26 January 2018
EMA/CVMP/156095/2017
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Alarelin (All food producing species)

On 14 September 2017 the European Commission adopted a Regulation[1] establishing maximum residue limits for alarelin in all food producing species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Alarelin is intended for use in rabbits to induce ovulation at the time of artificial insemination. It is administered by the intravaginal route at doses of up to 50 µg/doe.

KUBUS S.A. submitted to the European Medicines Agency an application for the establishment of maximum residue limits on 31 October 2016.

Based on the data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 12 April 2017 the establishment of maximum residue limits for alarelin in all food producing species.

Subsequently the Commission recommended, on 11 July 2017, that maximum residue limits in all food producing species are established. This recommendation was confirmed on 2 August 2017 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 14 September 2017.

[1] Commission Implementing Regulation (EU) No 2017/1559, O.J. L237, of 15 September 2017

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Alarelin
Therapeutic class:	Agents acting on the reproductive system
Procedure number:	EMEA/V/MRL/004706/FULL/0001
Applicant:	KUBUS S.A.
Target species requested:	Rabbit
Intended therapeutic indication:	Ovulation inducer
Route(s) of administration:	Intravaginal

1. Introduction

Alarelin is a synthetic nonapeptide analogue of luteinizing-hormone releasing hormone (LHRH), also known as gonadotropin-releasing hormone (GnRH).

Alarelin is intended for use in rabbits, for administration by the intravaginal route to induce ovulation at the time of artificial insemination at doses of up to 50 µg/doe.

The company requested a scientific advice on the development program of alarelin in September 2015 and the advice was adopted in December 2015 (EMA/CVMP/SAWP/662015/2015). The questions raised were related to the types of studies needed to support the pharmacodynamic, pharmacokinetic and the toxicological properties of alarelin and the need for residue studies. The dossier provided is in line with the scientific advice provided.

2. Scientific risk assessment

Alarelin is a potent synthetic analogue of the endogenous hormone GnRH. The amino sequence of GnRH and the analogues discussed are presented in Table 1.

Table 1. Amino acid sequence of alarelin and other GnRH-agonist analogues

	1	2	3	4	5	6	7	8	9	10
GnRH	pGlu	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly NH_2
Alarelin	pGlu	His	Trp	Ser	Tyr	DAla	Leu	Arg	Pro	NHEt
Triptorelin	pGlu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	Gly NH2
Leuprolide	pGlu	His	Trp	Ser	Tyr	D-Nal	Leu	Arg	Pro	NHEt
Nafarelin	pGlu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	Gly NH2
Deslorelin	pGlu	His	Trp	Ser	Tyr	D-Trp	Leu	Arg	Pro	Ethylamide
Peforelin	pGlu	His	Trp	Ser	His	Asp	Trp	Lys	Pro	Gly NH_2
Buserelin	pGlu	His	Trp	Ser	Tyr	D-Ser	Leu	Arg	Pro	NHEt

2.1. Safety assessment

2.1.1. Overview of pharmacological properties

The primary pharmacodynamic effect of GnRH and GnRH analogues is to stimulate release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), with a resulting increase in circulating sex hormones.

Pharmacodynamic properties including mode of action

In-house studies were performed to establish the pharmacodynamic effects of alarelin in rabbits. These data were supported by published preclinical studies conducted on a commercial farm to demonstrate the efficacy of the substance following intravaginal administration.

In a preclinical study investigating pharmacokinetics and pharmacodynamics of alarelin, nulliparous New-Zealand white rabbits in receptive status received alarelin either intravaginally (23.58 µg per animal corresponding to 5.85-7.04 µg/kg, n=3) or intravenously (1 µg/kg n=3), resulting in increased LH peak levels, occurring 1.5 hours post-intravaginal administration and 0.25 hours after intravenous administration, respectively. LH exposure (AUC_{LH} and C_{max}) was slightly higher when alarelin was administered by the intravaginal as compared to the intravenous route. The plasma LH levels were negligible 3 hours after intravaginal administration.

All females had ovulated and showed implantations after ten days of treatment, and no statistical differences were observed between nulliparous and multiparous female rabbits.

In a published large-scale field trial (n=540), alarelin (25 µg), delivered in the seminal dose (n = 270) was compared against 20 µg of gonadorelin administered intramuscularly (n = 270). The results from this experiment indicated that the kindling rate was significantly higher ($p < 0.05$) when alarelin was added to the seminal dose (91.1% versus 85.6%, respectively, for treatment and control gonadorelin groups).

Pharmacokinetic properties (mainly in laboratory animals)

Based on the structural similarity with GnRH, the pharmacokinetics of alarelin are, in many aspects, expected to be comparable to other GnRH analogues, which show a longer terminal half-life than GnRH due to an amino acid substitution at position 6 (i.e. D-alanine instead of L-glycine), leading to higher stability against proteolytic degradation.

