

EU Risk Management Plan

For

Enzalutamide Accordpharma 40 mg film-coated tablets

Enzalutamide Accordpharma 80 mg film-coated tablets

Enzalutamide Accordpharma 160 mg film-coated tablets

(Enzalutamide)

RMP version to be assessed as part of this application:

RMP Version number	1.2
Data lock point for this RMP	05-Feb-2025
Date of final sign off	18-Mar-2025

Rationale for submitting an RMP: This RMP has been updated in line with CHMP Day 120 list of questions of Enzalutamide Accordpharma, (EMA/H/C/6612), dated 19-Feb-2025.

Summary of significant changes in this RMP: Significant changes have been made in following sections of RMP: Part III and Part VII (Annex 4).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: Not applicable

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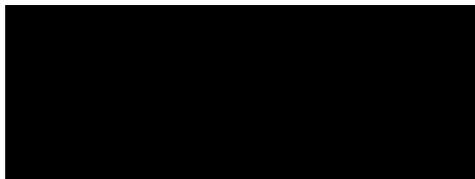


TABLE OF CONTENT

TABLE OF CONTENT	2
LIST OF TABLES	4
Part I: Products Overview	5
Part II: Safety specification	8
Part II: Module SI - Epidemiology of the indication(s) and target population(s).....	8
Part II: Module SII - Non-clinical part of the safety specification	8
Part II: Module SIII - Clinical trial exposure	8
Part II: Module SIV - Populations not studied in clinical trials	8
SIV.1 Exclusion criteria in pivotal clinical studies within the development programme.....	8
SIV.2 Limitations to detect adverse reactions in clinical trial development programmes.....	8
SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes	8
Part II: Module SV - Post-authorisation experience	8
SV.1 Post-authorisation exposure	8
Part II: Module SVI - Additional EU requirements for the safety specification	8
SVI.1 Potential for misuse for illegal purposes.....	8
Part II: Module SVII - Identified and potential risks	9
SVII.1 Identification of safety concerns in the initial RMP submission	9
SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP	9
SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP	9
SVII.2 New safety concerns and reclassification with a submission of an updated RMP.....	9
SVII.3 Details of important identified risks, important potential risks, and missing information	9
SVII.3.1. Presentation of important identified risks and important potential risks	9
SVII.3.2. Presentation of the missing information	9
Part II: Module SVIII - Summary of the safety concerns	10
Part III: Pharmacovigilance Plan (including post-authorisation safety studies)	11
III.1 Routine pharmacovigilance activities.....	11
III.2 Additional pharmacovigilance activities	11
III.3 Summary Table of additional Pharmacovigilance activities.....	11
Part IV: Plans for post-authorisation efficacy studies	12
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	13
V.1. Routine Risk Minimisation Measures	13
V.2. Additional Risk Minimisation Measures	13
V.3 Summary of risk minimisation measures.....	13

Part VI: Summary of the risk management plan	14
I. The medicine and what it is used for	14
II. Risks associated with the medicine and activities to minimise or further characterise the risks	15
II.A List of important risks and missing information	16
II.B Summary of important risks	16
II.C Post-authorisation development plan	16
II.C.1 Studies which are conditions of the marketing authorisation	16
II.C.2 Other studies in post-authorisation development plan	16
Part VII: Annexes	17
Annex 1 – EudraVigilance Interface.....	18
Annex 2 – Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	18
Annex 3 - Protocols for proposed, on-going and completed studies in the pharmacovigilance plan	18
Annex 4 - Specific adverse drug reaction follow-up forms	19
Annex 5 - Protocols for proposed and on-going studies in RMP part IV	24
Annex 6 - Details of proposed additional risk minimisation activities (if applicable).....	24
Annex 7 - Other supporting data (including referenced material)	24
Annex 8 – Summary of changes to the risk management plan over time	25

LIST OF TABLES

Table 1: Product Overview 5

Table 2: Summary of safety concerns 10



Part I: Products Overview

Table 1: Product Overview

Active substance (INN or common name)	Enzalutamide
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Hormone antagonists and related agents, anti-androgens ATC code: L02BB04
Marketing Authorisation Holder	Accord Healthcare S.L.U, Spain
Medicinal products to which this RMP refers	03
Invented name(s) in the European Economic Area (EEA)	Enzalutamide Accordpharma 40 mg film-coated tablets Enzalutamide Accordpharma 80 mg film-coated tablets Enzalutamide Accordpharma 160 mg film-coated tablets
Marketing authorisation procedure	EMA/H/C/6612
Brief description of the product	<u>Chemical class:</u> Enzalutamide is a potent androgen receptor signaling inhibitor that blocks several steps in the androgen receptor-signaling pathway.
	<u>Summary of mode of action:</u> 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

