RISK MANAGEMENT PLAN
For
Enzalutamide
Version 0.4

RMP Version to be Assessed as Part of this Application:

RMP Version Number	0.4
Data Lock Point for this RMP	15-May-2023
Date of Final Sign Off	21-Jun-2024
Rationale for Submitting an Updated RMP	RMP has been amended based on the comments received in Day 80 Rapp AR (Rapporteur assessment report), Day 120 LoQ (List of Questions), Day 150 JAR (Joint CHMP and PRAC assessment report) and Day 180 LoOI (List of Outstanding Issues) for procedure EMEA/H/C/006299 and to include the updated indication.
Summary of Significant Changes in this RMP	The following significant changes were made in the current RMP: • RMP version 0.1 has been amended to RMP version 0.2 based on the comments received in Day 80 Rapp AR (Rapporteur assessment report), Day 120 LoQ (List of Questions), Day 150 JAR (Joint CHMP and PRAC assessment report) and Day 180 LoOI (List of Outstanding Issues) for procedure EMEA/H/C/006299. • Specific adverse reaction targeted follow-up questionnaires for fall and fracture added. • New indication added inline with the reference medicinal product

Other RMP Versions Under Evaluation:

RMP Version Number	0.3
Submitted On	06-Jun-2024
Procedure Number	EMEA/H/C/006299

Details of the Current RMP:

Version Number	Not applicable
Approved with Procedure	Not applicable
Date of Approval (Opinion Date)	Not applicable

Approver	Dr Eiko Soehlke, MD MPH, EEA QPPV
Signature	The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.
E-mail address of contact person	PV.RMP@Viatris.com

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical Classification System
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CP	Centralized Procedure
CYP	Cytochrome P450
DDD	Daily Defined Dose
DHPC	Direct Healthcare Professional Communication
DLP	Data Lock Point
DNA	Deoxyribonucleic acid
EEA	European Economic Area
EPAR	European Public Assessment Report
EU	European Union
LHRH	Luteinising Hormone-Releasing Hormone
MAA	Marketing Authorization Application
MAH	Marketing Authorisation Holder
mHSPC	Metastatic Hormone-Sensitive Prostate Cancer
PL	Package Leaflet
PSUR	Periodic safety update reports
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

PART I: PRODUCT(S) OVERVIEW

Table 1: Part 1.1-Product Overview

Active Substance(s) (INN or Common Name)	Enzalutamide
Pharmacotherapeutic Group(s) (ATC Code)	Hormone antagonists and related agents, anti-androgens ATC Code: L02BB04
Marketing Authorisation Applicant	Viatris Limited, Ireland
Medicinal Products to Which this RMP Refers	01
Invented Name(s) in the European Economic Area (EEA)	Enzalutamide Viatris 40 mg film coated tablets Enzalutamide Viatris 80 mg film-coated tablets
Marketing Authorisation Procedure	Centralized
Brief Description of the Product	Chemical class Pharmacotherapeutic group: hormone antagonists and related agents, anti-androgens, ATC code: L02BB04. Summary of mode of action Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently; inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. Important information about its composition: Not applicable
Hyperlink to the Product Information:	PI available in section 1.3.1 of the dossier

Indication(s) in the EEA	Enzalutamide Viatris is indicated for: • As monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy. • In combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) • For the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) • For the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated • For the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.
Dosage in the EEA	The recommended dose is 160 mg enzalutamide (four 40 mg film-coated tablets or two 80 mg film-coated tablets) as a single oral daily dose.
Pharmaceutical Form(s) and Strengths	Enzalutamide Viatris 40 mg film-coated tablets: Each film-coated tablet contains 40 mg of enzalutamide. Enzalutamide Viatris 80 mg film-coated tablets: Each film-coated tablet contains 80 mg of enzalutamide.
Is/will the Product Be Subject to Additional Monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

Part II: Module SI - Epidemiology of the Indication(s) and Target Population(s)

Not applicable.

Part II: Module SII - Non-clinical Part of the Safety Specification

Not applicable.

Part II: Module SIII - Clinical Trial Exposure

Not applicable.

Part II: Module SIV - Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Not applicable.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Not applicable.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Not applicable.

Part II: Module SV - Post-authorisation Experience

Not applicable.

Part II: Module SVI - Additional EU Requirements for the Safety Specification

Not applicable.

Part II: Module SVII - Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

This is a MAA for a generic medicine in which the safety concerns available in the RMP for the reference medicinal product have been adopted by the MAH (XTANDI's: EPAR - Risk Management Plan Summary, version 18.0 dated: June 2023, last updated on the EMA website on 25-Apr-2024.

