27 June 2024
EMA/338096/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Enzalutamide Viatris

International non-proprietary name: Enzalutamide

Procedure No. EMEA/H/C/006299/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AES	atomic emission spectroscopy
AA	abiraterone acetate
AA+ P	abiraterone acetate plus prednisone
AAFP	abiraterone acetate fine particle
AAWS	antiandrogen withdrawal syndrome
ABI	abiraterone
ACTH	Adrenocorticotrophic hormone
ADT	androgen-deprivation therapy
AE	adverse event
AIPC	androgen-independent prostate cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Ames	Ames test for microbial mutagenesis
AMPK	AMP-dependent protein kinase
AP	alkaline phosphatase
API	active pharmaceutical ingredient
AR	androgen receptor
AR-V	AR variants
ARV7	AR splice variant 7
ASI	androgen signaling inhibitor
ASM	active substance manufacturer
ASMF	active substance master file = drug master file
AST	aspartate aminotransferase
AUC	area under the curve
AUC	area under the plasma concentration-time curve
BCS	biopharmaceutical classification system
BDL	below the limit of detection
BE	bioequivalence
BETi	bromodomain extra-terminal inhibitor
BMD	bone mineral density
BMI	body mass index
bPFS	biochemical progression free survival

AES	atomic emission spectroscopy
C trough	trough plasma concentration
CBR	clinical benefit rate
CCMG	caprylocaproyl macrogolglycerides
CDK4/6	cyclin-dependent kinases 4 and 6
CgA	chromogranin A
CI	confidence interval
Cmax	maximum plasma concentration
CN	chemonaive
CoA	certificate of analysis
CR	complete response
CRPC	castration-resistant prostate cancer
CRS	chemical reference substance
CTD	common technical document
CTX	carboxy-terminal collagen crosslinks
CVEs	cardiovascular events
DDI	drug-drug interaction
DDR	DNA damage response
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DL	detection limit
DMF	dimethylformamide
DSC	differential scanning calorimetry
DUBs	deubiquitinases
ECD	electrochemical detection
ECG	electrocardiogram
EDMF	European drug master file
EDQM	European Directorate for the Quality of Medicines
ee	enantiomeric excess
ENZ	enzalutamide
EP	European Pharmacopoeia

AES	atomic emission spectroscopy
ER+/PgR+	oestrogen receptor–positive/progesterone receptor–positive
ET	endocrine therapies
FID	flame ionisation detection
FTIR	Fourier transmission infrared (spectroscopy)
GC	gas chromatography
GM	geometric mean
GMP	good manufacturing practice
HDPE	high density polyethylene
HN	hormone-naive
HPLC	high performance liquid chromatography
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
HSP	heat shock protein
ICH	International Conference on Harmonization
ICP	inductively coupled plasma
IPA	isopropyl alcohol
IPC	in-process control test
IR	infra-red
KF	Karl Fischer
LBD	ligand binding domain
LC3B	light chain 3B
LC-MS/MS	liquid chromatography tandem mass spectrometry
LHRHa	luteinizing-hormone releasing hormone analogue
LLoQ	lower limits of quantification
LOD	loss on drying
LoD	limit of detection
LoQ	limit of quantitation
MCC	microcrystalline cellulose
mCRPC	metastatic castration-resistant prostate cancer

AES	atomic emission spectroscopy
MFS	metastasis free survival
mHSPC	metastatic hormone-sensitive prostate cancer
MS	metabolic syndrome
MS	mass spectroscopy
MTD	maximum tolerated dose
NDE	N-desmethyl ENZ
NHT	novel hormonal therapy
NIR	near infra-red
nmCRPC	non-metastatic castration resistant prostate cancer
NMR	nuclear magnetic resonance
OAA	originator abiraterone acetate
PCa	prostate cancer
PCTFE	polychlorotrifluoroethene
PDA	Photo diode array
PDE	permitted daily exposure
PDX	patient-derived xenograft
PET/CT	positron emission tomography/computed tomography
PFS	progression-free survival
PK	pharmacokinetic
PL	placebo
PSA	prostate-specific antigen
PSA-RR	PSA response rate
PSMA	prostate-specific membrane antigen
PTEN	phosphatase and tensin homolog
PVC	polyvinyl chloride
QL	quantitation limit
QOS	quality overall summary
Ra-223	radium-223 dichloride
RH	relative humidity
RLT	radioligand therapy
ROI	residue on ignition

AES	atomic emission spectroscopy
RR	risk ratio
RRt	relative retention time
RSABE	reference-scaled average bioequivalence
Rt	retention time
SAL	sterility assurance level
SD	stable disease
S-D	Sprague-Dawley
SEM	scanning electron microscopy
SOCS3	suppressor of cytokine signalling 3
TGA	thermo-gravimetric analysis
THF	tetrahydrofuran
TLC	thin layer chromatography
TTPP	time to PSA progression
ULN	upper limit of normal
V/F	volume of distribution
XRD	X-ray diffraction
XRPD	X-ray powder diffraction

This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Viatris Limited submitted on 26 June 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Enzalutamide Viatris, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 February 2023.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication

Enzalutamide Viatris 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).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Xtandi instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Xtandi 40 and 80 mg, film-coated tablet
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 21/6/2013
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/13/846/002-003

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xtandi 40 and 80 mg, film-coated tablet
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 21/6/2013
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/13/846/002-003

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Xtandi 40 mg, film-coated tablet
- Marketing authorisation holder: Astellas Pharma Europe B.V.
- Date of authorisation: 21/6/2013
- Marketing authorisation granted by: Union
- Marketing authorisation number: EU/1/13/846/002-003
- Bioavailability study number(s): ENZ-0123-2, ENZ-0123-3

1.3. Information on paediatric requirements

Not applicable

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP were:

Rapporteur: Tomas Radimersky

The application was received by the EMA on	26 June 2023
The procedure started on	17 August 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	6 November 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	20 November 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 February 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	28 May 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 June 2024
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	27 June 2024

2. Scientific discussion

2.1. Introduction

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 the nuclear translocation of activated receptors and the association of the activated androgen receptor with DNA. The inhibition happens 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.

Enzalutamide belongs to hormone antagonists and related agents, anti-androgens group. Enzalutamide is used in the treatment of adult men with metastatic hormone-sensitive prostate cancer. Can be asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom

chemotherapy is not clinically indicated yet, or whose disease has progressed on or after docetaxel therapy.

This application concerns the marketing authorisation for Enzalutamide Viatris 40 mg and 80 mg, film-coated tablets submitted as a centralised procedure, according to Regulation (EC) No 726/2004 as Generic of a Centrally Authorised Medicinal Product. The application has been submitted under Article 10(1) of directive 2001/83/EC as generic application. The reference product is Xtandi 40 mg and 80 mg film-coated tablets. The reference product was authorised in EU on 21 June 2013 via the centralised procedure. Current Marketing Authorisation Holder is Astellas Pharma Europe B.V.

