EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/CHMP/432249/2017
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on extension(s) of marketing authorisation

Xtandi

International non-proprietary name: enzalutamide

Procedure No. EMEA/H/C/002639/X/0029

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Administrative information

Name of the medicinal product:	Xtandi
MAH:	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden NETHERLANDS
Active substance:	ENZALUTAMIDE
International Non-proprietary Name/Common Name:	enzalutamide
Pharmaco-therapeutic group (ATC Code):	hormone antagonists and related agents, anti-androgens (L02BB04)
Therapeutic indication(s):	Xtandi is indicated for: • the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1) • the treatment of adult men with metastatic castration resistant prostate cancer whose disease has progressed on or after docetaxel therapy.
Pharmaceutical forms:	Capsule, soft; Film-coated tablet
Strengths:	40 mg and 80 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PCTFE/alu)
Package sizes:	112 capsules, 112 tablets and 56 tablets

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List of abbreviations

AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AR	Androgen receptor
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-72h}	Area under the concentration-time curve from time point 0 to time point 72 hours
AUC_{inf}	Area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	Area under the concentration-time curve from the time of dosing to the last measurable concentration
AUC_{tau}	Area under the concentration-time curve during one 24-hour dosing interval at steady state
BCS	Biopharmaceutics Classification System
BMI	Body mass index
CK	Creatine kinase
CL/F	Apparent total body clearance after extravascular dosing
C_{max}	Maximum concentration (observed)
C_{min}	Minimum (trough) concentration
CQA	Critical quality attribute
CTCAE	Common Terminology Criteria for Adverse Event
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DoE	Design of experiments
EC	European Commission
ECG	Electrocardiogram
ESV	End-of-study visit
FMEA	Failure mode effects analysis
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GMR	Geometric least squares mean ratio
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HPMCAS	Hypromellose acetate succinate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
KF	Karl Fischer titration
λz	Terminal elimination rate constant
LLOQ	Lower limit of quantitation
M1	Enzalutamide Metabolite 1 (MDPC0001)
M2	Enzalutamide Metabolite 2 (MDPC0002)
MPR	Metabolite-to-parent ratio
MPR (MWC)	MPR corrected for the difference in molecular weight
N/A	Not applicable
NCI	National Cancer Institute
NF	National Formulary
NIRS	Near infrared spectroscopy
PCTFE	Polychlorotrifluoroethylene
PE	Polyethylene
PK	Pharmacokinetics
PKAS	Pharmacokinetic analysis set
Ph. Eur.	European Pharmacopoeia

PVC	Polyvinyl chloride
QC	Quality Control
QTcF	Corrected QT interval using Fridericia's formula
QTPP	Quality target product profile
RH	Relative Humidity
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SDD	Spray-dried dispersion
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
t½	Terminal elimination half-life
t_{max}	Time to attain maximum concentration
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

Astellas Pharma Europe B.V. submitted on 7 March 2016 extensions of the marketing authorisation.

The MAH applied for addition of a new pharmaceutical form associated with two strengths: 40 mg and 80 mg film-coated tablets.

The MAH applied for the following indication for the new pharmaceutical form associated with the two new strengths:

- the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1);
- the treatment of adult men with metastatic castration resistant prostate cancer whose disease has progressed on or after docetaxel therapy.

Furthermore, the PI is brought in line with the latest QRD template version 10.

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) (d) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011on the granting of a class waiver.

Information relating to orphan market exclusivity

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.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 27 July 2014 and on 24 September 2015. The Scientific Advice pertained to quality and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Jorge Camarero Jiménez

- The application was received by the EMA on 7 March 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 21 June 2016.
- During the meeting on 8 July 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 16 May 2017.
- The following GMP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GMP inspection at 3 sites responsible for manufacturing and testing of the finished product in the United States of America between 20 and 24 March 2017. The outcome of the inspection carried out was issued on 28 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on 23 June 2017.
- During the PRAC meeting on 6 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension(s) of the marketing authorisation for Xtandi on 20 July 2017.

2. Scientific discussion

2.1. Problem statement

About the disease

The application concerns enzalutamide which is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

Worldwide, prostate cancer ranks second in cancer incidence and sixth in cancer mortality in men (Jemal, 2011). Castration-resistant prostate cancer (CRPC) is defined as prostate cancer that progresses despite castrate levels of testosterone while on treatment with a luteinizing-hormone releasing hormone analogue (LHRHa), or following bilateral orchiectomy. The majority of these resistant cancers overexpress the androgen receptor and may remain sensitive to more potent hormonal agents than those approved at the time (e.g., first generation antiandrogens such as flutamide or bicalutamide).

Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. The median survival of patients with castration-resistant disease is approximately 1–2 years (Lassi, 2010, Petrylak, 2004).

EU Clinical practice guidelines (ESMO Guidelines) recommend: abiraterone or enzalutamide for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC; Radium-223 for men with bone-predominant, symptomatic metastatic CRPC without visceral metastases; Docetaxel for men with metastatic CRPC; and sipuleucel-T is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC. Of note the marketing authorisation of sipuleucel-T was withdrawn by the MAH for marketing reasons. The optimal sequence or combination of these agents is unknown. In second line (post docetaxel), cabazitaxel, abiraterone and enzalutamide are recommended (ESMO Guidelines).

About the product

Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits binding of androgens to androgen receptors, 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. In preclinical studies enzalutamide lacks androgen receptor agonist activity (see SmPC section 5.1).

Enzalutamide was approved in the European Union (EU) on 21 June 2013 for the treatment of patients with metastatic CRPC patients who had received docetaxel therapy. Approval was subsequently granted in the EU on 28 November 2014 for the use of enzalutamide in 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. Enzalutamide has been approved in more than 56 countries.

The approved enzalutamide drug product is an immediate-release soft gelatin capsule containing 40 mg of enzalutamide. The recommended dose is 160 mg of enzalutamide (4 x 40 mg capsules) administered orally

once daily, with or without food, with the possibility of dose reduction to 120 or 80 mg should toxicity or intolerable side effects occur.

Difficulty swallowing and polypharmacy (use of ≥ 4 regular medications) are important issues in elderly prostate cancer patient populations and present challenges with regard to medication management, administration and adherence. To address the needs of this patient population, an alternative immediate-release dosage form of enzalutamide was pursued.

This application seeks to provide for a new immediate-release, film-coated dosage form to the currently approved liquid-filled, soft gelatin capsule. This submission is intended to obtain the Marketing Authorisation for new 40 mg and 80 mg immediate-release film-coated tablets.

Type of Application and aspects on development

The application is based on the results of a pivotal clinical study to demonstrate bioequivalence between enzalutamide capsules and tablets for single-dose AUC under fasted and fed conditions (Study 9785-CL-0014), simulations of steady-state concentration-time profiles (derived from nonparametric superposition) in order to assess Cmax under conditions of clinical use, and an exposure-response analysis to evaluate the relationship between exposure and clinical efficacy using data from study CRPC2. No changes are proposed to the approved indications for the currently approved capsule formulation.

Scientific Advice was received from the CHMP on the bioequivalence strategy between enzalutamide tablet and capsule formulations (EMA/CHMP/SAWP/430462/2014), and on CMC aspects (dissolution test methods) of the tablet development program (EMA/CHMP/SAWP/589626/2015).

Inspection

Following a GMP inspection of the drug product manufacturer in February 2016, a statement of GMP non-compliance was issued for the concerned site. Upon request, the MAH provided a risk assessment with the aim of assessing the impact of the deficiencies that were identified during the inspection and to support the validity of the data on the manufacture and testing of Enzalutamide spray-dried dispersion (SDD) and related tablet Drug Product with regard to quality, safety and efficacy. In addition, another inspection at the site was performed and a GMP certificate was issued on 27th April 2017.

2.2. Quality aspects

2.2.1. Introduction

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

Other ingredients are:

Tablet core: hypromellose acetate succinate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium and magnesium stearate.

Tablet coating: hypromellose, talc, macrogol (8000), titanium dioxide (E171) and iron oxide yellow (E172).

The product is available in a cardboard wallet incorporating PVC/PCTFE/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Xtandi 40 and 80 mg film-coated tablets contain the same active substance, enzalutamide, as that used to manufacture the already-authorised soft capsules. The active substance is sourced from the same manufacturer, manufactured with the same process and released in accordance with the same active substance specifications. Therefore, the applicant presented no new information in the active substance part of the dossier (3.2.S) to support this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Xtandi film-coated tablets contain either 40 or 80 mg of enzalutamide as active substance. The composition of the tablets is shown in table 1, the two strengths being qualitatively and quantitatively proportional in terms of composition.

Table 1: composition of Xtandi film-coated tablets

Component	Function	Reference to Quality Standard	Target Amount per 80 mg Tablet (mg)	Target Amount per 40 mg Tablet (mg)
Enzalutamide [a]	Active Ingredient	In-house	80 [b]	40 [b]
Hypromellose Acetate Succinate [a]	Diluent	NF	4.2 1st ind	
Acetone [a, c]	Processing Agent	Ph. Eur.		
Cellulose, Microcrystalline	Filler	Ph. Eur.		
Silica, Colloidal Anhydrous	Glidant	Ph. Eur.		
Croscarmellose Sodium	Disintegrant	Ph. Eur.		
Magnesium Stearate	Lubricant	Ph. Eur.		
Core Tablet Weight				
OPADRY® Yellow 03F42210	Non-functional Color Film Coat	In-house		
Purified Water [c]	Processing Agent	Ph. Eur.		
Total Tablet				

4.2 1st ind

N/A, not applicable; NF, National Formulary; Ph. Eur., European Pharmacopoeia; SDD, spray-dried dispersion

The composition of the film-coating is shown in table 2.

Table 2: composition of the film-coating

Component	Reference to Quality Standard	Quantity (% w/w)	Theoretical Amount per 80 mg Tablet (mg) [a]	Theoretical Amount per 40 mg Tablet (mg) [a]
Hypromellose	Ph. Eur.	4.2 1st ind [redacted]		
Talc	Ph. Eur.			
Macrogol 8000	Ph. Eur.			
Titanium Dioxide	Ph. Eur.			
Iron Oxide Yellow	Directive 95/45/EC (E172)			

[a] Calculated based on the quantity (% w/w) and the amount of OPADRY® Yellow 03F42210 per Tablet

Ph. Eur., European Pharmacopoeia

Xtandi is currently available in the EU as liquid-filled soft capsules containing 40 mg enzalutamide. The posology is 160 mg once daily, with the potential to reduce to 120 or 80 mg depending on side effects and tolerability. The applicant is proposing to introduce an alternative formulation, film-coated tablets, containing either 40 or 80 mg enzalutamide in order to reduce the number and size of daily dosage units.