	<p>death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.</p>
	<p><u>Important information about its composition:</u></p> <p><i>Enzalutamide Accordpharma 40 mg film-coated tablets</i> Each film-coated tablet contains 40 mg of enzalutamide.</p> <p><i>Enzalutamide Accordpharma 80 mg film-coated tablets</i> Each film-coated tablet contains 80 mg of enzalutamide.</p> <p><i>Enzalutamide Accordpharma 160 mg film-coated tablets</i> Each film-coated tablet contains 160 mg of enzalutamide.</p>
<p>Hyperlink to the Product Information</p>	<p>Refer Module 1.3.1 for SmPC and PIL</p>
<p>Indication(s) in the EEA</p>	<p>Current:</p> <p>Enzalutamide Accordpharma is indicated:</p> <ul style="list-style-type: none"> • 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.

	<ul style="list-style-type: none"> for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.
Dosage in the EEA	<p>Current:</p> <p>Posology</p> <p>The recommended dose is 160 mg enzalutamide (four 40 mg film-coated tablets or two 80 mg film-coated tablets or one 160 mg film-coated tablets) as a single oral daily dose.</p> <p>Method of administration</p> <p>Enzalutamide Accordpharma is for oral use. The film-coated tablets should not be cut, crushed or chewed but should be swallowed whole with water, and can be taken with or without food.</p>
Pharmaceutical forms and strengths	<p>Current:</p> <p>Film-coated tablet</p> <p>40 mg, 80 mg and 160 mg</p>
Is the product 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

SV.1 Post-authorisation exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

SVI.1 Potential for misuse for illegal purposes

Not applicable



Part II: Module SVII - Identified and potential risks

The safety concerns of this RMP have been considered as per European Public Assessment Report (EPAR) – RMP available for the reference product XTANDI® (enzalutamide), version 18.0; dated Jun-2023, published by EMA on 25-Apr-2024. There is no change proposed by MAH in these safety concerns mentioned in Module SVIII which is in-line with RMP summary of reference product (XTANDI®).

Hence this section remains “Not applicable”.

SVII.1 Identification of safety concerns in the initial RMP submission**SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP**

Not applicable

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

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

SVII.3.2. Presentation of the missing information

Not Applicable

Part II: Module SVIII - Summary of the safety concerns**Table 2: Summary of safety concerns**

Important identified risks	<ul style="list-style-type: none">• Seizure• Fall• Non-pathological fracture• Ischemic heart disease
Important potential risks	<ul style="list-style-type: none">• None
Missing information	<ul style="list-style-type: none">• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities including collection and reporting of adverse reactions and signal detection as stated in pharmacovigilance system master file are sufficient for the safety concerns mentioned in “Module SVIII - Summary of the safety concerns”.

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Specific adverse reaction follow-up questionnaires

Description	Purpose	Safety concern(s) addressed
Fall TDQ for spontaneous reports	<ul style="list-style-type: none"> Monitoring, standardised collection, and documentation of AE reports of fall to determine whether additional measures for prevention are needed. To gain further knowledge into the nature of reported AEs of fall in order to determine any preceding events and risk factors. 	<ul style="list-style-type: none"> Fall
Fracture TDQ for spontaneous reports	<ul style="list-style-type: none"> Monitoring, standardised collection, and documentation of AE reports of fracture to determine whether additional measures for prevention are needed. To gain further knowledge into the nature of reported AEs of fracture in order to determine any preceding events and risk factors. 	<ul style="list-style-type: none"> Non-pathological fracture

AE: Adverse Event; TDQ: Targeted Data Questionnaire.