Pharmacotherapeutic group: Hormone antagonists and related agents, anti-androgens. ATC code: L02BB04

The final product is manufactured in two strengths, 40mg and 80 mg. During the procedure the applicant took the opportunity to further align the indications with the reference product as per post authorisation procedure for the reference medicinal product Xtandi II/63.

The final approved indications are:

Enzalutamide Viatris 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.

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.

Two bioequivalence (BE) studies ENZ-0123-2 and ENZ-0123-3 have been performed using the originator Xtandi as a reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 40 and 80 mg of enzalutamide as active substance.

Other ingredients are: methacrylic acid-ethyl acrylate copolymer, colloidal anhydrous silica, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose, macrogol, titanium dioxide, iron oxide yellow, talc, as described in section 6.1.

The product is available in aluminium-OPA/Alu/PVC blister pack for both strengths as described in section 6.5 of the SmPC. Three types of package are available: common blister pack, blister calendar pack and unit-dose blister pack.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of enzalutamide is 4-[3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl]-2-fluoro-N-methylbenzamide corresponding to the molecular formula $C_{21}H_{16}F_4N_4O_2S$. It has a relative molecular mass of 464.44 and the following structure:

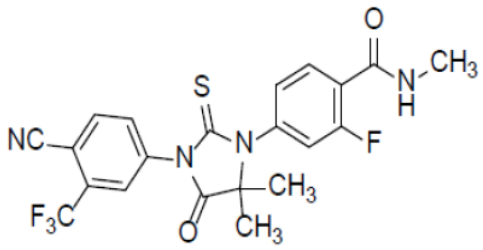

Figure 1: Active substance structure

The chemical structure of enzalutamide was elucidated by a combination of infrared spectrum (IR), NMR (^{1}H-NMR and ^{13}C-NMR) and mass spectrum. UV maxima and elemental analysis data are also presented. The polymorphic form of enzalutamide commercial scale batches was demonstrated by X-ray powder diffraction (XRPD).

Enzalutamide is a white or almost white, non-hygroscopic, crystalline powder, freely soluble in acetonitrile, methylene chloride and practically insoluble in water an aqueous solutions regardless of pH. The melting point is around 200°C. The BCS classification is Class 2. Enzalutamide has a non-chiral molecular structure.

The active substance (AS) exhibits polymorphism. Satisfactory information regarding polymorphism has been submitted. The active substance manufacturer consistently produces a single polymorphic form; the polymorph is controlled by XRPD. Stability results indicate that the desired polymorph is stable.

2.2.2.2. Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The synthesis process of enzalutamide consists of several chemical transformation steps involving well-defined starting materials (SMs). Following a Major Objection (MO) raised by the CHMP, the selection of SMs was further justified in line with ICH Q11, and their specification was updated thus resolving the MO. The starting materials are considered acceptable.

Critical process parameters have been presented for each intermediate with acceptable justification. In-process controls have also been presented including methods description.

Potential and actual impurities were discussed with regards to their origin and characterised. Regarding genotoxic impurities, ICH M7 guideline does not apply for active substances which are intended for advanced cancer indications, like enzalutamide. Verification of the method used for determination of carry over impurities has been assessed and was satisfactorily discussed.

The AS packaging has been clearly described and is acceptable. The primary packaging complies with EC 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for appearance, identity (IR, HPLC), polymorphic form (XRPD), water content (Ph. Eur.), sulphated ash/residue on ignition (Ph. Eur.), related substances (HPLC, LC-MS), assay (HPLC), residual solvents (GC).

The proposed limits for specified impurities have been set in accordance with ICH Q3A and are acceptable.

The proposed specification limits for residual solvents are in-line with the ICH Q3C guideline for residual solvents. The discussion concerning residual solvents (class 1) has been provided and new testing of residual solvents has been included in the updated specification as was requested.

The potential presence of nitrosamine impurities was discussed, and experimental data performed on three batches of AS was provided. Nitrosamines impurities were not detected.

The evaluation for elemental impurities has been performed according to ICH Q3D and the analytical results are satisfactory (results lower than 30% of daily PDE limit).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Forced degradation studies were performed for the stability indicating methods. Satisfactory information on the in-house reference standards used has been provided.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.1. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Moreover stability study on three commercial scale and alternative batches recently started.

The following parameters were tested: appearance, identification, water content, related substances, assay) and Impurity A. The analytical methods used were the same as for release and were stability indicating.

No significant changes or trends have been observed at accelerated and long-term stability. Hence, the stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

Forced degradation studies under stress conditions UV, acid stress, base stress, hydrogen peroxide stress thermal stress and photostability testing were also performed. The AS is most sensitive towards oxidative stress and hydrolysis under basic and acidic conditions.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. Based on the presented stability data re-test period of 36 months is proposed.

The stability results justify the proposed retest period and the proposed storage conditions.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as film coated tablets in two strengths 40 and 80 mg. The appearance is as follows:

40 mg: Yellow, round, film-coated tablets, debossed with "40" on one side, with diameter 10.1 mm;

80 mg: Yellow, oval, film-coated tablets, debossed with "80" on one side, with dimensions 17.1 mm.

The finished product has been developed to be a generic equivalent to the reference medicinal product Xtandi 40 mg film-coated tablets packaged in PVC/PCTFE/Al blister wallets. Consequently, the objective was to prepare a film-coated tablets being essentially similar to the reference medicinal product.

Composition of tested finished product is not the same as composition of the reference product, but it is similar. Different qualitative composition has been justified.

All excipients are well-known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except of coating mixture and 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 of excipients have been discussed. The type of three excipients has been clarified. 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.

Compatibility study has been performed using AS and all excipients used in the finished product formulation. No compatibility issues have been identified between the active substance and the excipients in the final product.

The quality target product profile (QTPP) and the critical quality attributes have been identified and discussed.

Comparative assay and impurity profile of the developed finished product and reference finished product have been considered similar.

Spray-drying approach has been adopted in manufacturing process, leading to a spray-dried dispersion intermediate of the active substance.

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

The pharmaceutical equivalence was established by appropriate comparative dissolution, assay and impurity studies between the generic product enzalutamide 80 mg film-coated tablets and the reference product (Xtandi 40 mg film-coated tablets).