Enzalutamide is a crystalline BCS class II (low solubility, high permeability) substance with low aqueous solubility across the physiological pH range. Dissolution is the rate limiting step for absorption. The approved soft capsules circumvent this issue by having the active substance already dissolved in the capsule contents. In order to enhance the solubility of the active substance and ensure rapid and complete dissolution from a tablet formulation, methods to generate amorphous enzalutamide were investigated. Hot melt extrusion was ruled out due to the high melting point of the active substance so a spray-drying approach was adopted. Prior to initiating the development program, a quality target product profile (QTPP) was defined (table 3).

Table 3: QTPP for enzalutamide tablets

Items	Target
Dosage form	Film−coated tablet
Route of administration	Oral
Dosage form strength	80 mg and 40 mg
Pharmacokinetics	Bioequivalent to the liquid-filled soft capsule
Stability	Stable for at least 2 years at 25°C.

This was then used to identify critical quality attributes (CQAs) of the finished product which would ensure the robust performance of the tablets (table 4).

Table 4: CQAs of enzalutamide tablets

Critical Quality Attribute	Target
Appearance	Oval, yellow film-coated tablet with debossing (80 mg) Round, yellow film-coated tablet with debossing (40 mg)
Assay	95.0% - 105.0%
Uniformity of dosage units	Meets Ph. Eur. 2.9.40
Dissolution	Immediate Release
Degradants	Meets ICH guideline Q3B (R)
Residual solvent (Acetone)	Meets ICH guideline Q3C (R)
Hardness and friability	Sufficient strength for compression, coating and subsequent shipping and handling.

Various polymers were investigated as additives prior to spray-drying in order to stabilise amorphous enzalutamide and to enhance the dissolution rate of the dispersed active substance. Hypromellose acetate succinate (HPMCAS) was found to offer excellent stability of the active substance in its amorphous state whilst ensuring rapid and complete dissolution and was selected for further development. Drug loading was next investigated and a level of 4.2 was selected based on the pharmacokinetic (PK) profiles of the different loadings investigated.

Stability studies for the enzalutamide SDD intermediate stored in bulk were performed under controlled room temperature conditions (20-25 °C). No significant changes were observed over the 12 month study period. In addition, no significant changes were observed in the appearance or the assay for the SDD intermediate stored at 40 °C / 75% RH for up to 6 months. These results support the conclusion that the components used for manufacturing the enzalutamide SDD intermediate, namely the HPMCAS and acetone, are compatible with the active substance. The proposed holding time of 12 months for enzalutamide SDD in the proposed packaging is acceptable.

A risk assessment was then carried out using failure mode effects analysis (FMEA) to assess properties of the spray-dried dispersion (SDD) likely to impact the CQAs of the finished product. Only the impact of the HPMCAS properties on dissolution was identified as high risk. Different acetate and succinate substitution patterns and ratios were investigated since these can impact hydrophilicity and ionization potential of the polymer. Finished product batches manufactured with different types of HPMCAS were compared in dissolution and in relative bioavailability studies. Both tablets showed a rapid and complete dissolution within 30 minutes, regardless of the HPMCAS used. The AUC and the C_{max} values obtained confirmed that the HPMCAS attributes have little to no impact on the *in vivo* pharmacokinetics of this product.

The enzalutamide SDD is a low bulk density poorly flowing powder. However, addition of liquids to the formulation risks generating crystalline material. Therefore, a dry granulation approach was pursued for tablet manufacture. Standard pharmaceutical excipients common in tablets, (filler, glidant, disintegrant and lubricant), were selected and the relative amounts investigated using design of experiments (DoE) methodology. However, the relative amounts had little impact on dissolution rate. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards or, for HPMCAS, with national formulary (NF) standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.3. of this report.

To ensure compatibility with all of the tablet components, a study was conducted to examine binary mixtures of the SDD intermediate with each tablet excipient. These mixtures were then stored in open or tightly closed glass vials at either 50 °C / ambient RH or 40 °C / 75% RH for one month. The blends were then evaluated for their appearance, assay and related substances. No significant changes were observed, indicating that the tablet excipients selected are compatible with the SDD intermediate and that they do not impact the critical quality attributes or stability of this product under normal storage and use conditions.

A risk assessment of the impact of material attributes on the product performance was then undertaken. SDD bulk density and particle size were identified as having the biggest risk so tablets were prepared using batches of SDD with different bulk densities and particle sizes. However, no impact on dissolution performance was observed. Therefore, it was concluded that none of the tablet CQAs is impacted by any of the formulation component material attributes. Nonetheless, suitable acceptance criteria for the SDD intermediate have been set.

In order to develop a discriminatory dissolution method for quality control (QC), various parameters were investigated including medium pH and agitation rate. Studies were carried out on the 80 mg tablet. In the

presence of HPMCAS, greater dissolution of the active substance occurs at higher pH. A medium of pH 7.5 with a paddle stirring speed of 50 rpm was found to give complete dissolution of the proposed commercial formulation within 30 minutes. Significant differences were seen between the commercial formulation and batches with different drug loadings and where different fillers were used. Differences were also noted between standard batches and those manufactured with SDDs containing different polymers. Based on the properties of the active substance, the method is considered to be sufficiently discriminatory.

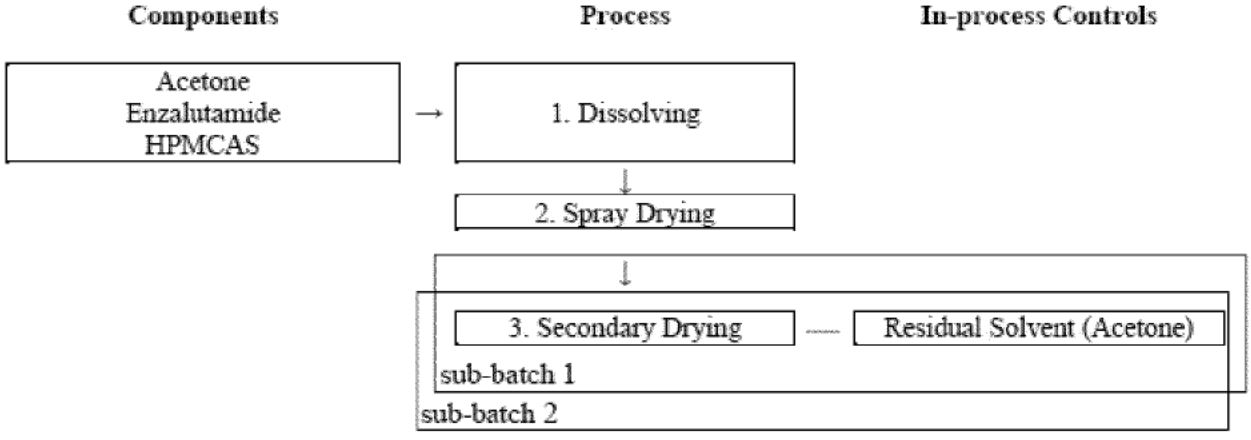
The dissolution profile of the 80 and 40 mg tablets were compared in 0.1 M HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer and using the QC method. Profiles were found to be similar across the pH range. Bioequivalence between the capsule and tablet formulation was demonstrated in clinical studies as the dissolution profiles of the formulations were significantly different across all media investigated.

A series of risk assessments and subsequent DoEs were carried out in order to identify critical process parameters in each step of the manufacturing process. Suitable parameters were identified for spray drying, granulation, final blending and compression. The impact of the ranges studied on the tablet CQAs was found to be low and no critical steps were identified. The set-points and ranges for process parameters in each step of the manufacturing process have been adequately justified.

The primary packaging is a cardboard wallet incorporating PVC/PCTFE/aluminium blisters as described in section 6.5 of the SmPC. The materials comply 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.

Manufacture of the product and process controls

The manufacturing process consists of 2 parts: production of the enzalutamide SDD intermediate which is performed by one manufacturer, and production of enzalutamide film-coated tablets which is carried out by a second. The manufacturing process of the SDD intermediate consists of dissolution of the active substance and HPMCAS in acetone, spray drying and secondary drying (scheme 1). The batch is divided into 2 sub-batches for the secondary drying operation. The in-process control of acetone content and specifications of the SDD intermediate are adequate to ensure quality. As discussed in the pharmaceutical development section, the proposed packaging and holding time for the SDD has been justified by stability data and is considered acceptable.

