[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MRAbit 1.5 mg/g powder for vaginal solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains:

Active substance:
Alarelin acetate equivalent to alarelin 1.5 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White powder for vaginal solution.
After reconstitution: clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Target species

Female rabbits for reproduction

4.2 Indications for use, specifying the target species

Ovulation induction of female rabbits for reproduction.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

All clinical studies to demonstrate the efficacy of the medicinal product were performed with the same sperm concentration. Therefore, the recommended concentration for the sperm dose is a minimum of $20x10^6$ spermatozoa per dose.

4.5 Special precautions for use

Special precautions for use in animals

Not applicable.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

- People with a known hypersensitivity to any of the excipients should avoid contact with the veterinary medicinal product.
- Due to the reproductive effects of the active substance, the veterinary medicinal product cannot be prepared or administered by pregnant women.

- This product may cause irritation of the respiratory tract. Therefore, it should be handled with care to avoid dust production and inhalation. Use in a well-ventilated area away from draughts. Operators should wear a mask (either a disposal half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143) and gloves when handling the medicinal product.
- Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

None

4.7 Use during pregnancy, lactation or lay

Can be used during lactation.
Do not use during the whole of the pregnancy.

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

Administration route: vaginal use.

Dose: one dose of 0.5 ml of medicinal product (0.03 mg of alarelin) per female rabbit given with the semen dose.

1- Veterinary medicinal product preparation

It must be reconstituted at a Stud for administration as rabbit semen extender

1. Pre-warm double distilled water to 37°C
2. Measure required double distilled water depending on format (using volumetric cylinder or weighing scale):
    a. 40 g. Measure 1,000 ml of double distilled water
    b. 12 g. Measure 300 ml of double distilled water
    c. 4 g. Measure 100 ml of double distilled water
3. Add veterinary medicine.
4. Mix 5 minutes manually or use magnetic stirrer until complete dissolution of the powder.

2- Semen addition

After evaluating ejaculate quality, transfer required semen depending on recommended sperm cell concentration per dose and as appropriate for artificial insemination.
The recommended semen dose is 20 $x10^6$ sperm cells.

The final dose for each doe is 0.5ml of the veterinary medicine (0.03mg of alareline) having the appropriately considered sperm cell concentration per mm^3 for artificial insemination.
Mix ejaculates with extender avoiding temperature differences above 1-2°C.

3- Product administration

Administer 0.5ml via vaginal delivery to each doe in accordance with typical artificial insemination and semen dose handling practices:

a. Utilise a disposable insemination cannula. Connect the canula to the syringe.
b. Place and hold doe facing up aided by someone else.
c. Insert the insemination cannula in the vagina.
d. When the tip of the cannula is near the cervix, push the syringe plunger to deposit the medicine with the semen dose.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

A maximum dose of 0.05 mg of alarelin per animal did not cause systemic effects in the inseminated animals or their offspring.

4.11 Withdrawal period(s)

Zero days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: gonadotropin-releasing hormones
ATC vet code: QH01CA

5.1 Pharmacodynamic properties

Alarelin is a synthetic polypeptide which acts as a LHRH (Luteinizing-hormone releasing hormone) agonist. LHRH, also known as GnRH (gonatropin-releasing hormone) or gonadorelin, is a decapeptide hormone which is synthesized in neurosecretory cells within the hypothalamus and released in a pulsatile fashion into the pituitary portal circulation. LHRH regulates reproductive functions and the development and maintenance of secondary sex characters in males and females since it controls the secretion of the gonadotropins LH (luteinizing hormone) and FSH (follicle-stimulating hormone) from the anterior pituitary gland. LH and FSH act on the ovaries and the testes and are responsible of the fertility effects of LHRH. Pulsatile secretion is essential for reproductive functions, sexual development and differentiation.