Following intravaginal administration of alarelin in rabbits, the bioavailability was low (about 3-4%) with a rapid elimination (half-life of approximately 0.5 hours). There is no information on the bioavailability following other routes of administration. However, due to the susceptibility to inactivation by gastrointestinal peptidase degradation, the oral bioavailability of this class of peptide analogue in laboratory animals as well as in humans is generally very low, e.g. estimated to be less than 1% in humans.

2.1.2. Calculation of pharmacological ADI, if relevant

Human systemic exposure to alarelin following ingestion of animal derived food is expected to be negligible and therefore, in line with the CVMP guideline on the approach to establish a pharmacological ADI (EMA/CVMP/SWP/355689/2006), it is not considered necessary to establish a pharmacological ADI.

2.1.3. Overview of toxicology

Except for a single-dose toxicity study, which in general is not required for establishment of maximum residue limits, none of the standard tests for establishment of maximum residue limits were provided. References relating to supporting toxicological data generated with other GnRH analogues were provided. The results from the single oral dose toxicity study indicate that alarelin does not induce mortality or signs of toxicity in female rats following oral administration of a single dose of 300 mg/kg.

While the results of the efficacy studies in rabbits supported the intended primary pharmacodynamic effects of alarelin, e.g. an increase in LH levels and an increased pregnancy rate, there were no indications of any toxic effects on reproduction, e.g. in terms of pregnancy failure rate or mortality at birth, following an intravaginal (23.58 µg) or intravenous (1 µg/kg) administration of alarelin.

No toxicological data generated with alarelin were provided in relation to reproductive toxicity, genotoxicity or carcinogenicity.

Studies of other effects including immunotoxicity and neurotoxicity

No data were provided. The absence of such data is considered acceptable due to the chemical nature of alarelin and an expected negligible human exposure following oral administration.

2.1.4. Calculation of the toxicological ADI or alternative limit

Due to the chemical nature of the peptide analogue leading to rapid elimination and enzymatic inactivation/ degradation in the gastrointestinal tract, resulting 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 rabbit tissues is considered negligible. Thus, there is no need to define an ADI and consequently the absence of standard toxicology studies is acceptable. This position is further supported by the fact that the CVMP previously concluded that, due to the chemical nature and absence of systemic activity after oral dosing of GnRH analogues in animals, it was not necessary to define an ADI for deslorelin actetate, buserelin, perfolin, triptorelin or gonadorelin.

2.1.5. Overview of microbiological properties of residues

Due to the chemical nature of alarelin, i.e. a nonapeptide, microbiological effects are not expected.

2.1.6. Calculation of microbiological ADI

As no microbiological effects are expected the establishment of a microbiological ADI is not considered necessary.

2.1.7. Observations in humans

There are no observations or studies in humans conducted with alarelin. Due to the suppressive negative feed-back mechanism within the hypothalamic-pituitary-gonadal axis, chronic treatment with GnRH analogues (e.g. triptorelin) is currently approved for use in humans for the treatment of various hormone-dependent conditions including prostate cancer, precocious puberty, endometriosis, uterine fibroids and ovarian cancer. Observed side-effects for GnRH analogues include reversible, relatively minor effects which were all related to the secondary pharmacological action, i.e. loss of bone and sex drive in men and women, cessation of menses in women as well as hot flushes, vaginal dryness, transient headache, mild insomnia, emotional lability and slight weight gain in women.

2.1.8. Findings of EU or international scientific bodies

Not applicable.

2.1.9. Overall conclusions on the ADI

Neither a pharmacological nor a toxicological ADI is considered necessary as systemic exposure to residues will be negligible. A microbiological ADI is not considered necessary as, due to the chemical nature of the substance, microbiological effects are not expected.

2.2. Residues assessment

No standard studies investigating the pharmacokinetic behaviour of radiolabelled alarelin or the tissue depletion of alarelin residues in the target animal using the intended route, i.e. intravaginal administration, were presented. However a set of references on the pharmacokinetic properties of GnRH, alarelin and other GnRH analogues in several different species has been provided. Supporting information on the fate of alarelin in the target species (i.e. rabbit) following intravaginal administration consists of plasma concentration measurements of alarelin as well as LH data from preclinical studies investigating pharmacokinetics and pharmacodynamics. Since alarelin is expected to have negligible oral bioavailability in humans, the amount of residues present in target animal tissues is of limited relevance. However, based on the chemical structure and its similarity with other GnRH analogues alarelin is expected to be rapidly absorbed and eliminated in the target animal.

2.2.1. Pharmacokinetics in target species

Standard distribution and metabolism studies in the target species were not provided. Due to structural similarity between alarelin and other GnRH agonists this is acceptable. In general, these decapeptides and nonapeptides (e.g. alarelin) all show a similar pattern of distribution and metabolism and are widely distributed to various tissues, with the highest levels of the residue commonly observed in the pituitary gland, with degradation into biologically inactive fragments by peptidases mainly occurring in the kidney and the liver, and with a rapid and predominant clearance by the kidney.