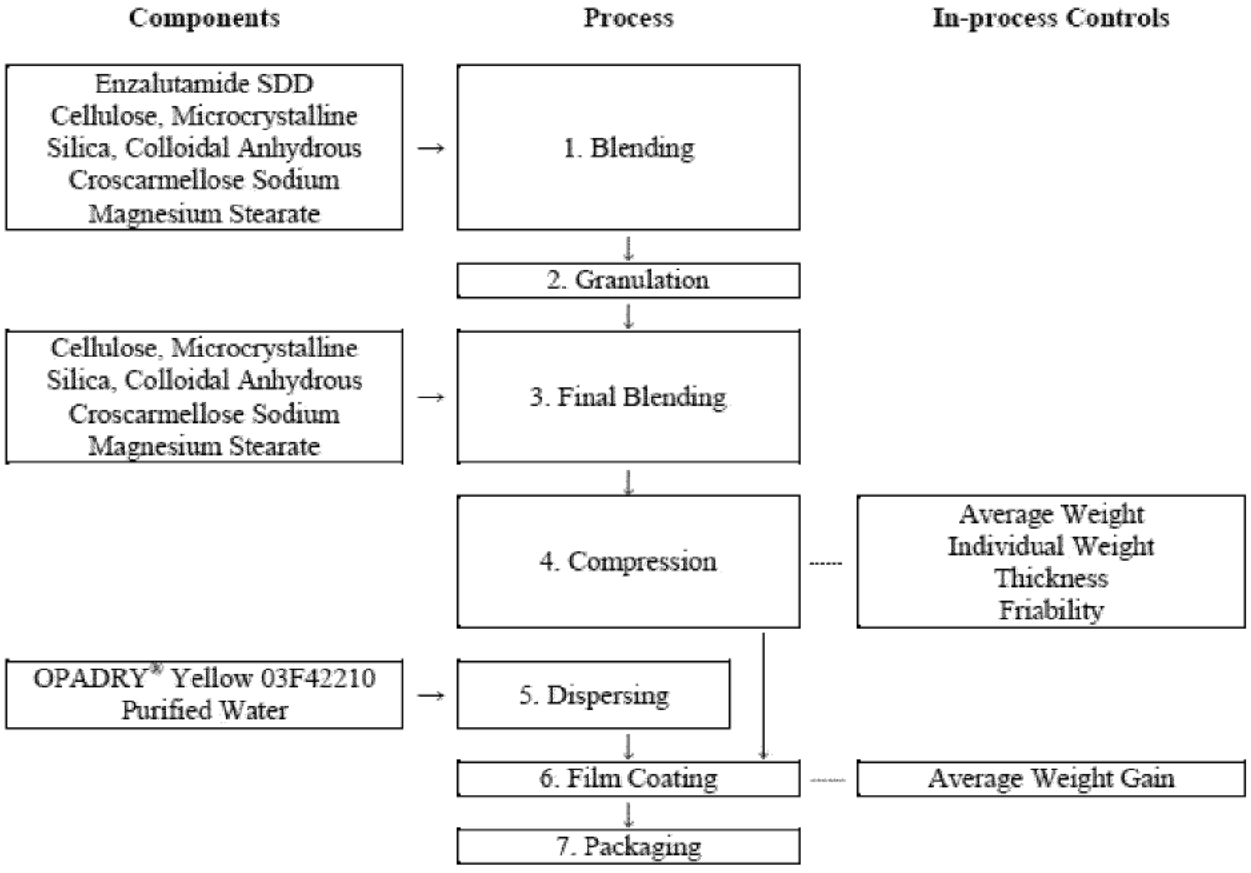


Scheme 1: manufacturing process for enzalutamide SDD

A GMP inspection of the SDD manufacturer revealed two critical and one major deficiencies relating to data integrity. Major deficiencies were also found with hygiene, identification of equipment and validation. In addition, issues from previous inspections had not been addressed. As a result, the validity of the data provided in the dossier was in question. The applicant was requested to provide a comprehensive risk assessment of the validity of data submitted in the dossier.

A risk assessment was conducted by the applicant's quality assurance department, focussing on product quality, the site quality system, data integrity and probability and detectability of any issues with batches used in clinical studies and to support quality development. The detailed risk assessment was submitted to the rapporteur's team and assessed. It was concluded that the applicant had adequately addressed all potential risks and that measures were in place to mitigate and reduce them to an acceptable level. Therefore, there is no evidence to question the validity of the data submitted in this line extension application.

The manufacturing process for the tablets (scheme 2) consists of six main steps: blending of intra-granular excipients; granulation (roller compaction); blending with extra-granular excipients; compression; film-coating; packaging. The process is considered to be a standard manufacturing process.



Scheme 2: manufacturing process for enzalutamide film-coated tablets

The applicant has justified the set-points and any associated ranges for process parameters using results from DoEs. However, no design space is claimed, despite the multi-variate experimental results.

An acceptable process validation scheme has been submitted and the process will be validated on three consecutive production scale batches of finished product prior to commercialisation. From the batches manufactured to date, it has been demonstrated that the manufacturing process is capable of producing finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications (Table 5) include appropriate tests for this kind of dosage form including description, identity (HPLC, UV), assay (HPLC), degradants (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC) and microbial limits.

Table 5: specifications for finished product

Attributes	Methods	Acceptance Criteria	
		Release	Shelf-life
Description	Visual observation	<40 mg> Round, yellow film-coated tablet, debossed with "E 40" <80 mg> Oval, yellow film-coated tablet, debossed with "E 80"	4.2 1st ind
Identification	1) HPLC	4.2 1st ind	
	2) HPLC-PDA		
Assay	HPLC		
Degradants	HPLC		
Uniformity of Dosage Units	HPLC	Conform to Ph. Eur. 2.9.40	
Dissolution	Ph. Eur. apparatus 2, 50 rpm 900 mL of pH 7.5 phosphate buffer HPLC assay	Conform to Ph. Eur. 2.9.3 Q = 80% at 30 min	Same as release
Microbial Limits [b]	Ph. Eur. 2.6.12, 2.6.13	TAMC: 10^3 cfu/g TYMC: 10^2 cfu/g Absence of *Escherichia coli*	4.2 1st ind

[a] 4.2 1st ind

[b] Microbial limits will be tested as a skip lot test on every tenth batch or once a year whichever comes first.

Impurity B is not present in the active substance but is both an oxidative degradant found in enzalutamide 40 mg and 80 mg tablets and a metabolite. The wider shelf-life limit is justified given the increase in the impurity during storage. The limits are well below what has been qualified in toxicology studies. No limit for solvent content is needed as a test for acetone content is performed on the SDD intermediate. No test for

water content is included as very little increase in water content was observed in stability studies. Open dish studies also indicated that even if water is taken up, there is no impact on any of the finished product quality attributes.

The absence of a test for physical form has been adequately justified. Enzalutamide tablets are designed to contain amorphous active substance and no crystallization has been detected in historical batches.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for 20 pilot to production scale batches covering both tablet strengths confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 pilot scale batches of each strength of finished product stored under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Up to 24 months' data is available for the 80 mg tablets whereas 18 months' data is available for 40 mg tablets. The batches were manufactured at the commercial site and using the intended commercial process and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradants, dissolution, microbial limits, water content (KF) and physical form (NIRs, XRPD). The analytical procedures used are stability indicating and those not in the release specification (KF and NIRs) were validated. No significant changes in appearance, assay, dissolution, microbial limit or physical form were observed when stored at the long term and accelerated conditions. The amount of impurity B and water content increased slightly over time, more so under accelerated conditions. However, no impact on other product attributes resulted. The wider shelf-life impurity limits are considered justified. A statistical analysis of trends was conducted indicating that impurity levels will remain within specification for over 36 months.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product is not photosensitive.

Results are also reported from batches stored in open HDPE bottles at higher temperature (50 °C, ambient humidity) or higher humidity (25 °C and 40 °C / 75% RH). No significant changes were observed other than an increase in water content and impurity B, within shelf-life limits. More impurity B is formed in the open bottles as compared to the blisters.

A bulk stability study was also carried out, with tablets of both strengths stored in double polyethylene bags in either aluminium pouches or HDPE drums. Samples were stored between 15-30 °C and 35-65% RH for up to 6 months (40 mg tablets) or up to 12 months (80 mg tablets). All parameters met with their acceptance criteria. Therefore, a bulk holding time under warehouse conditions as described above is considered acceptable.

Based on available stability data, the proposed shelf-life of 36 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate 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 clinical use. The risk assessment provided by the applicant to address GMP deficiencies at the SDD manufacturer leads to the conclusion that the validity of data provided in the dossier to support the line extension should not be questioned.

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.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

No new non-clinical data were submitted in support of this application which is considered acceptable.

2.3.1. Ecotoxicity/environmental risk assessment

The target disease indication in the current line extension applications has not changed, and the new tablet form is not expected to result in an increase in the environmental exposure. The MAH's justification for not providing an updated ERA is considered acceptable.

2.3.2. Discussion on non-clinical aspects

No new data were submitted as part of this application which is considered acceptable considering the scope of this procedure. Any unused medicinal product or waste material should be disposed of in accordance with local requirements as already mentioned in the current wording of the SmPC, section 6.6.

2.3.3. Conclusion on the non-clinical aspects

There is no objection for an approval from non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

- Tabular overview of clinical studies

Design Feature	Single-dose Studies (160 mg)				Multiple-dose Study (160 mg/day)
	Study MDV3100-05	Study 9785-CL-0010	Study MDV3100-19	Study 9785-CL-0014	Study 9785-CL-0003
Study report location	[Module 5.3.1.2]	[Module 5.3.1.2]	[Module 5.3.1.2]	[Module 5.3.1.2]	[Module 5.3.1.2]
Tablet formulation	Tablet A	Tablets B and C	Tablets E and F	To-be-marketed tablet	Tablet A
Tablet strength	160 mg	80 mg	80 mg	80 mg	160 mg
PK objectives	Relative BA and food effects	Relative BA	Relative BA	Pivotal BE and food effects	Relative BA and food effects
Subjects	Healthy males	Healthy males	Healthy males	Healthy males	CRPC patients
No. of subjects treated	60	55	45	59	27
Food conditions	Fasted and fed	Fasted	Fasted	Fasted and fed	Fasted and fed
Design for formulation comparison	2-period crossover	1-period, parallel group	1-period, parallel group	2-period crossover	1-period, parallel group
Design for food-effect comparison	Parallel group	NA	NA	Parallel group	Crossover
Duration of PK sampling	41 days postdose	49 days postdose	28 days postdose	20 - 48 days postdose†	24 hours postdose‡

Tablets A, B, C, E and F were development tablet formulations. The formulation was the same for the to-be-marketed tablet and Tablet E.
All studies used commercial capsules (4 x 40 mg) as the reference treatment. For studies with 80 mg tablets, 2 x 80 mg tablets were administered to achieve the 160 mg dose.
BA: bioavailability; BE: bioequivalence; NA: not applicable; PK: pharmacokinetic; CRPC: castration-resistant prostate cancer
† PK samples were collected up to 48 days postdose in period 1 and up to 20 days postdose in period 2.
‡ Full PK profiles were obtained up to 24 hours postdose on days 1, 56 and 57.
Source: Study reports MDV3100-05, 9785-CL-0010, MDV3100-19, 9785-CL-0014 and 9785-CL-0003

2.4.2. Pharmacokinetics

Four single dose and one multiple dose studies were submitted (see table above). These studies assessed the pharmacokinetics of enzalutamide either after a single-dose or after multiple-dose administration at 160 mg/day. Four of these studies assessed the relative bioavailability of various tablet formulations (MDV3100-05, 9785-CL-0010, MDV3100-19, 9785-CL-0003) and one was a pivotal bioequivalence study (9785-CL-0014) of the to-be-marketed tablet. Food-effect analyses were tested within two of the relative bioavailability studies (MDV3100-05 and 9785-CL-0003), as well as the pivotal bioequivalence study (9785-CL-0014).

An analysis based on simulated pharmacokinetics data to assess steady-state C_{max} and exposure-response analysis from CRPC2 was also conducted.

Relative Bioavailability

Single-dose Studies

Study MDV3100-05, Relative Bioavailability and Food-effect of Tablet A

This study was a pilot phase 1, single-center, open-label, randomized, 2-period cross-over relative bioavailability and food-effect study following a single 160 mg dose of enzalutamide in healthy male subjects. The objectives were to compare Tablet A to the capsule under fasted and fed conditions and to assess food effects for Tablet A and the capsule.

The Applicant conducted 2x2 cross-over studies (one fasted and one fed) to obtain estimates of inter- and intra-subject variability to adequately power future bioequivalence studies. The minimum 6-week washout period separated the single doses in Periods 1 and 2 corresponded to approximately six times the average t1/2 of MDV3100 in patients (Study S-3100-1-01). For the food-effects assessments, a parallel study design was considered appropriate because the mean t1/2 is long (85.9 to 94.3 hours in this study) and inter-subject variability in PK is low (≤ 33.3%CV in this study).