Bioequivalence was established by two in vivo bioequivalence studies (refer to clinical part) for the 80 mg strength versus the 40 mg reference product. The CHMP raised a Major Objection about the batch

size of the finished product which according to the Guideline on Investigation on Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) should originate from a biobatch of at least 1/10 of production scale or 100,000 units, whichever is greater. Since the batch size of the biobatch 80 mg strength was smaller, this the smaller batch size should be considered as a maximum production scale. For 40 mg strength the proposed maximum batch size can be acceptable. The applicant in their response agreed to define the commercial batch size for the 80 and 40 mg strengths as requested (see also discussion about the other MO in "Manufacture of the product and process controls").

The dissolution profiles of the test and reference product used in the bioequivalence study respectively, have been compared in four different buffers: QC method, HCl 0.1N, acetate buffer pH 4.5 and phosphate buffer pH 6.8. For HCl 0.1N, acetate buffer pH 4.5 and phosphate buffer pH 6.8, the selected conditions are paddle apparatus, 50 rpm and 900 mL medium volume.

The dissolution profiles have been shown similar in most of cases in almost all tested dissolution conditions but one. The reason of differences between dissolution profiles of biobatch and reference product where difference is observed has been adequately discussed. According to the Guideline on Investigation on Bioequivalence, "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." Therefore, it can be concluded that the test product is considered to be similar to the reference product based on the presented in vivo bioequivalence data, the comparative dissolution data and justifications.

A strength biowaiver for the 40 mg has been applied. Since the general requirements according to Guideline on Investigation on Bioequivalence are met, the biowaiver can be accepted.

The choice of container closure system finished product is Aluminium-OPA/Alu/PVC blisters. It is considered appropriate for this dosage form and has been justified. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process of finished product includes the preparation of the enzalutamide spray-dried dispersion (non-standard manufacturing process - wet granulation step) and manufacture of the final pharmaceutical formula (standard manufacturing process). The tabletting mixture is prepared by dry mixing of all tablet core components. The tablet cores are undergoing the film coating.

The 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 presented.

Corresponding in-process controls (IPC) have been stated for each manufacturing step with corresponding specification. Analytical methods used during in-process controls have been described or references on methods used have been stated. The proposed IPCs are adequate for this type of manufacturing process.

The calculation of the expiry date of the finished product has been set according to EMA guideline EMA/CHMP/QWP/245074/2015.

Satisfactory information on holding times has been provided.

The manufacturing process is considered a non standard process because of the spray dried dispersion part of the process. Consequently, it should be validated in a full scale according to the Process validation guideline ((EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1). In this regard the CHMP raised a major objection (MO) about the originally proposed batch size for the 80 mg strength. In their response the applicant agreed to define the batch size of the finished product based on the batch size of spray dried dispersion and clarified the exact batch size of the finished product. This was considered satisfactory and the MO was resolved.

Process validation and evaluation for both manufacturing processes (intermediate and final product) has been performed according to the Guideline on process validation. Validation protocols have been submitted and all results obtained were within the acceptance limits set. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.2.3.3. Product specification(s)

The finished product release and shelf life specifications include appropriate tests for this kind of dosage form: description (visual), identification of enzalutamide (HPLC, UV), identification of titanium dioxide (In-house), identification of iron oxide (In-house), 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.).

Parameters in release and shelf-life specifications of Enzalutamide spray-dried dispersion controlled by the intermediate manufacturer and adopted by finished product manufacturer are identical. Tests included in the specifications of the intermediate product are acceptable. The limit for acetone in SDD has been tightened and is acceptable. Test demonstrating amorphous form of the finished substance and evaluation of particle size have been included as in-process test of spray dried dispersion. The microbial testing is performed on each batch of spray-dried dispersion.

Release and shelf-life specifications of Enzalutamide 40 and 80 mg film-coated were set according to the Ph. Eur. and the relevant requirements of ICH Guideline Q6A. Tests for water content and test demonstrating amorphous form of the active substance were omitted and that was satisfactorily justified. Parameters typical for dosage form tablets (friability and resistance to crushing) are controlled as IPC. Skip testing is proposed for microbiological testing of the finished product what has been appropriately justified.

The limit for dissolution in release and shelf-life specification was tightened during the procedure following an MO raised by the CHMP to be according to the analytical results of the biobatch and in line with the "Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action".

Probable genotoxic impurities have been discussed. Their limits are acceptable (see also non-clinical assessment report).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with Q3D guideline. 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 potential presence of nitrosamine impurities in the finished product Enzalutamide 40 mg and 80 mg has been performed considering all suspected and actual root causes. Based on the information provided it is accepted that no risk was identified on the possible presence of

nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

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

Sufficient information regarding the reference standards of impurities used for analysis of spray dried dispersion and used for analysis of the finished product have been enclosed. Information on primary reference standard of Enzalutamide used for spray dried dispersion and finished product has been adequately updated.

Batch analysis results were provided for three commercial scale batches of each strength of the finished product which were consequently used for process validation and stability testing.

Batch analysis results were also provided for three batches of spray dried dispersion which were used for process validation and stability testing.

Analytical results obtained for both spray dried dispersion and film-coated tablets are within the specification limits and confirm the consistency of production and good performance of the analysis methods.

2.2.3.4. Stability of the product

Stability data for enzalutamide SDD and the finished product Enzalutamide 40 and 80 mg film-coated tablets have been provided.

Stability data from 3 commercial batches of each strength stored for up to 18 months under long term conditions (25ºC / 60% RH), intermediate (30ºC / 75% RH), and for six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. 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.

Stability of amorphous form has been demonstrated in the finished product (film-coated tablets) during stability studies. Results obtained met the acceptance criteria. An observed change for dissolution at accelerated conditions and long-term conditions has been discussed and justified and does not pose any concern with regard to the proposed shelf life or the quality of the product over time.

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

Stability testing will be on-going up to 48 months for Enzalutamide film-coated tablets both strengths.

In addition, bulk products have been tested. All results obtained for bulk products packed in the intended storage containers are in line with acceptance criteria set. It has been confirmed that shelf-life starts from the date that the intermediate is mixed with the tablet excipients, but not exceeding 4 months from the manufacturing date of the respective intermediate batch of SDD used in the manufacturing of the finished product, in line with the requirements defined in the Guideline EMA/CHMP/QWP/245074/2015.

Stability of Enzalutamide SDD

Stability data at long-term conditions are available for up to 18 months for SDD packed in LDPE bag at long term (25ºC / 60% RH), intermediate (30ºC / 75% RH), and for six months under accelerated

conditions (40ºC / 75% RH). The batches of Enzalutamide spray-dried dispersion are identical to those proposed for manufacturing of the final product.

The analytical methods used were the same as for release and were stability indicating. Results obtained met the acceptance criteria set. No significant changes have been observed. No obvious trends apparent in case of SDD. The stability of form has been satisfactorily discussed. Stability testing will be on-going up to 24 months for sprayed dried dispersion. The proposed shelf-life of spray dried dispersion of 24 months without any special storage conditions is acceptable.

