EU Risk Management Plan

For

Camcevi 21 mg prolonged-release suspension for injection

Camcevi 42 mg prolonged-release suspension for injection

(Leuprorelin Mesilate)

RMP version to be assessed as part of this application:

RMP Version number	2.0
Data lock point for this RMP	05-Feb-2025
Date of final sign off	28-Feb-2025

Rationale for submitting an updated RMP: To update risk management plan (RMP) has been updated to add Camcevi 21 mg prolonged-release suspension for injection as an additional product and to adapt the new template of EU RMP in GVP Module V (Rev. 2).

Summary of significant changes in this RMP: Significant changes have been done in following sections of RMP: Part I, Part II (SVII), Part VI and Part VII (Annex 7 and Annex 8).

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

RMP Version number	Approved with procedure	Date of approval (opinion date)
0.3 (1.0)	Centralised Procedure (EMEA/H/C/005034)	24-Mar-2022

QPPV name: Arletta Werynska

QPPV signature: 

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Part I: Product(s) Overview

Table 1: Product Overview

Active substance(s) (INN or common name)	Leuprorelin mesilate
Pharmacotherapeutic group(s) (ATC Code)	**Pharmacotherapeutic group(s):** Endocrine therapy, Gonadotropin releasing hormone analogues **ATC code:** L02AE02
Marketing Authorisation Holder	Accord Healthcare S.L.U., Spain
Medicinal products to which this RMP refers	02
Invented name(s) in the United Kingdom (EU)	Camcevi 21 mg prolonged-release suspension for injection Camcevi 42 mg prolonged-release suspension for injection
Marketing authorisation procedure	EMEA/H/C/005034
Brief description of the product	Chemical class: Leuprorelin is a nonapeptide. Chemical name: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-Dleucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide mesylate (salt)
	Summary of mode of action: Leuprorelin is a synthetic nonapeptide agonist of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular steroidogenesis in males. This effect is reversible upon discontinuation of medicinal product therapy. However, the agonist possesses greater potency than the natural hormone and the time to recovery of testosterone levels may vary

	between patients. Administration of leuprorelin results in an initial increase in circulating levels of luteinising hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids, testosterone and dihydrotestosterone in males. Continuous administration of leuprorelin results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold (⩽ 50 ng/dL).
	Important information about its composition *Current:* *Camcevi Accord 42 mg prolonged-release suspension for injection* Each pre-filled syringe with prolonged-release suspension for injection contains leuprorelin mesilate, equivalent to 42 mg leuprorelin. *Proposed:* *Camcevi Accord 21 mg prolonged-release suspension for injection* Each pre-filled syringe with prolonged-release suspension for injection contains leuprorelin mesilate equivalent to 21 mg leuprorelin.
Hyperlink to the Product Information	Please refer Module 1.3.1 for SmPC and PIL.
Indication(s) in the EU	Camcevi is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

Dosage in the EU	*Current:* **<u>Posology</u>:** *Camcevi Accord 42 mg prolonged-release suspension for injection* Camcevi is administered as a single subcutaneous injection every six months. The injected solution forms a solid medicinal product delivery depot and provides continuous release of leuprorelin over a six-month period. **<u>Method of administration</u>:** CAMCEVI should be administered subcutaneously.
	Proposed: **<u>Posology</u>:** *Camcevi Accord 21 mg prolonged-release suspension for injection* CAMCEVI 21 mg is administered as a single subcutaneous injection every three months. The injected suspension forms a solid medicinal product delivery depot and provides continuous release of leuprorelin over a three-month period. **<u>Method of administration</u>:**

[redacted]

	CAMCEVI should be administered subcutaneously.
Pharmaceutical form(s) and strengths	*Current:* **Pharmaceutical form(s):** Prolonged-release suspension for injection. **Strengths:** 42 mg
	Proposed: **Pharmaceutical form(s):** Prolonged-release suspension for injection **Strengths:** 21 mg
Is the product subject to additional monitoring in the EU?	No

Part II: Safety specification

Module SI - Epidemiology of the indication(s) and target population(s)

Not applicable

Module SII - Non-clinical part of the safety specification

Not applicable

Module SIII - Clinical trial exposure

Not applicable

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

Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Not applicable

Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable - there is no potential for misuse for illegal purposes.