The total caloric content was 917 kcal, of which 547 kcal (59.6%) was due to fat, 116 kcal (12.7%) due to proteins and 254 kcal (27.7%) due to carbohydrates.

Results

The results showed that, regardless of food condition (fasted or fed), the extent of absorption (as reflected by AUC_{last} and AUC_{inf}) was similar for Tablet A versus the capsule, and the rate of absorption (as reflected by the lower C_{max} and later t_{max}) was slower with Tablet A than the capsule. Based on GMR, C_{max} was approximately 42.77% lower for Tablet A than the capsule under fasted conditions and approximately 21.80% lower under fed conditions

In the food effects assessment, administration of the capsules after high-fat, high-caloric breakfast, resulted in a 30% reduction in C_{max} compared to the fasted conditions, while AUC was not affected.

No significantly food effect on the Tablet A formulation was observed.

The inter-subject variability of the primary pharmacokinetic parameters was low and did not appear to be affected by formulation.

In both fated and fed conditions, the 90% CIs for AUC_{0-t}, AUC_{0-inf}, and C_{max} were all within the predefined equivalence criteria limit (80.00%, 125.00%), indicating that both the total and peak exposures for MDPC0001 and MDPC0002 met the acceptance criteria for metabolites exposure.

Exploratory metabolite equivalence and food-effects analyses for metabolites MDPC0001 and MDPC0002 demonstrated that differences in C_{max} for MDV3100 did not translate into meaningful differences in exposure to these metabolites

Study 9785-CL-0010, Relative Bioavailability of Tablets B and C (EudraCT number 2012-002502-49)

This was a phase 1, single-center, open-label, randomized, parallel group, relative bioavailability study following a single 160 mg dose of enzalutamide in healthy male subjects. The objectives were to compare Tablet B and Tablet C to the capsule under fasted conditions.

Due to the long elimination half-life of enzalutamide (~5.8 days), a parallel group design was chosen and it is considered acceptable. However, AUC_{0-72} is not able to predict the results obtained for AUC_{0-t} and AUC_{0-inf}. Therefore the use of AUC_{0-t} and AUC_{0-inf} is necessary.

Results

Based on the results, the Tablet B formulation was not bioequivalent to the capsule formulation. Enzalutamide AUC_{0-t} and AUC_{0-inf} were similar to the capsule formulation, although C_{max} and AUC_{0-72h} were 46.40% and 23.75%, respectively, lower compared to the capsule. Interestingly, AUC_{0-72h} data show that the absorption is not complete after 3 days since it is not predictive of AUC_{0-t} and AUC_{0-inf}.

The Tablet C formulation was also not bioequivalent to the capsule formulation since the total exposure was slightly above the acceptance criteria for bioequivalence and peak exposure (C_{max}) was below. Enzalutamide

AUC_{0-t} and AUC_{0-inf} were approximately 10% higher compared to the capsule formulation. C_{max} and AUC_{0-72h} were 18.44% and 13.62%, respectively, lower compared to the capsule.

For the enzalutamide metabolite M1, generally comparable AUC_{0-t}, AUC_{0-inf} and C_{max} geometric mean values for the capsule and both tablet formulations were observed.

For the enzalutamide metabolite M2, comparable AUC_{0-t} and AUC_{0-inf} geometric mean values for the capsule and both tablet formulations were observed, while C_{max} was 22.6% and 18.5% lower for Tablet B and Tablet C, respectively.

For the sum of enzalutamide plus its metabolite M2, AUC_{0-t} geometric mean value was comparable for the capsule and both tablet formulations, while C_{max} geometric mean value was 46.2% and 18.3% lower for Tablet B and Tablet C, respectively.

Study MDV3100-19, Relative Bioavailability of Tablets E and F

This was a phase 1, single-center, open-label, randomized, parallel group, relative bioavailability study following a single 160 mg dose of enzalutamide in healthy male subjects. The objectives were to compare Tablet E and Tablet F to the capsule under fasted conditions.

Results

In the statistical comparisons of tablet E and tablet F formulations (test) versus the capsule formulation (reference), the 90% CIs for AUC_{0-t}, AUC_{0-72} and AUC_{inf} were fully contained within the typical boundaries for bioequivalence (0.8000 and 1.2500); however, the lower range of the 90% CI for C_{max} for both tablets was below the boundary for bioequivalence (0.8000). Based on the geometric mean ratios, the C_{max} of tablet E was 18.66% lower than that of the capsule, and the C_{max} of tablet F was 16.81% lower than that of the capsule. The median t_{max} of tablet E and tablet F occurred approximately 1.0 hour and 0.5 hours later, respectively, than that of the capsule, suggesting that the decreases in C_{max} reflect an apparent decrease in the rate of absorption of enzalutamide with the tablets.

Multiple-dose Studies

Study 9785-CL-0003, relative bioavailability and food-effect of Tablet A

This was a phase 1, multicenter, open-label, randomized, one-period relative bioavailability and food-effect study of enzalutamide 160 mg/day in male subjects with castration-resistant prostate cancer. The objectives were to compare Tablet A to the capsule under fasted and fed conditions and to assess food effects for Tablet A and the capsule with enzalutamide dosed to steady state.

After multiple 160 mg doses of enzalutamide under fasted conditions or after a high-fat, high-calorie meal, enzalutamide AUC_{tau} and C_{trough} for the tablet and capsule formulations were comparable.

In this study the composition of the meal varied between sites and the composition of the meals is in accordance with the Guideline on investigation of bioequivalence that requires approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.

After multiple 160 mg doses of enzalutamide, compared to the capsule formulation, the C_{max} of the tablet formulation was 17.52% and 10.78% lower under fasted conditions and after a high-fat, high-calorie meal, respectively.

No effect of food on enzalutamide C_{max} for either the tablet or capsule was observed.

In addition, an exploratory assessment to determine whether Tablet A differs from the capsules with regard to steady-state exposure to N-desmethyl enzalutamide was performed. The results show that the steady-state exposures to N-desmethyl enzalutamide were essentially the same for the tablet and capsule formulations, regardless of food condition.

Bioequivalence

Study Protocol Number: 9785-CL-0014 (EudraCT number 2014-002641-21)

This is a pivotal phase 1, single-center, open-label, 2-period, crossover bioequivalence study comparing a capsule and tablet formulation of enzalutamide following a single 160 mg dose under fasted and fed conditions in healthy male subjects.

The total caloric content was 982 kcal, of which 590 kcal (60%) was due to fat, 125 kcal (13%) was due to proteins and 268 kcal (27%) was due to carbohydrates.

Results

Table 6: Summary of the statistical comparisons of the formulations are presented in the following table (all subjects)

Fasted Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	29	27	--	--	--
AUC_{0-72h} (µg·h/mL)	102	105	97.26	95.13	99.43
AUC_{last} (µg·h/mL)	225	223	100.94	96.26	105.84
AUC_{inf} (µg·h/mL)	235	232	101.17	96.77	105.77
C_{max} (µg/mL)	3.39	4.71	71.82	66.75	77.28
t_{max} (h)†	2.00 [0.50–6.02]	1.00 [0.50–3.02]	--	--	--
Fed Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	28	28	--	--	--
AUC_{0-72h} (µg·h/mL)	102	106	95.56	88.35	103.35
AUC_{last} (µg·h/mL)	250	267	93.56	84.34	103.78
AUC_{inf} (µg·h/mL)	259	276	93.75	85.25	103.11
C_{max} (µg/mL)	2.68	2.97	90.01	79.94	101.36
t_{max} (h)†	3.00 [0.50–8.03]	2.99 [0.50–8.00]	--	--	--

AUC_{0-72h}: area under the concentration-time curve from time point 0 to time point 72 hours; AUC_{inf}: area under the concentration-time curve from the time of dosing extrapolated to time infinity; AUC_{last}: area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max}: maximum concentration; CI: confidence interval; n: sample size; t_{max}: time to attain maximum concentration.

Table 7: Statistical Summary of Food-Effect Comparison for Enzalutamide for the Tablet Formulation

Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet - Fed (Test)	To-be-marketed Tablet - Fasted (Reference)		Lower	Upper
n	28	28	--	--	--
AUC_{0-72h} (µg·h/mL)	102	102	99.24	88.91	110.76
AUC_{last} (µg·h/mL)	250	225	111.01	96.78	127.33
AUC_{inf} (µg·h/mL)	259	234	110.64	96.59	126.74
C_{max} (µg/mL)	2.68	3.38	79.18	68.58	91.43
t_{max} (h)†	3.00 [0.50–8.03]	2.00 [0.500–6.02]	--	--	--

AUC_{0-72h}: area under the concentration-time curve from time point 0 to time point 72 hours; AUC_{inf}: area under the concentration-time curve from the time of dosing extrapolated to time infinity; AUC_{last}: area under the concentration-time curve from the time of dosing to the last measurable concentration; C_{max}: maximum concentration; CI: confidence interval; n: sample size; t_{max}: time to attain maximum concentration.

† Values reported for t_{max} are the median and range of observed values (minimum-maximum).

Table 8: Statistical Summary of Food-Effect Comparison for Enzalutamide for the Capsule Formulation

Parameter (Units)	Geometric LS Mean		Geometric LS Mean Ratio (Test/Reference) (%)	90% CI of Ratio (%)
	Fed (Test) n = 28	Fasted (Reference) n = 27		
AUC_{0-72h} (µg.h/mL)	106.3	103.6	102.63	94.79 - 111.12
AUC_{last} (µg.h/mL)	266.8	219.7	121.44	108.15 - 136.36
AUC_{inf} (µg.h/mL)	276.1	226.2	122.08	108.35 - 137.54
C_{max} (µg/mL)	2.972	4.693	63.34	56.76 - 70.69

The analysis was performed on log-transformed pharmacokinetic parameters using an analysis of variance (ANOVA) model with food condition and period as fixed effects.

CI: confidence interval; LS: least square; NA: not applicable

The formulation comparison of the to-be-marketed tablet versus the capsule under both fasted and fed conditions showed that the 90% CI for AUC_{last} and AUC_{inf} were within the bioequivalence criteria limits, and the 90% CI for C_{max} were below the lower boundary for bioequivalence. The 90% CI for AUC_{0-72h} was within the bioequivalence criteria limits under both fasted and fed conditions. Under fasted conditions, the median t_{max} occurred 1 hour later with the tablet than with the capsule (2.00 versus 1.00 hours). Under fed conditions, the median t_{max} of the tablet was essentially the same as that of the capsule (3.00 versus 2.99 hours).