In the female rabbits, ovulation does not occur spontaneously, but it has to be induced through a neurohormonal reflex, which is initiated during mating. Coitus results in ovulation after some hours and is followed by a rapid increase in serum LH levels. The GnRH is synthesized and released at hypothalamus, which promotes the synthesis and secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Elevated circulating concentrations of LH induce a cascade of events within the mature follicle, culminating in follicle rupture and evacuation.
In the female rabbit due to the lack of nervous stimuli evoked by the male, when AI (Artificial Insemination) is applied, ovulation has to be induced by artificial methods. The administration of GnRH synthetic analogues is the most reliable method for inducing ovulation. Alarelin can be used for ovulation induction in female rabbits vehiculated in the seminal dose

5.2 Pharmacokinetic particulars

- Absorption: Alarelin is rapidly absorbed after vaginal administration in female rabbits, presenting a peak concentrations generally at 45 minutes post-administration. Low alarelin concentrations can be quantified from 15 minutes to 2.5 hours post-insemination.
- Distribution: Alarelin concentrations were directly correlated with a clear increase in LH levels (pharmacodynamic surrogate of the test item) with a peak level concentration around 1.5 hours post-administration following the vaginal administration.
- Metabolism: Alarelin is rapidly metabolised and the bioavailability is very low between 3% and 4%.
- Excretion: Rapid excretion (half-life of approximately 0.5 hours).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Glucose anhydrous
- Sodium citrate
- Disodium edetate
- Sodium hydrogen carbonate
- Citric acid, anhydrous

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: use immediately
Shelf life after reconstitution according to directions: use immediately

6.4. Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
Transport under 25ºC.
Protect from light.

6.5 Nature and composition of immediate packaging

Laminate sachets (PET (12)+ ALU (9) + PEBD(70))

Pack sizes:

- Cardboard box containing 25x40 g sachets for 2100 doses
- Cardboard box containing 25x12 g sachets for 630 doses
- Cardboard box containing 25x4 g sachets for 210 doses
- Cardboard box containing 5x40 g sachets for 2100 doses
- Cardboard box containing 5x12 g sachets for 630 doses
- Cardboard box containing 5x4 g sachets for 210 doses

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

KUBUS LAB S.A.
C/Varsovia, 20. Las Rozas de Madrid. 28232.
Spain

Tel.: (0034) 916360268

kubus@kubus-sa.com

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

“To be supplied only on veterinary prescription not renewable”.(ITALY)

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE
CARDBOARD BOX LABEL
25 sachets of 40 g
25 sachets of 12 g
25 sachets of 4 g
5 sachets of 40 g
5 sachets of 12 g
5 sachets of 4 g

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MRAbit 1.5 mg/g powder for vaginal solution

2. STATEMENT OF ACTIVE SUBSTANCES

Each g contains:

Active substance:
Alarelin acetate equivalent to alarelin 1.5 mg

3. PHARMACEUTICAL FORM

White powder for vaginal solution.
Clear and colourless solution.

4. PACKAGE SIZE

25 sachets of 40 g : 25x2100 doses
25 sachets of 12 g : 25x630 doses
25 sachets of 4 g : 25x210 doses
5 sachets of 40 g : 5x2100 doses
5 sachets of 12 g : 5x630 doses
5 sachets of 4 g : 5x210 doses

5. TARGET SPECIES

Female rabbits for reproduction

6. INDICATION(S)

Ovulation induction of female rabbits for reproduction

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period: zero days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened and reconstituted use immediately.

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. (2 °C – 8 °C).
Transport under 25ºC.
Protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

"Disposal: read package leaflet".

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KUBUS LAB S.A.
C/Varsovia, 20. Las Rozas de Madrid. 28232.
Spain
Tel.: (0034) 916360268
kubus@kubus-sa.com

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

<Batch><Lot> {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE LABEL
Sachets of 40 g of powder
Sachets of 12 g of powder
Sachets of 4 g of powder

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MRAbit 1.5 mg/g powder for vaginal solution

2. STATEMENT OF ACTIVE SUBSTANCES

Each g contains:

Active substance:
Alarelin acetate equivalent to alarelin 1.5 mg

3. PHARMACEUTICAL FORM

White powder for vaginal solution.
Clear and colourless solution.

4. PACKAGE SIZE

40 g: 2100 doses
12 g: 630 doses
4 g: 210 doses

5. TARGET SPECIES

Female rabbits for reproduction

6. INDICATION(S)

Ovulation induction of female rabbits for reproduction..

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Withdrawal period: zero days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Once opened and reconstituted use immediately.

11. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. (2 °C – 8 °C).
Transport under 25ºC.
Protect from light.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

KUBUS LAB S.A.
C/Varsovia, 20. Las Rozas de Madrid. 28232.
Spain
Tel.: (0034) 916360268
kubus@kubus-sa.com

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

<Batch><Lot> {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

MRAbit 1.5 mg/g powder for vaginal solution

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:

KUBUS LAB S.A.
C/Varsovia, 20. Las Rozas de Madrid. 28232.
Spain
Tel.: (0034) 916360268
kubus@kubus-sa.com

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

MRAbit 1.5 mg/g powder for vaginal solution
Alarelin acetate

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each g contains:

Active substance:
Alarelin acetate equivalent to alarelin 1.5 mg
Excipients, q.s.

White powder for vaginal solution.
Clear and colourless solution after reconstitution.

4. INDICATION(S)

Ovulation induction of female rabbits for reproduction.

5. CONTRAINDICATIONS

Do not use in cases of hypersensitivity to the active substance or to any of the excipients

6. ADVERSE REACTIONS

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Alternatively you can report via your national reporting system.

7. TARGET SPECIES

Female rabbits for reproduction

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Administration route: vaginal use.

Dose: one dose of 0.5 ml of medicinal product (0.03 mg of alarelin) per female rabbit given with the semen dose.

9. ADVICE ON CORRECT ADMINISTRATION

1- Veterinary medicinal product preparation

It must be reconstituted at a Stud for administration as rabbit semen extender

1. Pre-warm double distilled water to 37°C
2. Measure required double distilled water depending on format (using volumetric cylinder or weighing scale):
    a. 40 g. Measure 1,000 ml of double distilled water
    b. 12 g. Measure 300 ml of double distilled water
    c. 4 g. Measure 100 ml of double distilled water
3. Add veterinary medicine.
4. Mix 5 minutes manually or use magnetic stirrer until complete dissolution of the powder.

2- Semen addition

After evaluating ejaculate quality, transfer required semen depending on recommended sperm cell concentration per dose and as appropriate for artificial insemination.
The recommended semen dose is 20 $x10^6$ sperm cells.

The final dose for each doe is 0.5ml of the veterinary medicine (0.03mg of alareline) having the appropriately considered sperm cell concentration per mm^3 for artificial insemination.
Mix ejaculates with extender avoiding temperature differences above 1-2°C.

3- Product administration

Administer 0.5ml via vaginal delivery to each doe in accordance with typical artificial insemination and semen dose handling practices:

e. Utilise a disposable insemination cannula. Connect the canula to the syringe.
f. Place and hold doe facing up aided by someone else.
g. Insert the insemination cannula in the vagina.
h. When the tip of the cannula is near the cervix, push the syringe plunger to deposit the medicine with the semen dose.

10. WITHDRAWAL PERIOD(S)

Zero days

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store in a refrigerator (2 °C – 8 °C).
Transport under 25ºC.
Protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label
Shelf life after first opening the immediate packaging: use immediately
Shelf life after reconstitution according to directions: use immediately

12. SPECIAL WARNING(S)

Special warnings for each target species:

All clinical studies to demonstrate the efficacy of the medicinal product were performed with the same sperm concentration. Therefore, the recommended concentration for the sperm dose is 20 x 10^6 spermatozoa per dose.
Can be used during lactation.
Do not use during the whole of the pregnancy.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

- People with a known hypersensitivity to any of the excipients should avoid contact with the veterinary medicinal product.
- Due to the reproductive effects of the active substance, the veterinary medicinal product cannot be prepared or administered by pregnant women.
- This product may cause irritation of the respiratory tract. Therefore, it should be handled with care to avoid dust production and inhalation. Use in a well-ventilated area away from draughts. Operators should wear a mask (either a disposal half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143) and gloves when handling the medicinal product.
- Wash hands after use.

Incompatibilities:

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

Overdose (symptoms, emergency procedures, antidotes):

A maximum dose of 0.05 mg of alarelin per animal did not caused systemic effects in the inseminated animals or their offspring.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste. Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

Package sizes:
Cardboard box containing 25x40 g sachets for 2100 doses
Cardboard box containing 25x12 g sachets for 630 doses
Cardboard box containing 25x4 g sachets for 210 doses
Cardboard box containing 5x40 g sachets for 2100 doses
Cardboard box containing 5x12 g sachets for 630 doses
Cardboard box containing 5x4 g sachets for 210 doses

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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