Based on available stability data, the FP shelf-life of 2 years without any special storage conditions as stated in the SmPC (sections 6.3 and 6.4) can be accepted.

2.2.3.5. Adventitious agents

No excipients of human and/or animal origin are used in the manufacture of Enzalutamide 40 and 80 mg film-coated tablets. The magnesium stearate used in the formulation is from vegetable origin. A Certificate from the supplier stating its vegetable origin has been provided. The suppliers of the excipients have provided declarations confirming their TSE/BSE status.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product have been presented in a satisfactory manner.

During the procedure three MOs had been raised related to the justification of the starting materials for the synthesis of the AS, the proposed batch size of the finished product and the dissolution specification limits. All three were resolved by provision of additional data, justifications and the respective updates in the dossier.

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.

2.2.5. 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.

2.2.6. Recommendations for future quality development

None.

2.3. 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.

2.3.1. Ecotoxicity/environmental risk assessment

Table 1: Summary of main study results

Substance (INN/Invented Name): Enzalutamide					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	2.13-4.33 (literature)			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	0.8	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	species

2.3.2. Discussion on non-clinical aspects

The applicant preformed Phase I exposure assessment and PBT screening. The Phase I exposure assessment resulted in a PEC value which was clearly above the action limit of 0.01 µg/L. The reported log Kow values were shown to be below the 4.5 threshold, and therefore, no further PBT screening is necessary. The absence of Phase II fate and effects assessment was justified by the generic nature of the product and similarity (in terms of indications and dosage) with the originator product.

Regarding to ERA, the risk to the environment cannot be excluded due to the increased consumption observed in recent years, the endocrine modulatory effects of the active substance, and the lack of relevant ecotoxicity data, therefore section 6.6 of the SmPC include the following information "Any unused medicinal product or waste material should be disposed of in accordance with local requirements."

The non-clinical sections of the SmPC are in line with the latest version of the originator (Xtandi - EMEA/H/C/002639 - Last updated 01.06.2022)

The rapporteur considers that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The discussion regarding to impurity profile is included and considered as sufficient.

2.3.3. Conclusion on the non-clinical aspects

There are no remaining issues from the non-clinical perspective.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablet containing enzalutamide. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with parallel design under fasting and fed conditions.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on Enzalutamide soft capsule 40 mg and film-coated tablet 40 mg & 80 mg product-specific bioequivalence guidance" (EMA/CHMP/371467/2021) in its current version is of particular relevance.

GCP aspect

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

Exemption

The applicant conducted two bioequivalence studies with 80 mg strength and requests a biowaiver for 40 mg strength. Single dose studies using the highest strength only (i.e. 80 mg strength) are appropriate for the drug with linear kinetics and low solubility.

According to the reference SmPC, no major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The pharmacokinetics for enzalutamide in the proposed dose range is linear once steady state is achieved.

For detailed assessment of dissolution profiles, manufacturing process, qualitative composition and quantitatively proportionality of the strengths please refer to the quality assessment report.

Table 2 Tabular overview of clinical studies

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

Type of Study	Bioequivalence study	Bioequivalence study
Study Identifier	ENZ-0123-2	ENZ-0123-3
Location of Study Report	Module 5	Module 5
Objective(s) of the Study	**Primary objective:** The aim of this study is to determine the bioequivalence of Test Product relative to Reference Product after a single oral dose of 80 mg Enzalutamide to healthy male adults under fasting conditions. **Secondary objective:** To assess the safety and tolerability of the Test and Reference formulation.	**Primary objective:** The aim of this study is to determine the bioequivalence of Test Product relative to Reference Product after a single oral dose of 80 mg Enzalutamide to healthy male adults under fed conditions. **Secondary objective:** To assess the safety and tolerability of the Test and Reference formulation.
Study Design and Type of Control	An open-label, randomized, single dose, two treatments, one period, parallel bioequivalence study of Enzalutamide film-coated tablets, 80 mg of PharOS LTD, Greece (one tablet) and Xtandi® (Enzalutamide) film-coated tablets, 40 mg of Astellas Pharma Europe B.V., The Netherlands (two tablets) in healthy, adult, male subjects under fasting conditions.	An open-label, randomized, single dose, two treatments, one period, parallel bioequivalence study Enzalutamide film-coated tablets, 80 mg of PharOS LTD, Greece (one tablet) and Xtandi® (Enzalutamide) film-coated tablets, 40 mg of Astellas Pharma Europe B.V., The Netherlands (two tablets) in healthy, adult, male subjects under fed conditions.
Test product(s): Dosage regimen, Route of Administration	Enzalutamide 80 mg film coated tablets, Single dose, oral	Enzalutamide 80 mg film coated tablets, Single dose, oral
Number of Subjects	Dosed: Period one - 160 subjects Completed the study: 160 subjects	Dosed: Period one - 160 subjects Completed the study: 160 subjects
	160 subjects considered for the pharmacokinetic and statistical analysis	160 subjects considered for the pharmacokinetic and statistical analysis
Healthy Subjects or Diagnosis of Patients	Healthy subjects	Healthy subjects
Duration of treatment	Single dose	Single dose
Study status	Complete: Full	Complete: Full

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study ENZ-0123-2:

Methods

- **Study design**

This study was a single centre, open-label, laboratory-blinded, randomised, single-dose, two-arm, two treatment, one period, parallel study design to compare the bioequivalence of enzalutamide from Test product and Reference Product given as a single dose of 80 mg enzalutamide under fasting conditions, in healthy adult male subjects. To compare the rate and extent of absorption of the test product, Enzalutamide 80 mg film-coated Tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of reference Xtandi 40 mg film-coated tablets of Astellas Pharma Europe B.V., the Netherlands, under fasting conditions, a total of 160 (plus 3 alternates) healthy, adult, male human subjects were enrolled in the study.

The primary objective of this study was to determine the bioequivalence of test product relative to reference product after a single oral dose of 80 mg enzalutamide to healthy male adults under fasting conditions.

The secondary objective of this study was to assess the safety and tolerability of the test and reference formulation.

On study day 1, following the overnight fast of at least 10 hours, the study drugs were administered according to a randomisation 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 80 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): Two 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.

Blood samples for the determination of drugs concentration were collected immediately before study drug administration (1 × 8 ml) at 0.00 hr (pre-dose) and at 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, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours (21 × 8 ml) after administration of study drugs. The number of blood collections in the study for drug analysis was 22 samples. The total amount of blood drawn during the whole study was 200.5 ml.

- **Protocol deviations**

Minor protocol deviation occurred; the plasma samples of 0.333 were not maintained in an ice bath until being stored in the freezer.

