[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Evomate RTU 400 mg/ml suspension for injection for cattle (NL)
Revozyn RTU 400 mg/ml suspension for injection for cattle (AT-BE-CZ-DK- HR-HU-IE-IT-PL-PT-SI-SK)
Revozyn 400 mg/ml suspension for injection for cattle (ES)
Revozyn RTU 308.8 mg/ml suspension for injection for cattle (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:
Active substance:
308.8 mg penethamate equivalent to 400 mg penethamate hydriodide

Excipients:

Qualitative composition of excipients and other constituents
Lecithin (E322)
Ethyl oleate

A white to yellowish white, oily suspension.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (lactating cows).

3.2 Indications for use for each target species

For the treatment of clinical and subclinical mastitis in lactating cows caused by staphylococci and streptococci, susceptible to penicillin.

3.3 Contraindications

Do not use in cases of known hypersensitivity to the active substance, or to any of the excipients.
Do not administer by intravenous injection.

3.4 Special warnings

Cross-resistance has been shown between benzylpenicillin and penicillins and beta-lactam antimicrobials in staphylococci and streptococci. Use of benzylpenicillin should be carefully considered when susceptibility testing has shown resistance to penicillins or beta-lactam antimicrobials because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be based on identification and susceptibility testing of the target pathogens. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

The feeding of waste milk containing residues of penicillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria (e.g. ESBL) within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

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

This veterinary medicinal product can cause sensitisation and contact dermatitis.
Hypersensitivity to penicillins may lead to cross reactions to cephalosporins, and *vice versa*.
Allergic reactions to these substances may occasionally be serious.
Handle this product with great care to avoid direct skin contact or self-injection.
People with known hypersensitivity to penicillin should avoid contact with the veterinary medicinal product.
Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.
Wash hands after use.
In case of accidental contact with the skin, wash immediately with plenty of water. If symptoms following exposure such as skin rash develop or in case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (lactating cows):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Urticaria, Anaphylactic shock[a], death[a]. Sensitisation against penicillins.
Undetermined frequency (cannot be estimated from the available data):	Skin reactions (mild), such as dermatitis.

[a] Anaphylactic shock can be fatal, very rarely

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

Can be used during pregnancy or lactation.

3.8 Interaction with other medicinal products and other forms of interaction

The veterinary medicinal product should not be administered concurrently with bacteriostatic antibiotics.

3.9 Administration routes and dosage

Shake well before use.
For intramuscular administration only, preferably in the neck.
Administer alternately on the left and the right side.

Administer 10-15 mg penethamate hydriodide per kg body weight per day, once daily for 3 consecutive days, corresponding to 2.5-3.75 ml of the veterinary medicinal product per 100 kg body weight per day, once daily for 3 consecutive days.

Avoid underdosing. To ensure a correct dosage, body weight should be determined as accurately as possible.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In case of overdose, no adverse effects other than those mentioned in section 3.6 are to be expected.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Milk: 4 days.
Meat and offal: 10 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01CE90

4.2 Pharmacodynamics

In aqueous environments, penethamate is hydrolysed to form benzylpenicillin and diethylaminoethanol. The mode of action of benzylpenicillin is by prevention of cell wall synthesis during bacterial cell growth and its activity is primarily bactericidal and time-dependent. The antimicrobial spectrum of the active substance corresponds to that of benzylpenicillin which is active against beta-lactamase negative *Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus uberis* and *Staphylococcus aureus*. In 2011 the MIC_{90} values for penicillin in Sweden were 0.12 µg/ml for *S. aureus*, 0.12 µg/ml for *S. dysgalactiae* and 0.12 µg/ml for *S. uberis*. In 2012 the MIC_{90} values for penicillin in Germany were 0.031 µg/ml for *S. agalactiae*, 0.015 µg/ml for *S. dysgalactiae* and 0.125 µg/ml for *S. uberis*. In 2013 the MIC_{90} values for penicillin in Switzerland were 1.0 µg/ml for *S. aureus*, ≤0.12 µg/ml for *S. dysgalactiae* and ≤0.12 µg/ml for *S. uberis*. EUCAST reports an Epidemiological Cut OFF value (ECOFF) of 0.125 µg/ml for *S. aureus* and an ECOFF of 0.125 µg/ml for *S. agalactiae*. For *S. dysgalactiae* and *S. uberis* no ECOFF values are determined.

The most frequent mechanism of resistance is producing beta-lactamases (more specifically penicillinase especially in *S. aureus*), which break the beta-lactam ring of penicillins, making them inactive.

4.3 Pharmacokinetics

Penethamate hydriodide is the diethylaminoethyl ester of penicillin, which contains an acidic carboxylic acid grouping. The ester is non-ionised and has high lipid solubility. The major pharmacokinetic properties of penethamate hydriodide are its rapid absorption, with high

bioavailability and rapid metabolism *in vivo* to penicillin, the therapeutically active molecule. In circulation it is rapidly hydrolysed to diethylaminoethanol and penicillin, with approximately 90% existing as penicillin. The parent compound readily penetrates into milk, as a consequence of its high lipid solubility. In milk, it is hydrolysed to penicillin and this maintains the plasma/milk concentration gradient for the parent compound. This is a mechanism of passive diffusion from a fluid of pH 7.4 to a more acid pH in milk. With a pKa value of 2.7, penicillin is highly ionised in both plasma and milk. The pH gradient between plasma (pH 7.4) and milk (pH 6.6-6.8) is reduced in mastitis but nevertheless is not abolished.
C_{max} is 682 ng/mL, AUC_{last} is 7770 h*ng/mL and elimination half-life is 6.84 hours.
Apart from excretion in the milk, benzylpenicillin is also excreted via the kidneys.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Do not mix with any other veterinary medicinal product.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Store below 30 °C.
Keep upright.