Table 2: SVII- Summary of safety concerns

Summary of Safety Concerns	
Important Identified Risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important Potential Risks	• None
Missing Information	• None

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable as all risks from reference product RMP have been considered in this RMP.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable as this is the initial RMP for enzalutamide.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable as this RMP for Enzalutamide follows the same safety concerns as the safety concerns of the reference substance RMP.

SVII.3.2. Presentation of the Missing Information

Not applicable as this RMP for Enzalutamide follows the same safety concerns as the safety concerns of the reference substance RMP.

Part II: Module SVIII – Summary of the Safety Concerns

Table 3: SVIII- Summary of safety concerns

Important Identified Risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important Potential Risks	• None
Missing Information	• None

PART III: PHARMACOVILIGANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the risks of Fall and Non-pathological fracture.

- Targeted Follow-up Questionnaire: Fall
- Targeted Follow-up Questionnaire: Fracture

The forms are provided in Annex 4 - Specific Adverse Drug Reaction Follow-up Forms of the RMP.

III.2 Additional Pharmacovigilance Activities

As current routine pharmacovigilance activities are sufficient, no additional pharmacovigilance activities are recommended.

III.3 Summary Table of Additional Pharmacovigilance Activities

None.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The safety information in the proposed product information is aligned to the reference medicinal product (XTANDI of Astellas Pharma Europe B.V., Netherlands).

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Not applicable.

V.2 Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of Risk Minimisation Measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Enzalutamide Viatris 40 mg and 80 mg film coated tablets (Enzalutamide)

This is a summary of the risk management plan (RMP) for Enzalutamide Viatris 40 mg and 80 mg film coated tablets. The RMP details important risks of enzalutamide how these risks can be minimised, and how more information will be obtained about enzalutamide's risks and uncertainties (missing information).

Enzalutamide Viatris 40 mg and 80 mg film coated tablets' summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

This summary of the RMP for Enzalutamide Viatris 40 mg and 80 mg film coated tablets should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Enzalutamide Viatris 40 mg and 80 mg film coated tablets' RMP.

I. The Medicine and What it is Used For

Enzalutamide Viatris 40 mg and 80 mg film coated tablets is indicated:

- as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy.
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC)
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC)
- for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

It contains enzalutamide as active substance and is given by oral route of administration.

Further information about the evaluation of Enzalutamide Viatris 40 mg and 80 mg film coated tablets' benefits can be found in Enzalutamide Viatris 40 mg and 80 mg film coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Enzalutamide Viatris 40 mg and 80 mg film coated tablets, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.
In addition to these measures, information about adverse events is collected continuously and regularly analysed, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of Enzalutamide Viatris 40 mg and 80 mg film coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Enzalutamide Viatris 40 mg and 80 mg film coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine/use in special patient populations etc.).

Table 4: Part VI.1- Summary of safety concerns

List of Important Risks and Missing Information	
Important Identified Risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important Potential Risks	• None
Missing Information	• None

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Enzalutamide Viatris 40 mg and 80 mg film coated tablets.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Enzalutamide Viatris 40 mg and 80 mg film coated tablets.

Annex 4 - Specific Adverse Drug Reaction Follow-up Forms

Specific adverse reaction targeted follow-up questionnaires for the risks of Fall and Non-pathological fracture.

- Targeted Follow-up Questionnaire: Fall
- Targeted Follow-up Questionnaire: Fracture

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

1. Patients Details:

Patient's Initials	
Age/Date of birth	years/months (DD-MMM-YYYY)
Gender	☐ Male ☐ Female
Weight	lbs/kg
Height	ins/cms

Thank you for reporting the initial report related to Fall during the use of Viatris Enzalutamide.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case

SIGNS AND SYMPTOMS OF THE EVENT	
☐ Bleeding/Haematoma	☐ Shock
☐ Fracture	☐ Sprain/Strain
☐ Head injury	☐ Swelling
☐ Other local/systemic injury	☐ Other
☐ Pain	
UNDERLYNG CONDITIONS/RISK FACTORS	
☐ Alcohol use (Units per week) preceding fall	☐ Medical condition predisposing for fall
☐ Cognitive impairment	☐ Musculokeletal pain
☐ Difficulty walking	☐ Narcotics use preceding fall
☐ Dizziness/Vertigo	☐ Presyncope/Sncope
☐ Fatigue	☐ Seizure
☐ History of other fall in past year	☐ Unsteady gait
☐ Known joints problems (Joint pain, non-optimal functioning of certain joint, arthritis, knee hip prosthesis):	☐ Possible drug interaction ☐ Prosthesis
☐ Limb/Foot abnormality	☐ Smoking (Packs per week)
☐ Loss of consciousness	☐ Other

