threatening adverse events were reported during the course of the study. The test and reference products were found to be safe and well tolerated by the study subjects.

Pharmacokinetic Conclusion

Based on the presented bioequivalence studies Enzalutamide 160 mg Film-coated Tablet could is considered bioequivalent with Xtandi 40 mg, Film-coated Tablet at 160 mg dose.

Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.5.3. Discussion on clinical pharmacology

The reference product can be taken with or without food according to the SmPC. Since the specific formulation (solid dispersion) of the tablet is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, both fasted and fed state comparisons of test to reference formulations are required. Composition of served high fat breakfast in study ENZ-0623-61 is in accordance with guideline recommendations.

In accordance with "Enzalutamide soft capsule 40 mg and film-coated tablet 40 mg & 80 mg product-specific bioequivalence guidance" (EMA/CHMP/371467/2021), a cross-over design is preferable to a parallel study, but a parallel study is also acceptable considering the long half-life of enzalutamide (5.8 days - range 2.8 to 10.2 days).

The median time to reach maximum plasma enzalutamide concentrations (C_{max}) is 2 hours (range 0.5 to 6 hours), the sampling schedule is considered appropriate because it ensured reliable estimation of the peak exposure. Samples were collected up to 72 hours, this is sufficient for IR product despite the long half-life of enzalutamide.

The chosen population complies with the guidelines and both treatment groups in both studies are well balanced and comparable.

All protocol deviations in both studies were minor in nature and consequently, had no significant impact on the integrity of the study results or on subject safety. Some samples after confinement period were not withdrawn on scheduled time. Nevertheless, the effect of these time deviations in collection time on results is

minimal as the actual post-dose sample collection times were taken into consideration in the statistical analysis. There were no non-zero pre-dose concentration

Enzalutamide was determined in both studies by a LC/MS/MS method. developed and validated in compliance with ICH guideline M10 over the calibration range of 10 to 8000 ng/mL.

The compliance with SOPs and GLP principles was declared and the Quality Assurance Unit statement was enclosed in the Bioanalytical Report.

The results of between-run QC samples accuracy and precision demonstrated reliable performance of the method. QCs graphs trend analysis and internal standard plots were provided as outlined in the updated ICH M10 guideline.

The method was validated for the calibration range of 10 to 8000 ng/mL. The method was demonstrated to be selective, linear, and reliable. The newer type of detector was evaluated in the partial validation (within- and between-run accuracy, precision, and linearity). The extent of partial validation was acceptable.

Stability studies demonstrated that analyte was stable under conditions of samples shipment, treatment, and analysis. Study samples were analysed within a period covered by the long-term stability data.

100 % chromatograms were submitted for all validation and partial validation tests as outlined in the updated ICH guideline M10.

Overall, the method was suitable for the determination of enzalutamide in K3EDTA human plasma samples from bioequivalence studies over a calibration range of 10 ng/mL to 8000ng/mL. Enzalutamide was demonstrated to be stable under various storage conditions.

Based on the presented bioequivalence studies Enzalutamide 160 mg Film-coated Tablet could be considered bioequivalent with Xtandi 40 mg, Film-coated Tablet at 160 mg dose.

2.5.4. Conclusions on the clinical pharmacology

Based on the presented bioequivalence studies Enzalutamide 160 mg Film-coated Tablet is considered bioequivalent with Xtandi 40 mg, Film-coated Tablet at 160 mg dose.

2.6. Clinical efficacy

No new efficacy data have been provided as part of this submission. This is acceptable as the applicant is not seeking approval for any new indication.

2.7. Risk Management Plan

2.7.1. Safety concerns

2.7.1.1. Summary of safety concerns

Table 10: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Seizure Fall Non-pathological fracture Ischemic heart disease
Important potential risks	None
Missing information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

In line with the reference product the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xtandi. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

This application concerns a hybrid version of enzalutamide 160 mg film-coated tablets. The reference product Xtandi 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 (see section 5.1).
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) (see section 5.1).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- 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 (see section 5.1).
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Two bioequivalence studies (Study ENZ-0623-60 and Study ENZ-0623-61 form the pivotal basis for this application. Both studies were single centre, open-label, laboratory-blinded, randomized, single-dose, two-arm, two treatment, with parallel design comparing the bioequivalence of enzalutamide from Test product and Reference Product given as a single dose of 160 mg enzalutamide under fasting or fed conditions, in healthy adult male subjects.

A cross-over study design would have been preferable to a parallel study, but a parallel study is also acceptable considering the long half-life of enzalutamide (5.8 days - range 2.8 to 10.2 days) and is considered adequate to evaluate the bioequivalence of this formulation. In accordance with "Enzalutamide soft capsule 40 mg and film-coated tablet 40 mg & 80 mg product-specific bioequivalence guidance" (EMA/CHMP/371467/2021 the reference product can be taken with or without food according to the SmPC.

Both fasted and fed state comparisons of the test to the reference formulations were performed, since the specific formulation (solid dispersion) of the tablet is known to be critical to the performance of the formulation

in fed conditions and could not be assumed that the impact of food would have been the same regardless of formulation.

Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Enzalutamide 160 mg film-coated tablets met the protocol-defined criteria for bioequivalence when compared with the Xtandi 40 mg film-coated tablets (four tablets). The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product could therefore be concluded.

Conclusions

The overall benefit /risk balance of Enzalutamide 160 mg film-coated tablets is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and pharmacology, the CHMP considers by consensus that the benefit-risk balance of, Enzalutamide Viatris 160mg new strength is favourable in the following indications:

- 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 (see section 5.1).
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) (see section 5.1).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- 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 (see section 5.1).
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

The CHMP therefore recommends the extension of the marketing authorisation for Enzalutamide Viatris subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.