5.4 Nature and composition of immediate packaging

Multidose 50 ml uncoloured glass (type II, Ph. Eur.) vials, closed with fluoropolymer coated rubber type I (Ph. Eur.) stoppers secured with aluminium caps.
1 Vial in a cardboard box.

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

Medicines should not be disposed of via wastewater or <household waste>.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.

BE:
Dechra Regulatory B.V.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Carton 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Evomate RTU 400 mg/ml suspension for injection

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
308.8 mg penethamate equivalent to 400 mg penethamate hydriodide

3. PACKAGE SIZE

50 ml

4. TARGET SPECIES

Cattle (lactating cows)

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Intramuscular administration.

7. WITHDRAWAL PERIODS

Withdrawal period:
Milk: 4 days.
Meat and offal: 10 days.

8. EXPIRY DATE

Exp. {mm/yyyy}

Once broached, use within 28 days. Use by: _____/_____/_____

9. SPECIAL STORAGE PRECAUTIONS

Store below 30°C.
Keep upright.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.

BE:
Dechra Regulatory B.V.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Glass vial 50 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Evomate RTU

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Each ml contains:
308.8 mg penethamate equivalent to 400 mg penethamate hydriodide

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}
Once broached, use by: _____/_____/_____

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Evomate RTU 400 mg/ml suspension for injection for cattle

2. Composition

Each ml contains:

Active substance:
308.8 mg penethamate equivalent to 400 mg penethamate hydriodide

A white to yellowish white, oily suspension.

3. Target species

Cattle (lactating cows)

4. Indications for use

For the treatment of clinical and subclinical mastitis in lactating cows caused by staphylococci and streptococci, susceptible to penicillin.

5. Contraindications

Do not use in cases of known hypersensitivity to the active substance, or to any of the excipients.
Do not administer by intravenous injection.

6. Special warnings

Special warnings:
Cross-resistance has been shown between benzylpenicillin and penicillins and beta-lactam antimicrobials in staphylococci and streptococci. Use of benzylpenicillin should be carefully considered when susceptibility testing has shown resistance to penicillins or beta-lactam antimicrobials because its effectiveness may be reduced.

Special precautions for safe use in the target species:
Use of the product should be based on identification and susceptibility testing of the target pathogens. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

The feeding of waste milk containing residues of penicillin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria (e.g. ESBL) within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This veterinary medicinal product can cause sensitisation and contact dermatitis.
Hypersensitivity to penicillins may lead to cross reactions to cephalosporins, and *vice versa*.
Allergic reactions to these substances may occasionally be serious.
Handle this product with great care to avoid direct skin contact or self-injection.
People with known hypersensitivity to penicillin should avoid contact with the veterinary medicinal product.

Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product.
Wash hands after use.
In case of accidental contact with the skin, wash immediately with plenty of water. If symptoms following exposure such as skin rash develop or in case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.

Pregnancy and lactation:
Can be used during pregnancy or lactation.

Interaction with other medicinal products and other forms of interaction:
The veterinary medicinal product should not be administered concurrently with bacteriostatic antibiotics.

Overdose:
In case of overdose, no adverse effects other than those mentioned in section "Adverse events" are to be expected.

Special restrictions for use and special conditions for use:

Major incompatibilities:
Do not mix with any other veterinary medicinal product.

7. Adverse events

Cattle (lactating cows):
Very rare (<1 animal / 10,000 animals treated, including isolated reports): Urticaria, Anaphylactic shock[a], death[a]. Sensitisation against penicillins.
Undetermined frequency (cannot be estimated from the available data): Skin reactions (mild), such as dermatitis.
[a] Anaphylactic shock can be fatal, very rarely

Reporting adverse events is important. It allows continuous safety monitoring of a product. 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 contact, in the first instance, your veterinarian. You can also report any adverse events to (the local representative of) the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system {national system details}.

8. Dosage for each species, routes and method of administration

For intramuscular administration only, preferably in the neck.
Administer alternately on the left and the right side.

Administer 10-15 mg penethamate hydriodide per kg body weight per day, once daily for 3 consecutive days, corresponding to 2.5-3.75 ml of the veterinary medicinal product per 100 kg body weight per day, once daily for 3 consecutive days.

9. Advice on correct administration

Shake well before use.

Avoid underdosing. To ensure a correct dosage, body weight should be determined as accurately as possible.

10. Withdrawal periods

Milk: 4 days.
Meat and offal: 10 days.

11. Special storage precautions

Keep out of the sight and reach of children.

Store below 30 °C.
Keep upright.

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after Exp. The expiry date refers to the last day of that month.

Shelf life after first opening the immediate packaging: 28 days.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater <or household waste>.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

<Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.>

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

Cardboard box with 1 x 50 ml vial.

15. Date on which the package leaflet was last revised

<{MM/YYYY} or <{DD/MM/YYYY}> or <{DD month YYYY}>

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder <and contact details to report suspected adverse reactions>:

Eurovet Animal Health B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Tel: +31 (0)348-563434

BE:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Marketing authorisation holder:

Eurovet Animal Health B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

BE:
Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Manufacturer responsible for batch release:

Eurovet Animal Health B.V.
Handelsweg 25
5531 AE Bladel
The Netherlands

Produlab Pharma B.V.
Forellenweg 16
4941 SJ Raamsdonksveer
The Netherlands

<Local representatives and contact details to report suspected adverse reactions:>

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

17. Other information