Taken together, the results of the formulation comparison showed that, regardless of food condition (fasted or fed), the extent of absorption (as reflected by AUC_{last} and AUC_{inf}) was the same for the to-be-marketed tablet and the capsule, and the rate of absorption (as reflected by the lower C_{max} and later t_{max}) was slower for the tablet. Based on GMR, C_{max} was approximately 28.18% lower for the tablet than the capsule under fasted conditions and approximately 10% lower under fed conditions.

The food-effect comparison (fed versus fasted conditions) for the to-be-marketed tablet showed that the 90% CI for AUC_{last} and AUC_{inf} extended slightly above the upper boundary of the bioequivalence criteria limits, the 90% CI for C_{max} extended below the lower boundary and AUC_{0-72h} was within the bioequivalence criteria limits. The median t_{max} occurred 1 hour later with fed conditions than with fasted conditions (3.00 versus 2.00 hours).

The pharmacokinetic exposure parameters of N-desmethyl enzalutamide (AUC_{last}, AUC_{inf} and C_{max}) appear not to be affected by formulation or food condition.

Median t_{max} values were similar for all regimens with peak concentrations reached after approximately 168 hours (i.e., 7 days). Mean t1/2 was comparable after administration of tablet and capsule formulations under fasted and fed conditions and ranged from 174.2 and 195.6 hours (i.e., 7.3 and 8.2 days).

Between subjects variability in N-desmethyl enzalutamide AUC_{last}, AUC_{inf} and C_{max} was low and similar for the different treatments, with values ranging from 12.3% to 26.4%.

AUC_{last} and AUC_{inf} of the sum of enzalutamide plus N-desmethyl enzalutamide appear not to be affected by formulation or food condition. Compared to administration of the capsule under fasted conditions, mean C_{max} for the sum of enzalutamide plus N-desmethyl enzalutamide of the capsule under fed conditions and of the tablet under fasted and fed conditions were 35%, 31%, and 34% lower, respectively.

Under both fasted and fed conditions, median t_{max} values for the tablet (2.000 hours and 3.500 hours, respectively) were 1 hour later than for the capsule (1.000 hours and 2.490 hours, respectively). For both formulations, median t_{max} was 1.5 hours later under fed compared to under fasted conditions.

Between subjects variability for the sum of enzalutamide plus N-desmethyl enzalutamide AUC_{last}, AUC_{inf} and C_{max} was low for the different regimens, with values ranging from 16.1% to 34.4%.

Non-parametric superposition

Using individual single-dose PK profiles from study MDV3100-05, the Applicant performed PK simulations to steady-state to validate the model.

The geometric mean values for AUC_{tau}, C_{max} and C_{min} were similar for the observed data and the data predicted by non-parametric superposition. The geometric mean ratios and corresponding 90% CI for Tablet A versus the capsule were nearly identical for the observed and predicted data (see the table below).

Table 9: Summary of Observed and Predicted Multiple-dose Parameters for Tablet A and Capsule under Fasted Conditions

Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	Tablet A (Test)	Capsule (Reference)		Lower	Upper
Observed in Multiple-dose Study 9785-CL-0003					
AUC_{tau} (µg.h/mL)	290	318	91.19	82.63	100.63
C_{max} (µg/mL)	13.9	16.9	82.48	74.28	91.60
C_{min} (µg/mL)	12.4	12.8	97.04	85.55	110.07
Predicted from Single-dose Data in Study MDV3100-05					
AUC_{tau} (µg.h/mL)	262	279	94.03	81.97	107.86
C_{max} (µg/mL)	12.7	15.4	82.81	73.53	93.28
C_{min} (µg/mL)	9.9	10.3	96.53	83.39	111.75

AUC_{tau}: area under the concentration-time curve during one 24-hour dosing interval at steady state; C_{max}: maximum concentration; C_{min}: minimum (trough) concentration; CI: confidence intervals

Predicted values were obtained by nonparametric superposition.

Taken together, the results of the validation study, comparison between data obtained from simulation and the observed steady-state data obtained from study 9785-CL-003 shows that the non-parametric superposition is good to predict steady-state C_{max} since the differences between the observed and predicted for C_{max} was < 10%.

Nonparametric Superposition of Data from the Pivotal Bioequivalence Study

Non-parametric superposition was applied to single-dose data from the pivotal bioequivalence study 9785-CL-0014 to determine if the to-be-marketed tablet formulation would meet bioequivalence criteria under the conditions of once-daily dosing to steady state

The simulated multiple-dose data show that the to-be-marketed tablet is predicted to be bioequivalent to the capsule for AUC_{tau}, C_{max}, and C_{min} with once-daily dosing in steady state under fasted and fed conditions since the 90% CI fall within the bioequivalence criteria limits.

Table 10: Summary of Simulated Multiple-dose Pharmacokinetic Parameters for the Capsule and To-be-marketed Tablet

Formulation	Food Condition	Subjects	C_{min} (µg/mL)	C_{max} (µg/mL)	t_{max} (h)	AUC_{tau} (µg.h/mL)	Peak-to-trough Ratio
Tablet	Fasted	n=29	9.3 (3.3)	12.6 (3.6)	2.00 (0.50-6.00)	247 (81)	1.39 (0.18)
Capsule	Fasted	n=27	8.7 (2.6)	13.3 (2.9)	1.00 (0.50-3.00)	234 (63)	1.58 (0.21)
Tablet	Fed	n=28	10.4 (2.9)	12.9 (3.5)	2.00 (0.50-6.00)	269 (72)	1.26 (0.11)
Capsule	Fed	n=28	11.0 (3.0)	13.8 (3.2)	2.00 (0.50-6.00)	285 (73)	1.28 (0.12)

Results are for the capsule and to-be-marketed tablet in Study 9785-CL-0014.

Mean values (standard deviations in parentheses) are reported for all parameters except for t_{max}, for which median and range (minimum-maximum) values are reported.

AUC_{tau}: area under the concentration-time curve during one 24-hour dosing interval at steady state; C_{max}: maximum concentration; C_{min}: minimum (trough) concentration; n: number of subjects; t_{max}: time to attain maximum concentration.

The statistical comparison of the predicted steady-state parameters for the to-be-marketed tablet versus the capsule formulation showed that under both fasted and fed conditions is presented below.

Table 11: Statistical comparison of the predicted steady-state parameters for the to-be-marketed tablet versus the capsule formulation

Fasted Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	29	27	--	--	--
AUC_{tau} (µg·h/mL)	235	232	101.19	96.75	105.83
C_{max} (µg/mL)	12.09	13.29	90.94	87.06	95.00
C_{min} (µg/mL)	8.76	8.56	102.35	97.53	107.42
t_{max} (h)†	2.00 [0.50–6.00]	1.00 [0.50-3.00]	--	--	--
Fed Conditions					
Enzalutamide Pharmacokinetic Parameters (Units)	Geometric Means		Ratio (Test/Reference) (%)	90% CI for Ratio (%)	
	To-be-marketed Tablet (Test)	Capsule (Reference)		Lower	Upper
n	28	28	--	--	--
AUC_{tau} (µg·h/mL)	259	276	93.70	85.13	103.12
C_{max} (µg/mL)	12.43	13.47	92.30	83.92	101.51
C_{min} (µg/mL)	9.92	10.59	93.66	85.15	103.03
t_{max} (h)†	2.00 [0.50–6.00]	2.00 [0.50–6.00]	--	--	--

AUC_{tau}: area under the concentration-time curve from the time of dosing extrapolated to time infinity; C_{max}: maximum concentration; C_{min}: minimum concentration; CI: confidence interval; n: sample size; t_{max}: time to attain maximum concentration.

Exposure-response analyses

The original marketing application included exposure-response analyses of data from the phase 3 study CRPC2, in which a total of 1199 patients with metastatic castration-resistant prostate cancer were randomized 2:1 to enzalutamide (n = 800) or placebo (n = 399). The dose of enzalutamide was 160 mg/day (4 × 40 mg capsules/day). Predose (C_{min}) plasma samples were obtained from all patients to assess plasma concentrations of enzalutamide and its major metabolites. The primary efficacy endpoint was overall survival. Key secondary and exploratory endpoints included time to prostate-specific antigen (PSA) progression, radiographic progression-free survival, time to first skeletal-related event and PSA response rate (50% and 90% reductions from baseline). The analysis of exposure-response between enzalutamide Cmin values and efficacy showed a consistency of results favouring enzalutamide therapy across all primary, key secondary, other secondary and exploratory efficacy endpoints.

Exposure-response analyses explored relationships between enzalutamide Cmin values and efficacy endpoints (overall survival, radiographic progression-free survival, time to PSA progression and several other clinical endpoints). The Cmin values were evaluated as continuous and discrete parameters. When evaluated as discrete parameters, the Cmin values were classified into quartiles (Q) that divided the derived nonzero exposure parameters into 4 approximately equal groups from lowest exposure quartile (Q1) to highest exposure quartile (Q4) after sorting by rank order. Exposure categories included the placebo-randomized patients as 1 category (Cmin = 0) and 4 categories (quartiles) of exposure for the enzalutamide-randomized patients.

Table 12 : Summary statistics for Cmin exposure quartiles in study CRPC2

C_{min} (µg/mL) Quartile											
Q1			Q2			Q3			Q4		
N	Median	Min, Max	N	Median	Min, Max	N	Median	Min, Max	N	Median	Min, Max
192	8.93	0.56, 10.15	190	10.83	10.16, 11.57	191	12.18	11.57, 12.96	190	14.40	12.97, 22.80

C_{min}: minimum (trough) concentration; Max: maximum; Min: minimum; N: number of subjects; Q: quartile

Log-rank tests for homogeneity assessed differences between Kaplan-Meier exposure category curves, and pairwise log-rank tests compared exposure categories to one another. In addition, a Cox proportional hazard analysis of Cmin as a continuous variable assessed the association between exposure and event risk. Where a statistically significant slope was observed, pairwise Cox proportional hazard estimates compared exposure categories. Statistical significance was assigned using a nominal 2-sided type I error rate of 5% with no adjustments made for multiplicity.