The presented data demonstrated a low bioavailability (approximately 3%) of alarelin when administered by the intravaginal route and a rapid elimination from plasma in the treated animals, which together justifies the omission of substance-specific tissue depletion data. The kinetics of alarelin in rabbits following other routes of administration has not been studied. However, in general for this class of peptide analogues the elimination half-lives are short (a few hours) and the oral bioavailability is very limited (less than 1%) in humans due to rapid metabolism and inactivation in the gastrointestinal tracts and poor absorption through mucous membranes.

2.2.2. Residue depletion studies

Based on the provided data, together with the documented pharmacokinetic properties of other GnRH agonists, 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.

The absence of residue depletion studies is considered justified since the data provided are sufficient to support a rapid absorption, low intravaginal bioavailability and fast elimination of alarelin in rabbits. In addition, the oral bioavailability of GnRH analogues in humans is expected to be negligible.

2.2.3. Monitoring or exposure data

No monitoring or exposure data other than those described elsewhere in this report are available.

2.2.4. Analytical method for monitoring of residues

No analytical method for residue monitoring purposes was proposed, which is acceptable for a “no MRL required” recommendation.

2.2.5. Findings of EU or international scientific bodies

No information on evaluations by other scientific bodies was available.

3. Risk management considerations

Rabbits are considered a minor species and therefore the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005) and the note for guidance on the risk analysis approach for residues of veterinary medicinal products in food of animal origin (EMEA/CVMP/187/00-FINAL) were taken into account for the evaluation of the reduced data package which complied with the requirements of the guidelines mentioned above.

3.1. Potential effects on the microorganisms used for industrial food processing

No relevant data were provided but due to the chemical nature of the compound, i.e. a decapeptide, microbiological effects are not expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

No such considerations were identified.

3.3. Elaboration of MRLs

Based on the chemical nature and an expected low oral bioavailability of alarelin (less than 1%) the likelihood that a human may be exposed to biologically relevant levels of alarelin after the intake of rabbit tissues is concluded to be negligible. Consequently, the establishment of numerical MRLs is not necessary for the protection of human health.

In addition, it is noted that,

- as is the case for other GnRH analogues, alarelin is expected to be rapidly absorbed and eliminated or deactivated in the target species,
- based on the intended use (single intravaginal administration in each reproduction cycle to induce ovulation in rabbits at the time of artificial insemination) it is unlikely that alarelin will accumulate in animals or that animals will be slaughtered during the period between insemination and confirmation of pregnancy.
- based on the pharmacology of the substance, other uses of the substance are not foreseen.

A “No MRL required” classification is further supported by previous assessments made by the CVMP for GnRH (gonadorelin) and other GnRH analogues (e.g. triptorelin, peforelin, deslorelin, lecirelin and buserelin) which are structurally similar to alarelin, and for which a “No MRL required” classification was accepted.

3.4. Considerations on possible extrapolation of MRLs

In line with implementing Regulation (EC, 2016) No 470/2009, the CVMP considered the possibility of extrapolating the maximum residue limits recommended for alarelin ("No MRL required") in rabbits (minor species) to other food producing species and commodities. Taking into account the current scientific knowledge, the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	Extrapolation possible (Yes/No)	Justification
All food producing species	Yes	The recommendation for a "No MRL required" classification for rabbits is based on the low oral bioavailability in humans. As the low oral bioavailability in humans is independent of the pharmacokinetic/residue depletion profile in the target species the conclusion for rabbits can be extrapolated to all other food producing species. In addition, metabolism of alarelin (i.e. enzymatic degradation) is expected to be conserved across species resulting in rapid elimination in all food producing species.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- the establishment of an ADI is not considered necessary for alarelin,
- oral bioavailability of tissue residues in humans is expected to be negligible,
- alarelin is rapidly metabolised and quickly degraded/eliminated by the target animal,
- alarelin is a peptidergic substance closely related to naturally occurring GnRH, which has been previously assessed and included in Table 1 of the annex to Regulation 37/2010 with a "No MRL required" classification for all food producing species,
- a consumer's systemic exposure to residues of alarelin will not be affected by the target species treated,

The Committee concludes that the establishment of maximum residue limits for alarelin for rabbits is not necessary for the protection of human health, and that this conclusion can be extrapolated to all food producing species, and therefore recommends the inclusion of alarelin in table 1 of the Annex to Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Alarelin	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	Agents acting on the reproductive system

4. Background information on the procedure

Submission of the dossier	31 October 2016
Steps taken for assessment of the substance	
Application validated:	16 November 2016
Clock started:	17 November 2016
CVMP opinion adopted:	12 April 2017