- **Randomisation**

Subjects were randomly assigned to each treatment group, as per the randomisation schedule. A two-arm parallel design was selected. Before study drug administration subjects were assigned enrolment numbers in sequential order. The subjects retained their enrolment numbers for the whole duration of the study. For subsequent data processing and reporting, subjects were identified by their enrolment numbers.

- **Blinding**

This was an open-label study and subjects as well as clinic staff was not blinded to randomisation. The bioanalytical staff was not having access to the randomisation scheme until the analysis was complete.

Table 3 Test and reference products

Product Characteristics	**Test product**	**Reference Product**
Name	Enzalutamide 80 mg film-coated tablets	Xtandi® 40 mg film-coated tablets
Strength	80 mg	40 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufacturer	Manufactured for PharOS Pharmaceutical Oriented Services Single Member Ltd., Greece	Manufactured for: Astellas Pharma Europe B.V., The Netherlands

This product was used in the following trials:	ENZ-0123-3	ENZ-0123-3

- **Sample size estimation**

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 inter-subject variability of 30% and a T/R ratio of 111.1%, power of 80%, 160 subjects were considered sufficient to establish bioequivalence between formulations.

- **Population(s) studied**

A total number of 282 healthy subjects were screened to evaluate fulfilment of selection criteria described in the study protocol. Fifty four subjects dropped out from the study and 65 subjects were not included due to screening failure. A total of 160 subjects plus 03 alternates were enrolled before study drug administration and 03 alternate subject were excluded by the CRO due to protocol requirement after successful dosing of 160 subjects. A total of 160 subjects were dosed in two separate dosing groups and completed the study.

Table 4: Demographic characteristics

Variable		Profile		Percentage
Sex		Males		100.00%
Race		Middle Eastern		100.00%
Smoking status		Non-smokers		100.00%
	Mean	SD	Min	Max
Age (Years)	30	8.56	19	49
Height (cm)	175	5.56	160	190
Weight (Kg)	74	12.32	53	105
BMI (Kg/m^2)	24.3	3.44	18.5	29.9

The chosen population complies with the guidelines, comparison for the demographics between the different treatment groups is provided.

- **Analytical methods**

The LC-MS/MS method for the estimation of enzalutamide was developed and validated at bioanalytical department of IPRC. The method was validated for the calibration range of 10 to 4000 ng/mL first, then the range was extended up to 8000 ng/mL. The method was successfully validated with respect to specificity/selectivity, linearity, precision and accuracy, dilution integrity, recovery, matrix effect and matrix factor, batch size, carry-over, re-injection reproducibility, short-term and long-term stability at -20°C, freeze-and-thaw stability, post-preparative stability, and the stability of the stock and working solutions.

Enzalutamide in the study samples was estimated over the calibration range of 10 ng/mL – 8000 ng/mL. Incurred sample reanalysis (ISR) was performed in both studies with 100% and 99.69 % within difference $\leqslant$ 20.0% of the mean of original and re-assayed concentrations, respectively. All study samples were stored at -20°C within known long-term stability. The GLP was declared and the QAU statement was submitted.

Pharmacokinetic Variables

Pharmacokinetic parameters of enzalutamide were estimated using standard non-compartmental methods. The maximum plasma concentration (Cmax) and the time to peak plasma concentration (tmax) were taken directly from the measured data.

The area under the plasma concentration-time curve (truncated AUC0-72) was calculated from measured data points from the time of administration to time of last quantifiable concentration (Clast) by the linear trapezoidal rule.

The pharmacokinetic calculations were performed by WinNonlin statistical software, version 8.3.4.

Primary pharmacokinetic variables:

Cmax	Maximum measured plasma concentration over the time span specified.
Truncated AUC0-72	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:

AUC0-∞	The area under the plasma concentration versus time curve from time (0) to infinity. AUC0-∞ was calculated as the sum of the AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.
tmax	Time of the maximum measured plasma concentration. If the maximum value occurred at more than one time point, tmax was defined as the first time point with this value.
t1/2el	The elimination or terminal half-life was calculated as 0.693/ Kel.
Kel	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 Cmax.
AUC%Extrap_obs	Percent of AUC0-∞ extrapolated, represented as

[(AUC0-∞ - AUC0-t)/AUC0-∞] × 100.

The secondary pharmacokinetic parameters AUC0-∞, Kel, t1/2el and AUC%Extrap_obs were calculated for information purposes only.

Values below LLOQ were treated as zero for all pharmacokinetic and statistical analyses. Any missing concentration values were treated as missing and not included in the pharmacokinetic calculations.

No value of Kel, AUC0-∞, AUC%Extrap_obs or t1/2el was reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

- **Statistical methods**

Statistical analysis was performed using WinNonlin statistical software, version 8.3.4.

The statistical evaluation of bioequivalence included analysis of variance (ANOVA) in the logarithmically transformed data of Cmax and truncated AUC0-72 calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed Cmax and truncated AUC0-72 parameters.

An analysis of variance (ANOVA) tested for treatment and group effects was used. ANOVA was performed on ln truncated AUC0-72 and ln Cmax for enzalutamide. Fixed effects model was used. Treatment and group effects were tested at the 0.05 level of significance for Cmax and truncated AUC0-72. Inter-subject variability was calculated using residual variance of ANOVA for ln-transformed analysis of Cmax and truncated AUC0-72.

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 80-125% 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

One hundred and sixty (160) subjects were enrolled into the study, of which 160 subjects completed the study. All 160 subjects were included in PK and statistical analysis of enzalutamide.

Table 5: Pharmacokinetic parameters for enzalutamide (non-transformed values)

Pharmacokinetic parameter	• **Test (N=80)**		• **Reference (N=80)**	
	• **arithmetic mean**	• **SD**	• **arithmetic mean**	• **SD**
$AUC_{(0-72h)}$	• 64742.8	• 19206.10	• 64940.3	• 23889.79
$AUC_{(0-\infty)}$	• 210836.2	• 113575.86	• 245563.3	• 174606.56
C_{max}	• 1809.04	• 473.55	• 1841.32	• 493.81
T_{max}*	• 1.67	• 0.67-47.13	• 2.00	• 0.33-5.00

- 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)
- N number of observations

Table 6: Statistical analysis for enzalutamide (ln-transformed values)

Pharmacokinetic parameter	**Geometric Mean Ratio Test/Reference**	**Confidence Intervals**	**Intersubject CV%***
$AUC_{(0-72h)}$	• 101.43	• 91.66- 105.37	• 34.06
C_{max}	• 98.28	• 91.66- 110.62	• 27.13

- * estimated from the Residual Mean Squares

- **Safety data**

No adverse event was reported during the study.

