DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

MRAbit 1.5 mg/g powder for vaginal solution

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0286/001/DC
Name, strength and pharmaceutical form	MRAbit 1.5 mg/g powder for vaginal solution
Applicant	KUBUS LAB S.A. C/Varsovia, 20. Las Rozas de Madrid. 28232. Spain
Active substance(s)	Alarelin acetate
ATC vet code	QH01CA
Target species	Female rabbits for reproduction
Indication for use	Ovulation induction of female rabbits for reproduction.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 29/07/2020
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	IT, PT

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.
It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 1.5 mg of alarelin as active substance and disodium edetate, sodium hydrogen carbonate, sodium citrate, citric acid and glucose as excipients.

The container/closure system are: Laminate sachets (PET (12)+ PET met (12) + PEBD (60)) of 4, 12 and 40 g.
The choice of the formulation has been justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is alarelin acetate, an new active substance that is not described in any Pharmacopoeia and the information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data based on the MRL Assessment Report which show that alarelin acts as a LHRH (Luteinizing-hormone releasing hormone) agonist. The primary pharmacodynamic effect of GnRH and GnRH analogues is to stimulate release of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH), with a resulting increase in circulating sex hormones. Alarelin, when administered intravaginally, stimulate an increase in plasma LH concentrations around 1 and 1.5 hours after administration. This increase in LH is sufficient to induce ovulation in does.

The applicant has also provided data which show that Alarelin is rapidly absorbed after vaginal administration in female rabbits, presenting a peak concentration generally 45 minutes post-administration. A clear increase in LH levels was observed around 1.5 hours after vaginal administration. Alarelin is rapidly metabolised and the bioavailability is very low between 3% and 4%. It is rapidly excreted (half-life of approximately 0.5 hours).

Toxicological Studies

- Single Dose Toxicity

The applicant has conducted a single oral dose toxicity study in female Sprague Dawley rats which show that alarelin does not induce mortality or signs of toxicity in rats following oral administration of a single dose of 300 mg/kg.

- Repeated Dose Toxicity

The absence of standard repeat dose toxicity studies is justified based on the chemical nature of the substance (a peptide analogue) leading to rapid elimination and enzymatic inactivation/ degradation in the gastrointestinal tract result in an oral bioavailability of less than 1% in humans. The likelihood that a human may be exposed to biologically relevant levels of alarelin after the intake of any rabbit tissues or animal organs is therefore considered negligible. The pharmacokinetics of the compound including a low bioavailability by the intended clinical route of administration further support the argument that additional repeat dose studies are unnecessary.

- Reproductive Toxicity, including Teratogenicity:

No studies on the reproductive toxicity including developmental toxicity of alarelin have been provided. However, reproductive toxicity in the target species has been evaluated in the studies regarding tolerance. According to these studies, no adverse effects regarding fertility and offspring size were observed after the administration of the product at a doses of 0.03 mg/0.5 ml and an overdose of 0.01 mg/0.5 ml dose.

- Mutagenicity

No studies on the genotoxicity of alarelin have been provided. In general, peptidergic substances, such as GnRH analogues, have not been associated with genotoxicity and there is no structural alert for this class of compounds.

Observations in Humans

There are no observations or studies in humans conducted with alarelin. Other GnRH agonists are well established therapeutic agents in humans with a wide range of clinical applications. These analogues cannot be administered orally because they are readily degraded by peptidases in the gastrointestinal system.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the main risks are related with the inhalation exposure. No concerns regarding the potential irritant effects of the formulation have been identified.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil (PECsoil, initial = 0.154 µg/kg) is less than 100 µg/kg.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because the intravaginal administration of alarelin to the target species is considered to be characterised by rapid absorption and extensive distribution to various organs, including pituitary, kidney and liver, followed by degradation into biologically inactive fragments by peptidases mainly in the kidney and the liver, and a rapid clearance by the kidney. Since the amino acid composition/structure of alarelin is very similar to GnRH and the other GnRH analogues, the fate of alarelin residues following ingestion by a human is expected to be the same as that of GnRH and the other GnRH analogues. Due to the intended frequency of use, i.e. single intravaginal dosing at the time of artificial insemination, and the documented pharmacokinetic profile in rabbits, accumulation of residues in animal tissues is not expected.

MRLs

The active substance Alarelin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Alarelin	Not applicable	All food producing species	No MRL required	Not applicable	NO ENTRY

The excipients sodium hydrogen carbonate, glucose anhydrous, sodium citrate and citric acid are used as food additives with a valid E-number. Therefore, in accordance with Regulation (EU) No 37/2010, no MRL is required. Disodium edetate is also a “No MRL required” substance included in table 1 of the Annex to Regulation (EU) No 37/2010.

Withdrawal Periods

Based on the data provided above, a withdrawal period of zero days for meat in rabbits is justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has conducted two laboratory studies and provided bibliographical data to show that alarelin acts as a LHRH (Luteinizing-hormone releasing hormone) agonist. The primary pharmacodynamic effect of GnRH and GnRH analogues is to stimulate release of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH), with a resulting increase in circulating sex hormones. Alarelin, when administered intravaginally to female rabbits for reproduction, stimulate an increase in plasma LH concentrations around 1 and 1.5 hours after administration. This increase in LH is sufficient to induce ovulation.
Alarelin is rapidly absorbed after intravaginal administration in female rabbits for reproduction, presenting a peak concentration generally 45 minutes post-administration. A clear increase in LH levels was observed around 1.5 hours after intravaginal administration. Alarelin is rapidly metabolised and the bioavailability is very low between 3% and 4%. It is rapidly excreted (half-life of approximately 0.5 hours).

Tolerance in the Target Species of Animals

The applicant has not conducted a target animal tolerance study. Tolerance in the target species is based on data from preclinical and clinical studies and bibliographical data describing the nature of the active substance and the safety profile of natural GnRH and other GnRH analogues in different target species including rabbits. The results obtained in the studies are well documented in the SPC.
A specific local tolerance study concluded that 0.03 mg of alarelin when intravaginally administered showed to be safe. This study was GCP compliant, pkacebo-controlled, and double blinded. Three groups were assessed with a maximum alarelin 0.05 mg/ intravaginal dose. There were no statistical significant differences between the treatment groups regarding tolerance and no adverse reactions were observed. This result is well documented in the SPC.

IV.B Clinical Studies

Laboratory Trials

Dose determination and dose confirmation where performed in field trials.

Field Trials

The applicant has conducted three field studies on dose determination, safety and efficacy confirmation, and local tolerance respectively. All studies were performed according to the requirements set out in EU Directive 2001/82, VICH Topic GL9, and the guideline for veterinary medicinal products for zootechnical purposes (NtA Volume 7, 7AE7a). Bibliographical data also provided in the preclinical part was also supportive of the applicant's claim.

Dose determination study was GCP compliant, placebo-controlled, double blinded, unicentric (breeding farm located at Pontevedra, Spain). Four hundred animals were included and three different doses tested. The outcome from this study was that alarelin 0.03 mg/intravaginal dose can be considered as the optimum dose to achieve suitable efficacy without safety concerns.
Dose confirmation study was GCP compliant, positive-controlled, double blinded, multicentric (three breeding commercial farms, Spain). Nine hundred animals were included in two groups, using dalmarelin as positive control drug. The outcome from this study was that alarelin 0.03 mg/intravaginal dose proved to be clinically and satistically non-inferior to the reference product used, confirming the efficacy of the product. This dose also showed no safety concerns.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the veterinary Heads of Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

None