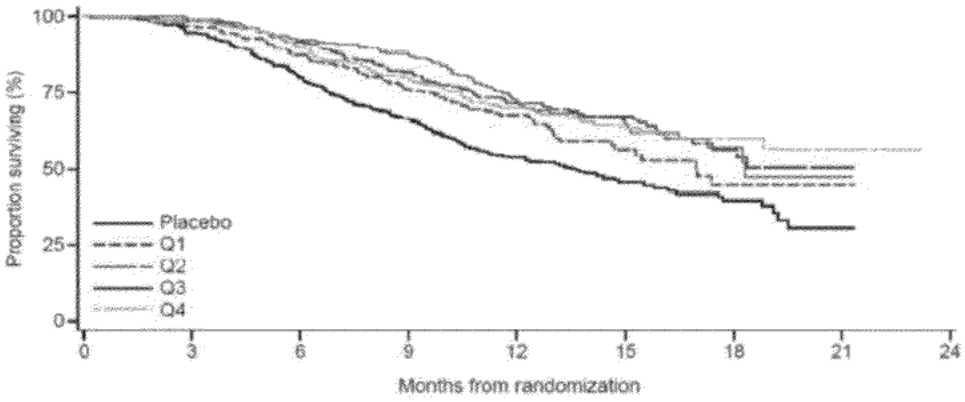
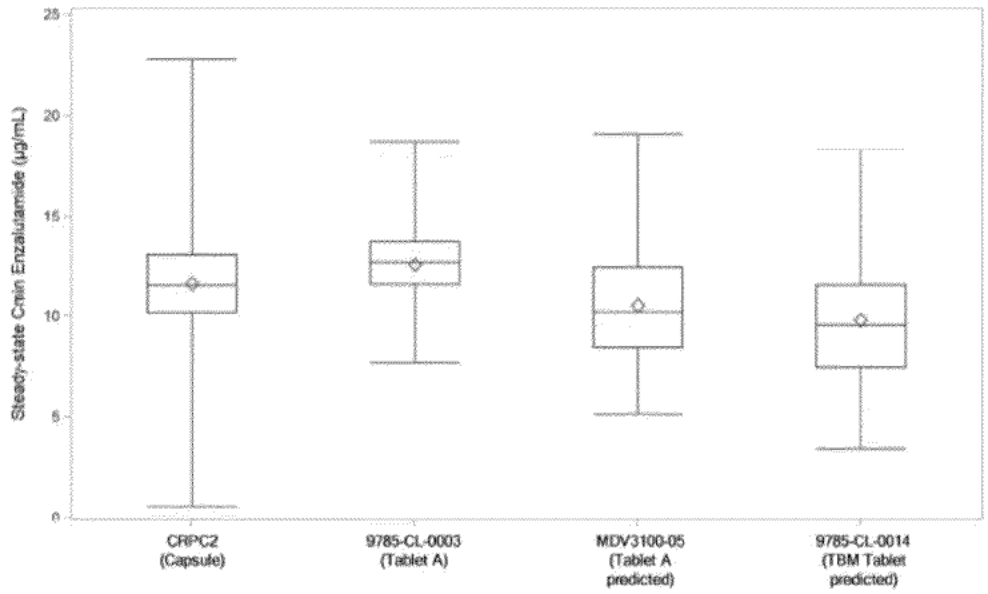


Figure 1: Comparison of Kaplan-Meier exposure-response analysis based on Cmin for enzalutamide versus overall survival with the capsule formulation in study CRPC2

In all pairwise comparisons versus placebo, the effects of the active treatment Cmin quartile groups were statistically significant ($P \leq 0.0039$) in favour of active treatment.

All assessments of efficacy endpoints versus enzalutamide Cmin values as a continuous variable resulted in statistically significant slopes ($P < 0.0001$). Although this suggests an association between higher levels of exposure and improved prognosis for patients, pairwise tests showed no difference in the risk of events among active treatment Cmin quartiles ($P \geq 0.5499$).

Steady-state Cmin concentrations of enzalutamide measured in Study 9785-CL-0003 (Tablet A), and predicted steady-state Cmin concentrations that were estimated by nonparametric superposition of single-dose data from studies MDV3100-05 (Tablet A) and 9785-CL-0014 (to-be-marketed tablet) were graphically compared to Cmin concentrations in the phase 3 study CRPC2 [see Figure below]. As illustrated by the box plots, values for all tablet formulations were within the range of Cmin values observed with the capsule in study CRPC2. In addition, a tabulation of data from studies CRPC2 and 9785-CL-0014 [see Table below] shows that the predicted Cmin concentrations for the to-be-marketed tablet are both similar to those for the capsule formulation and within the range of values associated with clinical benefit in the phase 3 study CRPC2.



C_{min}: minimum (trough) concentration; TBM: to-be-marketed C_{min} values for the capsule in studies CRPC2 and 9785-CL-0003 were observed values in patients. All other C_{min} values were derived from nonparametric superposition of single-dose data from the studies named in the xaxis. Line in the "middle" of each box corresponds to the median; diamond symbols correspond to the arithmetic means; lower and upper edges of the boxes correspond to the 25th and 75th percentiles, respectively; whiskers correspond to the minimum and maximum observed or predicted values

Figure 2: Comparisons of Cmin at steady state for capsule versus tablet formulations

Table 13: Comparison of steady-state Cmin for capsules versus the to-be-marketed tablet

	C_{min} (µg/mL)		
	CRPC2† Capsule	9785-CL-0014‡ Capsule	9785-CL-0014‡ To-be-marketed Tablet
N	763	27	29
Mean	11.62	8.71	9.30
Median	11.57	8.57	8.80
SD	2.57	2.57	3.32
Min, Max	0.56, 22.80	3.43, 14.7	3.39, 18.3

C_{min}: minimum (trough) concentration; Max: maximum; Min: minimum; N: number of subjects; SD: standard deviation

† Based on summary statistics for patients randomized to enzalutamide (160 mg/day)

‡ Based on nonparametric modeling of steady state with once-daily dose to steady state (160 mg/day)

An exposure-response analysis was also conducted for steady-state Cmax. The methods were identical to those of the analysis based on Cmin. Cmax values in individual patients were estimated by population pharmacokinetic modeling as described in (Medivation 02 Apr 2014). The summary statistics for the enzalutamide estimated Cmax exposure quartiles are summarized in [Table below].

Table 14: Summary statistics for Cmax exposure quartiles in study CRPC2

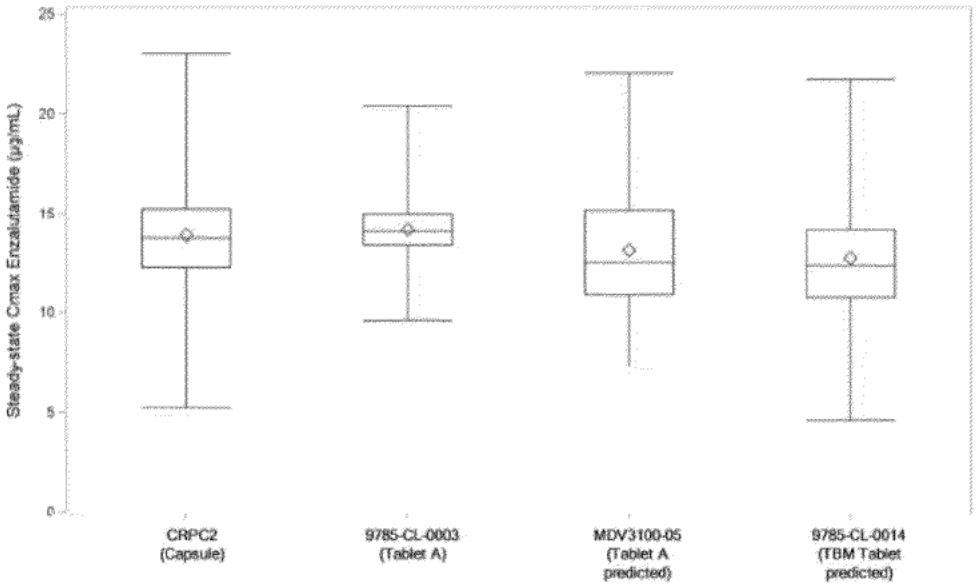
C_{max} (µg/mL) Quartile											
Q1			Q2			Q3			Q4		
N	Median	Min, Max	N	Median	Min, Max	N	Median	Min, Max	N	Median	Min, Max
189	11.19	5.21, 12.27	189	13.04	12.29, 13.73	189	14.36	13.74, 15.23	189	16.72	15.24, 23.07

C_{max}: maximum concentration; N: number of subjects; Max: maximum; Min: minimum; Q: quartile

Kaplan-Meier plots show a clear separation in the placebo group from all curves associated with enzalutamide Cmax groups [Figure below]. A significant difference between the Kaplan-Meier group curves of overall survival (placebo versus active treatment in any quartile) was demonstrated by a log-rank test for homogeneity of enzalutamide exposure categories ($P < 0.0001$). Significant differences ($P \leq 0.0003$) were also identified in each of the pairwise log-rank tests of active treatment enzalutamide Cmax groups versus the placebo group, while there were no significant differences in rates of survival among the active treatment Cmax quartiles when compared to each other. No differences in survival curves were identified ($P \geq 0.5841$) based on similar pairwise comparisons between active treatment enzalutamide Cmax groups.

dose data from Studies MDV3100-05 (Tablet A) and 9785-CL-0014 (to-be-marketed tablet) were graphically compared to Cmax concentrations in the pivotal phase 3 study CRPC2 [Figure below].

Values for all tablet formulations are within the range of Cmax values observed with the capsule in the pivotal phase 3 study CRPC2. In addition, a tabulation of data from CRPC2 and 9785-CL-0014 [Table below] showed that the predicted steady-state Cmax concentrations for the to-be-marketed tablet were both similar to those for the capsule formulation and within the range of values associated with clinical benefit in the phase 3 study.



C_{max}: maximum concentration; TBM: to-be-marketed

C_{max} values for the capsule in study CRPC2 were simulated by population pharmacokinetic modeling. C_{max} values for study 9785-CL-0003 were observed in patients. All other C_{max} values were derived from nonparametric superposition of single-dose data from the studies named in the x-axis. Line in the "middle" of each box corresponds to the median; diamond symbols correspond to the arithmetic means; lower and upper edges of the boxes correspond to the 25th and 75th percentiles, respectively; whiskers correspond to the minimum and maximum observed or predicted values.

Figure 5: Comparisons of Cmax at steady state for capsule versus tablet formulations

Table 1: Comparison of steady state Cmax values for capsules versus the to-be-marketed tablet

	C_{max} (µg/mL)		
	CRPC2† Capsule	9785-CL-0014‡ Capsule	9785-CL-0014‡ To-be-marketed Tablet
N	756	27	29
Mean	13.88	13.32	12.55
Median	13.74	13.13	12.17
SD	2.49	2.86	3.62
Min, Max	5.21, 23.07	7.90, 19.7	6.87, 21.7

C_{max}: maximum concentration; Max: maximum; Min: minimum; N: number of subjects; SD: standard deviation

† Based on summary statistics for patients randomized to enzalutamide (160 mg/day)

‡ Based on nonparametric modeling of steady state with once-daily dose to steady state (160 mg/day)

2.4.3. Pharmacodynamics

No data submitted which is considered acceptable considering the scope of this procedure.