Study ENZ-0123-3:

Methods

- **Study design**

This study was a single centre, open-label, laboratory-blinded, randomised, single-dose, two-arm, two treatment, one period, parallel study design to compare the bioequivalence of enzalutamide from Test product and Reference Product given as a single dose of 80 mg enzalutamide under fed conditions, in healthy adult male subjects. To compare the rate and extent of absorption of the test product, Enzalutamide 80 mg film-coated Tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of reference Xtandi 40 mg film-coated tablets of Astellas Pharma Europe B.V., the Netherlands, under fed conditions, a total of 160 (plus 4 alternates) healthy, adult, male human subjects were enrolled in the study.

The primary objective is to determine the bioequivalence of test product relative to reference product after a single oral dose of 80 mg enzalutamide to healthy male adults under fed conditions.

The secondary objective is to assess the safety and tolerability of the test and reference formulation.

On study day 1, following the overnight fast of at least 10 hours, the study drugs were administered according to a randomisation 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 80 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): Two 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.

Subjects received a standardised, high-fat high-calorie breakfast 30 minutes prior to administration of the study drug. The subjects were asked to finish the breakfast within 30 minutes before the scheduled dosing time. High fat, high calories meal was served in the study. The volume of blood taken was 8 ml per sample. Blood samples for the determination of drugs concentration were collected immediately before study drug administration (1 × 8 ml) at 0.00 hr (predose) and at 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, 8.00, 12.00, 24.00, 36.00, 48.00 and 72.00 hours (21 × 8 ml) after administration of study drugs. The number of blood collections in the study for drug analysis was 22 samples. The total amount of blood drawn during the whole study was 200.5 ml.

- **Protocol deviations**

All protocol deviations in this study were minor in nature.

- **Randomisation**

Subjects were randomly assigned to each treatment group, as per the randomisation schedule. A two-arm parallel design was selected. Before study drug administration subjects were assigned enrolment numbers in sequential order. The subjects retained their enrolment numbers for the whole duration of the study. For subsequent data processing and reporting, subjects were identified by their enrolment numbers.

- **Blinding**

This was an open-label study and subjects as well as clinic staff was not blinded to randomisation. The bioanalytical staff was not having access to the randomisation scheme until the analysis was complete.

- **Test and reference products**

Table 7: Test and reference products

Product Characteristics	Test product	Reference Product
Name	Enzalutamide 80 mg film-coated tablets	Xtandi® 40 mg film-coated tablets
Strength	80 mg	40 mg
Dosage form	Film-coated tablet	Film-coated tablet
Manufacturer	Manufactured for PharOS Pharmaceutical Oriented Services Single Member Ltd., Greece	Manufactured for: Astellas Pharma Europe B.V., The Netherlands
This product was used in the following trials:	ENZ-0123-3	ENZ-0123-3

- **Sample size estimation**

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 inter-subject variability of 30% and a T/R ratio of 111.1%, power of 80%, 160 subjects were considered sufficient to establish bioequivalence between formulations.

- **Population(s) studied**

A total number of 204 subjects were screened. 13 subjects dropped out from the study and 27 subjects were not included due to screening failure. A total of 160 subjects plus 04 alternates were enrolled before study drug administration and 01 alternate subject was excluded by IPRC staff due to protocol requirement and 03 alternate subjects were excluded due to personal reason after successful dosing of 160 subjects. A total of 160 subjects were dosed in two separate dosing groups and completed the study.

Table 8: Demographic characteristics

Variable		Profile		Percentage
Sex		Males		100.00%
Race		Middle Eastern		100.00%
Smoking status		Non-smokers		100.00%
	Mean	SD	Min	Max
Age (Years)	30	8.56	18	48
Height (cm)	175	5.77	162	187
Weight (Kg)	74	11.50	55	102
BMI (Kg/m^2)	24.1	3.34	18.5	29.8

- **Analytical methods**

The LC-MS/MS method for the estimation of enzalutamide was developed and validated at bioanalytical department of IPRC. The method was validated for the calibration range of 10 to 4000 ng/mL first, then the range was extended up to 8000 ng/mL.

Enzalutamide in the study samples was estimated over the calibration range of 10 ng/mL – 8000 ng/mL. Incurred sample reanalysis (ISR) was performed in both studies with 100% and 99.69 % within difference ≤ 20.0% of the mean of original and re-assayed concentrations, respectively. All study samples were stored at -20°C within known long-term stability.

- **Pharmacokinetic variables**

Pharmacokinetic parameters of enzalutamide were estimated using standard non-compartmental methods. The maximum plasma concentration (Cmax) and the time to peak plasma concentration (tmax) were taken directly from the measured data.

The area under the plasma concentration-time curve (truncated AUC0-72) was calculated from measured data points from the time of administration to 72 h time concentration (C72) by the linear trapezoidal rule via truncated AUC.

The pharmacokinetic calculations were performed by WinNonlin statistical software, version 8.3.4.

Primary pharmacokinetic variables:

Cmax — Maximum measured plasma concentration over the time span specified.

Truncated AUC0-72 — The area under the plasma concentration versus time curve, from time (0) hour to the measurable concentration (72 h), as calculated by the linear trapezoidal method via truncated AUC.

Secondary pharmacokinetic variables:

AUC0-∞ — The area under the plasma concentration versus time curve from time (0) to infinity. AUC0-∞ was calculated as the sum of the AUC0-t plus the ratio of the last measurable plasma concentration to the elimination rate constant.

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

t1/2el — The elimination or terminal half-life was calculated as 0.693/ Kel.

Kel 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 Cmax.

AUC%Extrap_obs Percent of AUC0-∞ extrapolated, represented as

[(AUC0-∞ - AUC0-t)/AUC0-∞] × 100.

The secondary pharmacokinetic parameters AUC0-∞, Kel, t1/2el and AUC%Extrap_obs were calculated for information purposes only.

Values below LLOQ were treated as zero for all pharmacokinetic and statistical analyses. Any missing concentration values were treated as missing and not included in the pharmacokinetic calculations.

No value of Kel, AUC0-∞, AUC%Extrap_obs or t1/2el was reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

- **Statistical methods**

The statistical evaluation of bioequivalence included analysis of variance (ANOVA) in the logarithmically transformed data of Cmax and truncated AUC0-72 calculation of formulations ratios (point estimates) and parametric 90% confidence interval for ln-transformed Cmax and truncated AUC0-72 parameters.

An analysis of variance (ANOVA) tested for treatment and group effects was used. ANOVA was performed on ln truncated AUC0-72 and ln Cmax for enzalutamide. Fixed effects model was used. Treatment and group effects were tested at the 0.05 level of significance for Cmax and truncated AUC0-72. Inter-subject variability was calculated using residual variance of ANOVA for ln-transformed analysis of Cmax and truncated AUC0-72.