2. Drug information at the time of event:

Product	**Batch No. / Expiry Date**	**Route** (oral, etc.)	**Daily Dose** (e.g. 20 mg tablet 3 times a day)		**Treatment Dates**		**Indication** (what drug is being taken for)
			Dose/ Unit	**Frequency**	**Start Date**	**Stop Date**	

TARGETED FOLLOW UP FORM
Viatris Case No.:

Product(s) suspected to have caused the Adverse Event (Check box to indicate confirmed Viatris products)							
Concomitant Product(s) *(additional products taken within the 30 days period prior to the adverse event(s) occurring)*							
AE Treatment drug(s)							

TARGETED FOLLOW UP FORM
Viatris Case No.:

RELEVANT INVESTIGATIONS *Provide results at time of of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy*		
Investigation	Date dd-Mmm-yyyy	Result/Unit

Additional/supporting information:

(Please give additional details on the adverse events, sequence of events, including hospitalisation details, treatment, and/or laboratory tests. This includes start and stop dates. This box can also be used to add extra information if you have run out of space in the other fields)

3. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name/Initials:

Occupation:

☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other Healthcare Professional

☐ Patient/Consumer

Signature and Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

VIATRIS

TARGETED FOLLOW UP FORM
Viatris Case No.:

1. Patients Details:

Patient's Initials	
Age/Date of birth	years/months (DD-MMM-YYYY)
Gender	☐ Male ☐ Female
Weight	lbs/kg
Height	ins/cms

Thank you for reporting the initial report related to Fracture during the use of Viatris Enzalutamide.
With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case

SIGNS AND SYMPTOMS OF THE EVENT	
☐ Bleeding/Haematoma	☐ Shock
☐ Pain	☐ Other
SPECIFY THE UNDERLYING CAUSE OF THE FRACTURE	Fall (specify the underlying cause of the fall)
☐ Incidental finding	☐ Accident/ Trauma
☐ Fracture at the site of bone metastases	☐ Other underlying cause
UNDERLYNG CONDITIONS/RISK FACTORS	
☐ Alcohol use (Units per week)	☐ Over weight
☐ ADT therapy, ☐ Surgical castration, ☐ LHRH agonist/Antagonist	☐ Previous fracture(s)
☐ Arteriosclerosis obliterans (or peripheral arterial disease)	☐ Prosthesis
☐ Bone metastases	☐ Under weight
☐ Diabetes	☐ Possible drug interaction
☐ Osteopenia	☐ Smoking (Packs per week)
☐ Osteoporosis	☐ Other

2. Drug information at the time of event:

Product	**Batch No. / Expiry Date**	**Route** (oral, etc.)	**Daily Dose** (e.g. 20 mg tablet 3 times a day)		**Treatment Dates**		**Indication** (what drug is being taken for)
			Dose/ Unit	**Frequency**	**Start Date**	**Stop Date**	

TARGETED FOLLOW UP FORM
Viatris Case No.:

Product(s) suspected to have caused the Adverse Event (Check box to indicate confirmed Viatris products)							
☐ Bisphosphonates							
☐LHRH Agonist/antagonist							
☐Prednisolone therapy							
Concomitant Product(s) *(additional products taken within the 30 days period prior to the adverse event(s) occurring)*							
AE Treatment drug(s)							

TARGETED FOLLOW UP FORM
Viatris Case No.:

RELEVANT INVESTIGATIONS *Provide results at time of of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy*		
Investigation	Date dd-Mmm-yyyy	Result/Unit
☐ Bone density		
☐ Imaging		
☐ Other		

Additional/supporting information:

(Please give additional details on the adverse events, sequence of events, including hospitalisation details, treatment, and/or laboratory tests. This includes start and stop dates. This box can also be used to add extra information if you have run out of space in the other fields)

3. Reporter's Details:

I certify that this Questionnaire is accurate and truthful to the best of my knowledge and does not contain any false, fictitious, or fraudulent statements.

Name/Initials:

Occupation:
☐ Physician ☐ Pharmacist ☐ Nurse ☐ Other Healthcare Professional
☐ Patient/Consumer

Signature and Date:

Please be aware that information provided to Viatris relating to you, may be used to comply with applicable laws and regulations. Viatris processes your personal or sensitive data in accordance with applicable data protection laws and the Viatris Privacy Statement, available to you either on https://www.viatris.com/en/viatris-privacy-notice or upon request.

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (If Applicable)

Not applicable.