Adverse event follow-up questionnaires are provided in [Annex 4](#)

III.2 Additional pharmacovigilance activities

None proposed.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable



Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

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

V.1. Routine Risk Minimisation Measures

Not applicable

V.2. Additional Risk Minimisation Measures

None proposed

V.3 Summary of risk minimisation measures

Not applicable



Part VI: Summary of the risk management plan

Summary of risk management plan for Enzalutamide Accordpharma 40 mg / 80 mg / 160 mg film-coated tablets (Enzalutamide)

This is a summary of the risk management plan (RMP) for Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets. The RMP details important risks of Enzalutamide Accordpharma 40 mg / 80 mg / 160 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Enzalutamide Accordpharma 40 mg / 80mg / 160mg film-coated tablets' risks and uncertainties (missing information).

Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets' summary of product characteristics (SmPC) and package leaflets give essential information to healthcare professionals and patients on how Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets should be used.

This summary of the RMP for Enzalutamide Accordpharma 40 mg / 80mg / 160 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 Accordpharma 40 mg / 80mg / 160 mg film-coated tablets' RMP.

I. The medicine and what it is used for

Enzalutamide Accordpharma 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 the active substance and it is given by oral route.

Further information about the evaluation of Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets' benefits can be found in Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets' EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <[link to the EPAR summary landing page](#)>.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets' 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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment, 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 Accordpharma 40 mg / 80mg / 160 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. 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 Accordpharma 40 mg / 80mg / 160 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).

Important identified risks	<ul style="list-style-type: none"> • Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important potential risks	<ul style="list-style-type: none"> • None
Missing information	<ul style="list-style-type: none"> • 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 Accordpharma 40 mg / 80mg / 160 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Enzalutamide Accordpharma 40 mg / 80mg / 160 mg film-coated tablets.

Annex 4 - Specific adverse drug reaction follow-up forms

The MAH has proposed targeted follow up questionnaire for following safety concern concerning the use of enzalutamide and it is appended below.

- Fall
- Fracture

Fall Follow-up Questionnaire

Email to:		Case Number	
Fax to:		Patient Details:	Age/ Age group <input type="checkbox"/> Male <input type="checkbox"/> Female

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the case you reported for a fall experienced during the use of Enzalutamide Accord. Provide as much new information as possible, focusing on the information that has not previously been provided and that is relevant for the fall case. Consider the applicable data privacy restrictions in your country while completing this form. For cases not originating from clinical studies, attach any relevant anonymised supporting documentation, if available.

Thank you in advance for your cooperation.

Case Number:			
Reported Event:		Patient Details	Age /Age group <input type="checkbox"/> Male <input type="checkbox"/> Female

Thank you for reporting the initial report related to Fall during the use of Enzalutamide Accord. 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

<input type="checkbox"/> Bleeding/haematoma	<input type="checkbox"/> Shock
<input type="checkbox"/> Fracture:	<input type="checkbox"/> Sprain/Strain
<input type="checkbox"/> Head injury	<input type="checkbox"/> Swelling
<input type="checkbox"/> Other local/systemic injury:	<input type="checkbox"/> Other:
<input type="checkbox"/> Pain	

UNDERLYING CONDITIONS / RISK FACTORS

<input type="checkbox"/> Alcohol use (units per week) preceding fall:	<input type="checkbox"/> Medical condition predisposing for fall:
<input type="checkbox"/> Cognitive impairment:	<input type="checkbox"/> Musculoskeletal Pain
<input type="checkbox"/> Difficulty walking	<input type="checkbox"/> Narcotics use preceding fall
<input type="checkbox"/> Dizziness/vertigo	<input type="checkbox"/> Presyncope/Syncope
<input type="checkbox"/> Fatigue	<input type="checkbox"/> Seizure
<input type="checkbox"/> History of other falls in the past year	<input type="checkbox"/> Unsteady gait
<input type="checkbox"/> Known joints problems (joint pain, non-optimal functioning of certain joint, arthritis, knee/hip prosthesis):	<input type="checkbox"/> Possible drug interaction
	<input type="checkbox"/> Prostheses
<input type="checkbox"/> Limb/foot abnormality:	<input type="checkbox"/> Smoking (packs per week):
<input type="checkbox"/> Loss of consciousness	<input type="checkbox"/> Other:

MEDICATION

Drug Name	SUSPECT PRODUCTS (S) CONCOMITANT (C) AE TREATMENT (T)	INDICATION	DOSE/ FREQUENCY/ROUTE OF ADMINISTRATION	START DATE dd-mm-yyyy	STOP DATE dd-mm-yyyy or ongoing