2.4.4. Discussion on clinical pharmacology

The clinical data submitted in support of the Marketing Authorisation of a new film-coated (FC) tablet formulation of Xtandi, i.e. 80 mg and 40 mg tablets is considered acceptable and in line with the CHMP Scientific Advice that was given.

Although these studies are usually conducted at the highest strength, the Applicant conducted the studies at the therapeutic dose of 160 mg (i.e., 4 x 40mg capsules and 2 x 80 mg tablets), this is considered acceptable since no major deviations from dose proportionality were detected over the dose range 40 to 160 mg, neither after a single dose nor at steady state (see Xtandi EMA/CHMP/383457/2013).

Pharmacokinetic software and method for AUC_{0-t} and C_{max} in the fasting and fed single-dose studies and AUC_{tau}, C_{max} and C_{min} in the fasting and fed multiple-dose study estimation are considered acceptable. The non-compartmental linear-trapezoidal calculation is adequate. Pharmacokinetics variables are appropriate for a fasting and fed single dose and multiple-dose bioequivalence study of an immediate release product.

The parent compound and metabolite M2 PK parameters was used in the BA statistical and food effects comparisons in all studies with the exception of the relative bioavailability study 9785-CL-0019 in which only PK analysis of enzalutamide parent compound was performed. For M1 PK parameters and food effect comparisons were performed in studies MDV3100-05 and 9785-CL-0010. The use of the parent and M2 metabolite is adequate since the M2 metabolite is thought to contribute to enzalutamide clinical effects because it demonstrates key primary pharmacodynamics of similar *in vitro* potency to enzalutamide and also circulates at approximately the same plasma concentration as enzalutamide with multiple dosing of enzalutamide to steady state.

The use of non-parametric superposition was discussed with FDA and CHMP, and both agencies agreed that supplemental assessments based on this method were appropriate as supportive data in the marketing application.

Conventional and standard statistical methods have been employed. For non-parametric superposition, statistical analyses for bioequivalence at steady state used the same methods as the prior single-dose bioequivalence comparisons for tablet (test) versus capsule (reference) in study 9785-CL-0014 and this is considered acceptable.

The bioanalytical method was assessed previously in the initial MAA EU/1/13/846/001 and it was considered adequate. The storage period did not exceed the current validated storage period of 1106 days for Enzalutamide in its metabolites in human K_2EDTA plasma at the storage conditions. The in-study validations showed acceptable calibration standards and QCs.

Incurred Sample Reproducibility was performed in all studies. For the samples reanalysed, the ISR was acceptable as 92.4% and 88.0% of the reanalysed samples for MDV3100 and MDPC0002, respectively, were within the acceptance range (± 20%).

Several enzalutamide tablet formulations (Tablets A, B, C, E and F) were developed and assessed in relative bioavailability studies and according to the MAH, the critical quality attributes were achieved with Tablet E, which was selected as the formulation for the to-be-marketed tablet.

The pivotal bioequivalence study (9785-CL-0014) compared the to-be-marketed tablet to the capsule formulation after single-dose administration of enzalutamide. Under both fasted and fed conditions, the 90% CI for total exposure (AUC) were within the bioequivalence criteria limits, and the lower range of the 90% CI for peak exposure (C_{max}) was below the lower with the to-be-marketed tablet than with the capsule. Under fated condition C_{max} was 28% and under fed condition was 10% lower.

To assess whether the to-be-marketed tablet might meet all bioequivalence criteria relative to the capsule under the conditions of once-daily dosing to steady state, an analysis was performed based on with multiple-dose administration. The statistical comparison of the predicted steady-state parameters for the to-be-marketed tablet versus the capsule formulation showed that under both fasted and fed conditions, the 90% CI for AUC_{tau}, C_{max} and C_{min} fell within the bioequivalence criteria limits.

Based on GMR, C_{max} was approximately 9% lower for the to-be-marketed tablet than the capsule under fasted conditions and approximately 8% lower under fed conditions. Thus, consistent with the established pharmacokinetic properties of enzalutamide, the C_{max} differences between the formulations were smaller with multiple-dose administration to steady state than after single-dose administration.

In addition to supporting assessments of bioequivalence with once-daily dosing to steady state, nonparametric superposition was also used to support exposure-response analyses. The predicted steady-state C_{max} concentrations obtained by nonparametric superposition of data from the pivotal bioequivalence study (9785-CL-0014) were compared with C_{max} concentrations generated by pharmacokinetic modeling and simulation from the pivotal phase 3 CRPC2 trial (capsule). The predicted steady-state C_{max} values for the to-be-marketed tablet formulation were within the range of C_{max} values observed with the capsule in study CRPC2.

As an exposure-response analysis of efficacy in CRPC2 showed C_{max} quartiles to be uniformly beneficial relative to placebo across efficacy endpoints (overall survival, radiographic progression-free survival and time to PSA progression), it is unlikely that the to-be-marketed tablet formulation would differ from the capsule in terms of efficacy outcomes. Thus, in spite of nonequivalence between tablets and capsule for C_{max} in a single-dose setting, the clinical effectiveness of the to-be-marketed tablet formulation is expected to be comparable to that of the currently marketed capsule.

These data can be extrapolated to the 40 mg strength as all requirements described in section 4.1.6 of the Bioequivalence guideline are fulfilled (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Given the nature of the non-compliance of the site manufacturing the Enzalutamide SDD and tablet drug product used in the clinical trials, a risk assessment was provided. It was concluded that the provided clinical data can be considered reliable enough to support this marketing authorization.

2.4.5. Conclusions on clinical pharmacology

The new proposed pharmaceutical form, film-coated dosage tablet for Xtandi is considered comparable to the current capsule.

2.5. Clinical safety

Results from 5 biopharmaceutical studies with various development tablets (Tablets A, B, C, E and F) and the to-be-marketed tablet were presented. Of these 5 studies, 4 were single-dose studies involving a total of 219 healthy male subjects, and one was a multiple-dose study in 27 male patients with prostate cancer (9785-CL-0003).

There were no deaths reported in any of the 5 biopharmaceutical studies. In addition, no subject discontinued any of the 5 biopharmaceutical studies due to an AE.

There were no observable differences between the AE profiles, laboratory, vital signs or ECG data between treatment with capsule versus tablet formulations in any of the studies. In the one patient study (9785-CL-0003), the safety data for the tablet were consistent with the known safety profile of the enzalutamide capsule in its marketed indication.

Study 9785-CL-0003 compared Tablet A (1 x 160 mg) to the capsule (4 x 40 mg) under fasted and fed conditions and compared Tablet A and the capsule dosed to steady state. Across both treatment groups, a total of 24 (88.9%) patients experienced at least 1 TEAE including all 13 subjects in the capsule group and 11 (78.6%) patients in the Tablet A group. Nineteen (70.4%) patients experienced at least 1 treatment-related TEAE: 10 (76.9%) patients in the capsule group and 9 (64.3%) patients in the Tablet A group.

The majority of patients (16 [59.3%]) experienced at least 1 grade 1 TEAE, 6 (22.2%) patients experienced a grade 2 TEAE, 1 (3.7%) patient experienced a grade 3 TEAE and 1 (3.7%) patient experienced a grade 4 TEAE. The distribution of TEAEs by grade was comparable between the 2 treatment groups. Grade 1 treatment-related TEAEs were evenly distributed across the 2 treatment groups; 2 subjects taking capsules experienced at least 1 grade 2 TEAE compared to no grade 2 treatment-related TEAEs in the Tablet A group. One patient experienced grade 4 worsening of hypophosphatemia starting on day 8.

The SOCs with the most reported TEAEs across both treatment groups were Gastrointestinal disorders (11 [40.7%] patients), Investigations (9 [33.3%] patients), General disorders and administration site conditions (8 [29.6%] patients), and Nervous system disorders (7 [25.9%] patients).

Diarrhoea (6 [22.2%] patients) was the most frequently reported TEAE. Overall, observed TEAEs were comparable for the 2 formulations, with a difference of no more than 1 to 2 patients at the PT level.

2.5.1. Discussion on clinical safety

The data presented by the MAH regarding safety, for the tablet formulation of enzalutamide summarize 4 single-dose healthy volunteer studies and 1 multiple-dose study in male subjects with prostate cancer. The studies in healthy volunteers were limited to small study durations in small groups of subjects (data not shown). The study in male subjects with prostate cancer using the tablet formulation (9785-CL-0003) is limited by the small number of patients treated with the tablet formulation (n = 14), while the combined controlled safety population treated with the capsule is comparatively large (n = 1671).

The overall safety profile of the enzalutamide tablet was comparable to the safety profile of the capsule in the combined controlled population. No clinically significant differences in safety were observed for the tablet compared with the capsule in the multi-dose study, 9785-CL-0003, which enrolled patients with prostate cancer. No formulation-specific safety concerns were identified in the biopharmaceutical studies comparing the development Tablets A, B, C, E, and F, or the to-be-marketed tablet to the capsule.

2.5.2. Conclusions on the clinical safety

The new pharmaceutical form and strength are acceptable from safety perspective. The current SmPC and RMP are adequate to address the risks of enzalutamide tablets.