Module SVII - Identified and potential risks

The safety concerns for this Risk Management Plan (RMP) have been considered as per Public Assessment Report (PAR) available for the reference product Eligard® (V 7.8, dated 22-Sep-2022). However, important identified risk "Lack of efficacy due to medication error" was specifically related to depot formulations of reference product (Eligard®), and the MAH proposes this RMP for different formulation. Hence, this risk was not considered for this RMP. Apart from this, there is no change proposed by MAH in safety concerns mentioned in Module SVIII, which is in-line with RMP summary of the reference product.

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

The RMP for the reference product Eligard® (V 7.8, 22-Sep-2022) includes "Lack of efficacy due to medication error" as an important identified risk (see Public Summary).

Lack of efficacy due to medication error

Following an Article 31 referral under Directive 2001/83/EC, the European Medicines Agency (EMA) started a review of handling errors with depot formulations of leuprorelin medicines after reports indicated that such errors with the products during preparation and administration could cause some patients to receive insufficient amounts of their medicine, thus reducing the benefits of treatment (EMA/316598/2019 dated 14 June 2019). The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC) who made recommendations which were adopted by the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) on 24 June 2020. PRAC recommended that only healthcare professionals familiar with the preparation steps for leuprorelin depot medicines should prepare and administer the medicines to patients. In addition, patients should not prepare or inject these medicines themselves. For the medicine Eligard®, the product information was to be updated with warnings to strictly follow the instructions for preparation and administration and to monitor patients if a handling error occurs. In addition, the company marketing Eligard® was instructed to replace the current device used to administer the medicine with one that is easier to handle. The regulatory application for this modification was to be submitted by October 2021.

As outlined above, the referral included the proposed reference product, Eligard® 45mg powder and solvent for solution for injection (leuprorelin acetate), for this hybrid application. Eligard® is supplied in two separate syringes and mixed immediately prior to administration. Unlike Eligard®, Camcevi 42 mg will be supplied as a single, sterile, pre-filled syringe ready-to use; no premixing is required prior to subcutaneous injection. For this reason, the handling errors observed during preparation and administration with other leuprorelin medicines are not expected to occur with Camcevi 42 mg. Thus, applying a risk proportionality principle and the differences in formulation/presentation of Camcevi 42 mg with the reference product; lack of efficacy due to device failure or drug administration error is not considered to be a safety concern for Camcevi 42 mg.

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

[redacted]

Module SVIII - Summary of the safety concerns

Table 2: Summary of safety concerns

Important identified risks	• None
Important potential risks	• None
Missing information	• None

[redacted]

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.

III.2 Additional pharmacovigilance activities

None proposed

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable

[redacted]

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.

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 Camcevi 21 mg prolonged-release suspension for injection and Camcevi 42 mg prolonged-release suspension for injection and (Leuprorelin Mesilate)

This is a summary of the risk management plan (RMP) for Camcevi 21 mg prolonged-release suspension for injection and Camcevi 42 mg prolonged-release suspension for injection. Throughout this summary, the product name will be referred to as Camcevi. The RMP details important risks of Camcevi, how these risks can be minimised, and how more information will be obtained about Camcevi's risks and uncertainties (missing information).

Camcevi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Camcevi should be used.

This summary of the RMP for Camcevi 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 Camcevi's RMP.

I. The medicine and what it is used for

Camcevi is indicated for the treatment of hormone dependent advanced prostate cancer and for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

It contains Camcevi as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Camcevi's benefits can be found in Camcevi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/camcevi.

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

Important risks of Camcevi, together with measures to minimise such risks and the proposed studies for learning more about Camcevi's risks, are outlined below.

[redacted]

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 Camcevi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Camcevi. 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	• None
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

[redacted]

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 Camcevi.

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

There are no studies required for Camcevi.

[redacted]