<input type="checkbox"/>					
<input type="checkbox"/>					
<input type="checkbox"/>					
RELEVANT INVESTIGATIONS <i>Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.</i>					
INVESTIGATION		DATE dd-mm-yyyy		RESULT/UNIT	
<input type="checkbox"/>					
<input type="checkbox"/>					
<input type="checkbox"/>					
<input type="checkbox"/>					
<input type="checkbox"/>	Other:				
ADDITIONAL DETAILS/OTHER RELEVANT INFORMATION					
Additional details, including duration of signs and symptoms and details of fall (i.e. stumbled, slipped, etc.):					
REPORTER INFORMATION					
REPORTERS NAME/CREDENTIALS		Date (dd-mm-yyyy)	SIGNATURE (to confirm the accuracy of data)		

Fracture Follow-up Questionnaire

Email to:		Case Number	
Fax to:		Patient Details:	Age/ Age group <input type="checkbox"/> Male <input type="checkbox"/> Female

Instructions

With this questionnaire, we would like to request specific follow-up information regarding the case you reported for a fracture experienced during the use of Enzalutamide Accord. Provide as much new information as possible, focusing on the information that has not previously been provided and that is relevant for the fall case. Consider the applicable data privacy restrictions in your country while completing this form. For cases not originating from clinical studies, attach any relevant anonymised supporting documentation, if available.

Thank you in advance for your cooperation.

Case Number:					
Reported Event:		Patient Details	Age /Age group <input type="checkbox"/> Male <input type="checkbox"/> Female		
<i>Thank you for reporting the initial report related to fracture during the use of Enzalutamide Accord. With this questionnaire, we would like to request specific follow-up information, in order to perform a better scientific evaluation of the case.</i>					
SIGNS AND SYMPTOMS OF THE EVENT					
<input type="checkbox"/> Bleeding/haematoma			<input type="checkbox"/> Shock		
<input type="checkbox"/> Pain:			<input type="checkbox"/> Other		
SPECIFY THE UNDERLYING CAUSE OF THE FRACTURE:			<input type="checkbox"/> Fall (specify underlying cause of the fall):		
<input type="checkbox"/> Incidental finding (during imaging, etc)			<input type="checkbox"/> Accident/trauma		
<input type="checkbox"/> Fracture at site of bone metastases			<input type="checkbox"/> Other underlying cause:		
UNDERLYING CONDITIONS/RISK FACTORS					
<input type="checkbox"/> Alcohol use (units per week)			<input type="checkbox"/> Overweight		
<input type="checkbox"/> ADT therapy <input type="checkbox"/> Surgical castration <input type="checkbox"/> LHRH agonist/ antagonist			<input type="checkbox"/> Previous fracture (s)		
<input type="checkbox"/> Arteriosclerosis obliterans (or peripheral artery disease)			<input type="checkbox"/> Prosthesis		
<input type="checkbox"/> Bone metastases			<input type="checkbox"/> Underweight		
<input type="checkbox"/> Diabetes			<input type="checkbox"/> Possible drug interaction		
<input type="checkbox"/> Osteopenia			<input type="checkbox"/> Smoking (packs per week):		
<input type="checkbox"/> Osteoporosis			<input type="checkbox"/> Other		
MEDICATION					
Drug name	Suspect products (S) Concomitant (C)	indication	dose/ frequency/route of administration	start date	stop date dd-mm-yyyy or

	AE Treatment (T)			dd-mm-yyyy	ongoing
<input type="checkbox"/> Bisphosphonates					
<input type="checkbox"/> LHRH agonist/antagonist					
<input type="checkbox"/> Prednisolone therapy					
<input type="checkbox"/>					
RELEVANT INVESTIGATIONS <i>Provide results at time of the event. Provide other results (baseline, peak of event and resolution) in Additional Details field or attach as copy.</i>					
INVESTIGATION		DATE dd-mm-yyyy		RESULT/UNIT	
<input type="checkbox"/> Bone Density					
<input type="checkbox"/> Imaging					
<input type="checkbox"/> Other:					
ADDITIONAL DETAILS/ OTHER RELEVANT INFORMATION					
Provide additional details about the fracture, including the type and location of the fracture (and any previous fractures).					
REPORTER INFORMATION					
REPORTERS NAME/CREDENTIALS		Date (dd-mm-yyyy)		SIGNATURE (to confirm the accuracy of data)	