

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Revozyn RTU 400 mg/ml suspension for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

308.8 mg penethamate equivalent to 400 mg penethamate hydriodide

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.

A white to yellowish white oily suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (lactating cows).

4.2 Indications for use, specifying the target species

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

4.3 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.

4.4 Special warnings for each target species

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.

4.5 Special precautions for use

Special precautions for use in animals

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 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.

4.6 Adverse reactions (frequency and seriousness)

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.

4.7 Use during pregnancy, lactation or lay

Can be used during pregnancy or lactation.

4.8 Interaction with other medicinal products and other forms of interaction

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

4.9 Amount(s) to be administered and administration route

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.

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

In case of overdose, no adverse effects other than those mentioned in section 4.6 are to be expected.

4.11 Withdrawal period(s)

Milk: 4 days.

Meat and offal: 10 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Beta-lactamase sensitive penicillins.

ATCvet code: QJ01CE90.

5.1 Pharmacodynamic properties

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 MIC₉₀ 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 MIC₉₀ 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 MIC₉₀ 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.

5.2 Pharmacokinetic particulars

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethyl oleate
Lecithin (E322)

6.2 Major incompatibilities

Do not mix with any other veterinary medicinal product.

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: 28 days.

6.4 Special precautions for storage

Store below 30 °C.
Keep upright.

6.5 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.

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

Medicines should not be disposed of via wastewater.
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

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

8. MARKETING AUTHORISATION NUMBER

Vm 16849/5000

9. DATE OF FIRST AUTHORISATION

10 July 2017

10. DATE OF REVISION OF THE TEXT

February 2023

Approved 17 February 2023

A handwritten signature in black ink, appearing to read "Hunter.", is written below the approval date.