2.6. Risk Management Plan

Safety concerns

Summary of Safety Concerns

Important Identified Risks	Seizure Posterior reversible encephalopathy syndrome (PRES) Hypertension Fall Neutrophil count decreased Non-pathological fracture Cognitive/memory impairment Interactions with strong inhibitors or inducers of CYP2C8 Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19
Important Potential Risks	None
Missing Information	Patients with severe renal impairment Reproduction/fertility Patients of non-white race† Patients with ECOG PS ≥ 2 Patients with severe cardiovascular disease

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Seizure	SmPC Section 4.4 (Special warnings and precautions for use) includes: *Risk of seizure* *Caution should be used in administering XTANDI to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicinal products that lower the seizure threshold. The decision to continue treatment in patients who develop seizure should be taken case by case.* SmPC Section 4.7 (Effects on ability to drive and use machines) includes: *Enzalutamide may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported (see SmPC section 4.8). Patients with a history of seizures or other predisposing factors (see SmPC section 4.4) should be advised of the risk of driving or operating machines. No studies to establish the effects of enzalutamide on the ability to drive and use machines have been conducted.*	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Seizure *(continued)*	SmPC Section 4.8 (Undesirable effects): Listed as undesirable effect. Description of selected adverse reactions *Seizure* *In controlled clinical studies, 10 patients (0.5%) experienced a seizure out of 2051 patients treated with a daily dose of 160 mg enzalutamide, whereas one patient (< 0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.* *In the AFFIRM trial, seven patients (0.9%) experienced a seizure out of 800 post-chemotherapy patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients receiving placebo. Potentially contributing factors were present in several of these patients that may have independently increased their risk of seizure. In the PREVAIL trial, one patient (0.1%) out of 871 chemotherapy-naïve patients treated with a daily dose of 160 mg enzalutamide, and one patient (0.1%) receiving placebo experienced a seizure.* *In bicalutamide-controlled trials, 3 patients (0.8%) out of 380 chemotherapy-naïve patients treated with enzalutamide and 1 patient (0.3%) out of 387receiving bicalutamide experienced a seizure.* *In a single-arm trial to assess incidence of seizure in patients with predisposing factors for seizure (where of 1.6% had a history of seizures, 8 of 366 (2.2%) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.* *The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from in vitro studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.* SmPC Section 4.9 (Overdose) includes: *Patients may be at increased risk of seizures following an overdose.*	
Posterior reversible encephalo-pathy syndrome (PRES)	SmPC Section 4.4 (Special warnings and precautions for use) includes: *Posterior reversible encephalopathy syndrome* *There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI (see SmPC section 4.8). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of XTANDI in patients who develop PRES is recommended.* SmPC Section 4.8 (Undesirable effects): Listed as undesirable effect.	None
Hypertension **Fall** **Cognitive/ memory impairment** **Neutrophil count decreased** **Non-pathological fracture**	SmPC Section 4.8 (Undesirable effects): Listed as undesirable effects.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Interactions with strong inhibitors or inducers of CYP2C8 **Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19**	SmPC Section 4.2 (Posology and method of administration) includes: <u>*Concomitant use with strong CYP2C8 inhibitors*</u> *The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (see SmPC section 4.5).*	None
Interactions with strong inhibitors or inducers of CYP2C8 **Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19** ***(continued)***	SmPC Section 4.4 (Special warnings and precautions for use) includes: <u>*Concomitant use with other medicinal products*</u> *Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products (see examples in SmPC section 4.5). A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters (see SmPC section 4.5) should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.* *Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If XTANDI is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted (see SmPC section 4.5).*	
Interactions with strong inhibitors or inducers of CYP2C8 **Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19** ***(continued)***	SmPC Section 4.5 (Interaction with other medicinal products and other forms of interaction) includes: <u>*Potential for other medicinal products to affect enzalutamide exposures*</u> *CYP2C8 inhibitors* *CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of enzalutamide increased by 326% while C_{max} of enzalutamide decreased by 18%. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 77% while C_{max} decreased by 19%. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (see SmPC section 4.2).* *CYP3A4 inhibitors* *CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while C_{max} was again unchanged. No dose adjustment is necessary when XTANDI is co-administered with inhibitors of CYP3A4.* *CYP2C8 and CYP3A4 inducers* *Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampin (600 mg once daily) to healthy male subjects, the AUC of enzalutamide plus the active metabolite decreased by 37% while C_{max} remained unchanged. No dose adjustment is necessary when XTANDI is co-administered with inducers of CYP2C8 or CYP3A4.*	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Interactions with strong inhibitors or inducers of CYP2C8 **Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19 *(continued)***	*Potential for enzalutamide to affect exposures to other medicinal products* *Enzyme induction* *Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs – glucuronide conjugating enzymes). The transport protein P-gp may also be induced, and probably other transporters as well, e.g. multidrug resistance-associated protein 2 (MRP2), breast cancer resistance protein (BCRP) and the organic anion transporting polypeptide 1B1 (OATP1B1).* *In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S-warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. In a clinical study in patients with metastatic CRPC, XTANDI (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m^2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) = 0.882 (90% CI: 0.767, 1.02)] while Cmax decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)].* *Interactions with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution. The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.*	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Interactions with strong inhibitors or inducers of CYP2C8 **Interactions with medicinal products that are substrates of CYP3A4, CYP2C9 or CYP2C19 *(continued)***	*Groups of medicinal products that can be affected include, but are not limited to:* • *Analgesics (e.g. fentanyl, tramadol)* • *Antibiotics (e.g. clarithromycin, doxycycline)* • *Anticancer agents (e.g. cabazitaxel)* • *Anticoagulants (e.g. acenocoumarol, warfarin)* • *Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)* • *Antipsychotics (e.g. haloperidol)* • *Betablockers (e.g. bisoprolol, propranolol)* • *Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)* • *Cardiac glycosides (e.g. digoxin)* • *Corticosteroids (e.g. dexamethasone, prednisolone)* • *HIV antivirals (e.g. indinavir, ritonavir)* • *Hypnotics (e.g. diazepam, midazolam, zolpidem)* • *Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)* • *Thyroid agents (e.g. levothyroxine)* *The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19, or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days, see SmPC section 5.2), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment.*	None
Patients with severe renal impairment	SmPC Section 4.2 (Posology and method of administration) include: *Renal impairment* *No dose adjustment is necessary for patients with mild or moderate renal impairment (see SmPC section 5.2). Caution is advised in patients with severe renal impairment or end-stage renal disease (see SmPC section 4.4).* SmPC Section 4.4 (Special warnings and precautions for use) includes: *Renal impairment* *Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.* SmPC Section 5.2 (Pharmacokinetic properties) includes: *Renal impairment* *No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical trials. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.*	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Reproduction/ fertility	SmPC Section 4.3 (Contraindications) includes: Contraindications include women who are or may become pregnant (see SmPC section 4.6). SmPC Section 4.6 (Fertility, pregnancy and lactation) includes: *Women of childbearing potential* *There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant (see SmPC section 5.3).* *Contraception in males and females* *It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (see SmPC section 5.3).* *Pregnancy* *Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see SmPC sections 4.3 and 5.3).* *Breast-feeding* *Enzalutamide is not for use in women. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk (see SmPC section 5.3).* *Fertility* *Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs (see SmPC section 5.3).*	None
Patients of non-white race	SmPC Section 5.1 (Pharmacodynamic properties) includes: *Clinical efficacy and safety* ***MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients)*** *Patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range 42-93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% other or unknown races.*	None
Patients of non-white race (continued)	***CRPC2 (AFFIRM) study (patients who previously received chemotherapy)*** *The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41-92) and the racial distribution was 92.7% Caucasian, 3.9% Black, 1.1% Asian, and 2.1% Other.* SmPC Section 5.2 (Pharmacokinetic properties) includes: *Race* *Most patients in the clinical trials (>84%) were Caucasian. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.*	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Patients with ECOG PS ≥ 2	SmPC Section 5.1 (Pharmacodynamic properties) includes: <u>*Clinical efficacy and safety*</u> ***MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients)*** *Sixty-eight percent (68%) of patients had an ECOG performance status score of 0 and 32% patients had ECOG performance status 1.* ***CRPC2 (AFFIRM) study (patients who previously received chemotherapy)*** *The ECOG performance score was 0-1 in 91.5% of patients and 2 in 8.5% of patients.*	None
Patients with severe cardiovascular disease	SmPC Section 5.1 (Pharmacodynamic properties) includes: <u>*Clinical efficacy and safety*</u> ***MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients)*** *Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class 1 or 2)… were allowed.* ***CRPC2 (AFFIRM) study (patients who previously received chemotherapy)*** *The AFFIRM study excluded patients with …clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).*	None

Conclusion

No changes to the safety concerns, pharmacovigilance plan or risk minimisation measures have been proposed by the MAH due to the addition of the new pharmaceutical form and strength. This is acceptable.

The CHMP and PRAC considered that the risk management plan version 12 is acceptable.

2.7. Pharmacovigilance

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.

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.

2.8. Product information

The product information has been updated to reflect the new pharmaceutical form and strengths.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) which were reviewed by QRD and accepted by the CHMP.

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

This application is for a new immediate-release, film-coated dosage form for Xtandi (40 mg and 80 mg strength) in addition to the existing approved liquid-filled, soft gelatin capsule (40 mg) to be used in the currently approved indications:

- the treatment of adult men with metastatic castration-resistant prostate cancer (CPRC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)
- the treatment of adult men with metastatic castration-resistant prostate cancer (CPRC) whose disease has progressed on or after docetaxel therapy.

The application is based on the results of a pivotal clinical study evaluating the bioequivalence between enzalutamide capsules and tablets for single-dose AUC under fasted and fed conditions (Study 9785-CL-0014), simulations of steady-state concentration-time profiles (derived from nonparametric superposition) in order to assess Cmax under conditions of clinical use, and an exposure-response analysis to evaluate the relationship between exposure and clinical efficacy using data from study CRPC2.

3.2. Favourable effects

The bioequivalence of test and reference product (capsules) was demonstrated for 80 mg strength in both fasting and fed condition in terms of AUC but not in terms of C_{max}. In accordance with the CHMP Scientific Advice, a PK simulation to steady stated, using non-parametric superposition model was submitted and showed that C_{max} differences after single-dose are not clinical relevant. This is further supported by an exposure-response analysis using a population PK model showing that steady-state C_{max} differences are not relevant for efficacy. These data can be extrapolated to the 40 mg strength as all requirements described in section 4.1.6 of the bioequivalence guideline are fulfilled.

Therefore, the same favourable effects as shown for Xtandi capsule can be concluded for Xtandi film-coated tablets (40 mg and 80 mg).

3.3. Uncertainties and limitations about favourable effects

Not applicable.

3.4. Unfavourable effects

The overall safety profile of the enzalutamide tablet was comparable to the safety profile of the capsule. No formulation-specific safety concerns neither clinically significant differences in safety were observed for the tablet compared with the capsule.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on the data provided, the efficacy and safety of the currently approved liquid-filled, soft gelatine capsule formulation for Xtandi can be extrapolated to the new proposed pharmaceutical form (i.e. 40 mg film coated tablets and 80 mg film coated tablets).

3.7.2. Balance of benefits and risks

The benefits of Xtandi 40 mg film coated tablets and 80 mg film-coated tablets outweigh the risks. The product information includes relevant safety information and the RMP is adequate to manage the risks of the product.

3.8. Conclusions

The overall benefit risk balance of Xtandi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xtandi 40 mg and 80 mg film-coated tables is favourable in the following indication:

- the treatment of adult men with metastatic castration-resistant prostate cancer (CPRC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)
- the treatment of adult men with metastatic castration-resistant prostate cancer (CPRC) whose disease has progressed on or after docetaxel therapy.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Xtandi 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 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.