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 80-125% for truncated AUC0-72 (that defines the extent of absorption) and for Cmax (parameter that reflects rate of absorption) to conclude bioequivalence between formulations.

Results

One hundred and sixty (160) subjects were enrolled into the study, of which 160 subjects completed the study. All 160 subjects were included in PK and statistical analysis of enzalutamide.

Table 9: Pharmacokinetic parameters for enzalutamide (non-transformed values)

Pharmacokinetic parameter	Test (N=80)		Reference (N=80)	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	75254.2	23150.21	73775.6	25532.06
$AUC_{(0-\infty)}$	270368.7	170416.19	309619.7	347211.65
C_{max}	1653.81	416.58	1730.14	543.69
T_{max}*	4.50	0.33-35.47	2.67	0.33-8.00

Pharmacokinetic parameter	Test (N=80)		Reference (N=80)	
	arithmetic mean	SD	arithmetic mean	SD
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)			
N	number of observations			

Table 10: Statistical analysis for enzalutamide (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	Intersubject CV%*
$AUC_{(0-72h)}$	102.66	94.45- 111.59	32.69
C_{max}	96.90	90.07- 104.24	28.48
* estimated from the Residual Mean Squares			

Justification for Group Effect:

This is a parallel study conducted in two groups; to minimise the group effect the two groups were conducted in the same clinical site and separated by few days (first group 03/03/2023: and second group 09/03/2023), also the randomisation was generated in two blocks with each block having 80 subjects randomised in balanced design between both treatments.

The protocol established as inclusion criteria that all participants must be healthy within 18-50 years old and 18.5 to 30.0 kg/m2 body mass index. During the screening procedures, all included subjects had normal ECG, physical examination and all their laboratory results were within normal range. The exclusion criteria were drugs and alcohol abuse, smoking, as well as other limiting conditions such as hypersensitivity to the IMP, intake of other medications, health problems, special diet regimes, previous participation in other studies in the last 90 days, etc. During the conduct of the study, and immediately before dosing, vital signs determinations were performed to all participants. The study protocol established details on how to control the variables like: positioning, timing, degree of physical activity, composition of food, beverages, temperature of water administered during dosing, psychological status of subjects in turn effecting the bowel transit and drug absorption. The conduct of the study, as observed in the study's report and study's trial master file, proved that the subjects tested were healthy and their vital signs were recorded in each period. The subjects were confined at site for an adequate time period (12 hrs before dosing and 24 hrs after dosing). No exercise was allowed at least one day prior to study drug administration until donating the last sample of the study. Dosing and sample withdrawals were performed the same way for the groups as scheduled in the study's protocol and actual times for all events were documented accordingly. Food and beverages consumption was the same as observed in meals' records.

This study was a single centre, open-label, randomised, single-dose, parallel study to compare the bioavailability between the test product, enzalutamide 80 mg film-coated tablets, from Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, relative to XtandiTM 40 mg film-coated tablets (Reference Product), from Astellas Pharma Europe B.V., The Netherlands after a single oral dose administration of 80 mg enzalutamide to healthy male adults under fed conditions. The point estimate and the 90% confidence intervals of ln-transformed ratios of test /reference were within the accepted limits of 80% - 125% for Cmax and truncated AUC0→72.

Clinical assessment for all subjects was carried out to evaluate their tolerability to the study's medications. Study subjects demonstrated good tolerance to the study's drugs.

- **Safety data**

No adverse event was reported during the study.

2.4.2.2. Pharmacokinetic conclusion

Based on the presented bioequivalence studies Enzalutamide Film-Coated Tablet is considered bioequivalent with reference product.

The results of studies ENZ-0123-2 and ENZ-0123-3 with 80 mg formulation can be extrapolated to other strengths 40 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.4.2.3. Pharmacodynamics

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

2.4.3. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

Discussion on clinical aspects

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.

Study ENZ-0123-2 (Study under fasting conditions)

This study was a single centre, open-label, laboratory-blinded, randomised, single-dose, two-arm, two treatment, one period, parallel study design to compare the bioequivalence of enzalutamide from Test product and Reference Product given as a single dose of 80 mg enzalutamide under fasting conditions, in healthy adult male subjects.

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 chosen population complies with the guidelines, comparison for the demographics between the different treatment groups was provided.

The study was properly randomised and well controlled.

All protocol deviations in this study were minor in nature and consequently, had no significant impact on the integrity of the study results or on subject safety.

The median time to reach maximum plasma enzalutamide concentrations (Cmax) is 2 hours (range 0.5 to 6 hours), the sampling schedule is considered appropriate because is 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 LC-MS/MS method for the estimation of enzalutamide was developed and validated at bioanalytical department of IPRC. The method was successfully validated with respect to specificity/selectivity, linearity, precision and accuracy, dilution integrity, recovery, matrix effect and matrix factor, batch size, carry-over, re-injection reproducibility, short-term and long-term stability at -20°C, freeze-and-thaw stability, post-preparative stability, and the stability of the stock and working solutions. All acceptance criteria specified in the EMA Guideline on Bioanalytical Method Validation were met. Enzalutamide in the study samples was estimated over the calibration range of 10 ng/mL – 8000 ng/mL. The data of back-calculated calibration standards, calibration curves parameters and the results of between-run QC samples accuracy and precision demonstrated reliable performance of the method during analysis of study samples. The batch acceptance criteria followed the Guideline on Bioanalytical Method Validation. Representative chromatograms of 100 % of study subjects and Certificates of Analysis for the reference and internal standard were attached to the bioanalytical reports. The number of re-assayed study samples was not high and all reasons for re-assays were acceptable.

Overall, the method was suitable for the determination of enzalutamide in K3EDTA human plasma samples from clinical studies over the declared calibration range. The bioanalytical method was reliable. Enzalutamide was demonstrated to be stable under various storage conditions.

The point estimate and the 90% confidence intervals of ln-transformed ratios of test /reference were within the accepted limits of 80% - 125% for Cmax and truncated AUC0-72.

Clinical assessment for all subjects was carried out to evaluate their tolerability to the study's medications. Study subjects demonstrated good tolerance to the study's drugs.

Therefore, the bioequivalence of Enzalutamide Viatris 80 mg film-coated tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with XtandiTM 40 mg film-coated tablets of Astellas Pharma Europe B.V., The Netherlands under fasting conditions can be concluded.

Study ENZ-0123-3 (Study under fed conditions)

This study was a single centre, open-label, randomised, single-dose, parallel study to compare the bioavailability between the test product, enzalutamide 80 mg film-coated tablets, from Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, relative to XtandiTM 40 mg film-coated tablets (Reference Product), from Astellas Pharma Europe B.V., The Netherlands after a single oral dose administration of 80 mg enzalutamide to healthy male adults under fed conditions. The point estimate and the 90% confidence intervals of ln-transformed ratios of test /reference were within the accepted limits of 80 % - 125 % for Cmax and truncated AUC0→72.

This is a parallel study conducted in two groups; to minimise the group effect the two groups were conducted in the same clinical site and separated by few days (first group 03/03/2023: and second group 09/03/2023), also the randomisation was generated in two blocks with each block having 80 subjects randomised in balanced design between both treatments. Composition of served high fat breakfast in study ENZ-0123-3 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 study was properly randomised and well controlled.

The chosen population in study ENZ-0123-3 complies with the guidelines, comparison for the demographics between the different treatment groups is provided.

All protocol deviations in this study 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 this time deviation in collection time on results is minimal because using the actual post-dose sample collection times were taken into consideration in the statistical analysis. There were no non-zero pre-dose concentrations.

The median time to reach maximum plasma enzalutamide concentrations (Cmax) is 2 hours (range 0.5 to 6 hours), the sampling schedule is considered appropriate because is 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 LC-MS/MS method for the estimation of enzalutamide was developed and validated at bioanalytical department of IPRC. The method was validated for the calibration range of 10 to 4000 ng/mL first, then the range was extended up to 8000 ng/mL. The method was successfully validated with respect to specificity/selectivity, linearity, precision and accuracy, dilution integrity, recovery, matrix effect and matrix factor, batch size, carry-over, re-injection reproducibility, short-term and long-term stability at -20 °C, freeze-and-thaw stability, post-preparative stability, and the stability of the stock and working solutions. All acceptance criteria specified in the EMA Guideline on Bioanalytical Method Validation were met.

Enzalutamide in the study samples was estimated over the calibration range of 10 ng/mL – 8000 ng/mL The data of back-calculated calibration standards, calibration curves parameters and the results of between-run QC samples accuracy and precision demonstrated reliable performance of the method during analysis of study samples. The batch acceptance criteria followed the Guideline on Bioanalytical Method Validation. Representative chromatograms of 100 % of study subjects and Certificates of Analysis for the reference and internal standard were attached to the bioanalytical reports. The number of re-assayed study samples was not high and all reasons for re-assays were acceptable. Incurred sample reanalysis (ISR) was performed in both studies with 100 % and 99.69 % within difference ≤ 20.0% of the mean of original and re-assayed concentrations, respectively. All study samples were stored at -20 °C within known long-term stability.

The GLP was declared and the QAU statement was submitted. Overall, the method was suitable for the determination of enzalutamide in K3EDTA human plasma samples from clinical studies over the declared calibration range. The bioanalytical method was reliable. Enzalutamide was demonstrated to be stable under various storage conditions.

Clinical assessment for all subjects was carried out to evaluate their tolerability to the study's medications. Study subjects demonstrated good tolerance to the study's drugs.

In conclusion, the test product, enzalutamide 80 mg film-coated tablets investigated in this study were shown to be equivalent with the reference product Xtandi 40 mg film-coated tablets.

The applicant also conducted two pilot studies (ENZ-T1021/83, ENZ-T1021/94 discussed in short in the clinical summary (not shown)). Based on the information provided bioequivalence with the reference product was also shown in these studies.

The applicant performed bioequivalence studies with two 40 mg tablet of the reference medicinal product Xtandi, whilst the Product Specific Guideline (EMA/CHMP/371467/2021) indicates to use the 80 mg tablets. Xtandi 80 mg film-coated tablets was not available in the European market at the time of the bioequivalence studies (Feb/Mar 2023), the applicant´s approach, to perform studies with EU innovator product Xtandi 40 mg (2 x 40 mg), is acceptable.

Based on the presented bioequivalence studies Enzalutamide Film-Coated Tablet is considered bioequivalent with reference product.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence studies Enzalutamide Film-Coated Tablet is considered bioequivalent with reference product.

The results of studies ENZ-0123-2 and ENZ-0123-3 with 80 mg formulation can be extrapolated to other strengths 40 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 11: 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

2.5.2. Pharmacovigilance plan

The Pharmacovigilance System Master File contains details of the system and processes that the applicant has in place to identify and/or characterise the risks recognised in the safety specification.

Only routine pharmacovigilance activities are proposed by the MAA.

2.5.3. Risk minimisation measures

Routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.5.5. Pharmacovigilance system

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

2.5.6. 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.

2.6. Product information

2.6.1. 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 generic version of Enzalutamide Film-coasted tablet. 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;
- 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

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 is considered sufficient.

The bioequivalence studies form the pivotal basis with a single centre, open-label, laboratory-blinded, randomised, single-dose, two-arm, two treatment, one period, parallel study design to compare the bioequivalence of enzalutamide from the test product and reference product given as a single dose of 80 mg enzalutamide under fasting conditions, in healthy adult male subjects. To compare the rate and extent of absorption of the test product, Enzalutamide Viatris 80 mg film-coated Tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of reference Xtandi 40 mg film-coated tablets of Astellas Pharma Europe B.V., the Netherlands, under fasting conditions, a total of 160 (plus 3 alternates) healthy, adult, male human subjects were enrolled in the study and a single centre, open-label, laboratory-blinded, randomised, single-dose, two-arm, two treatment, one period, parallel study design to compare the bioequivalence of enzalutamide from the test product and reference product given as a single dose of 80 mg enzalutamide under fed conditions, in healthy adult male subjects. To compare the rate and extent of absorption of the test product, Enzalutamide Viatris 80 mg film-coated Tablets of Pharos Pharmaceutical Oriented Services Single Member Ltd., Greece, with that of reference Xtandi 40 mg film-coated tablets of Astellas Pharma Europe B.V., the

Netherlands, under fed conditions, a total of 160 (plus 4 alternates) healthy, adult, male human subjects were enrolled in the study.

The studies design are considered adequate to evaluate the bioequivalence of this formulation and were in line with the respective European requirements. 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).

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 and were conducted by the applicant. Choice of dose, sampling points as well as overall sampling time were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Enzalutamide Viatris met the protocol-defined criteria for bioequivalence when compared with the Xtandi. 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%.

Based on the presented bioequivalence studies Enzalutamide Film-Coated Tablet is considered bioequivalent with reference product.

The results of studies ENZ-0123-2 and ENZ-0123-3 with 80 mg formulation can be extrapolated to other strengths 40 mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

3.1. Conclusions

The overall benefit /risk balance of Enzalutamide Viatris is positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Enzalutamide Viatris 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 granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other 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.