1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Revozyn RTU 400 mg/ml suspension for injection for cattle

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml suspension contains:
Active substance:
Penethamate hydriodide 400 mg
(corresponding to 308.8 mg penethamate)
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

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

None.

4.5 Special precautions for use

Special precautions for use in animals
Use of the veterinary medicinal product should be based on susceptibility testing of the bacteria isolated from the animal.
If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of the target bacteria.
Official and local antimicrobial policies should be taken into account when the product is used.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to benzylpenicillin and may decrease the effectiveness of treatment with other beta-lactams due to the potential for cross-resistance.
The feeding of milk containing penicillin residues to calves should be avoided because it could select antimicrobial-resistant bacteria (e.g. ESBL) within the calves gut.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This 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.
Direct skin contact or self-injection should be avoided. Gloves should be worn when handling the veterinary medicinal product.

Do not handle this product if you know you are sensitised, or if you have been advised not to work with such preparations.
Wash hands after use.
When the product comes into contact with the skin, wash immediately with plenty of water. If symptoms following exposure such as skin rash develop, or in the event of self-injection, you should seek medical advice and show the physician the package leaflet. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

The symptoms of adverse reactions range from mild skin reactions, such as urticaria and dermatitis, to severe reactions, such as anaphylactic shock (very rarely, less than 1 animal in 10,000 animals treated), which very rarely may be fatal. In addition sensitisation against penicillins may occur.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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

Penicillins should not be administered concurrently with bacteriostatic antibiotics.

4.9 Amounts to be administered and administration route

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

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

To ensure a correct dosage, bodyweight should be determined as accurately as possible to avoid under-dosing.

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 or IMMUNOLOGICAL 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 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.

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

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.) vial, closed with a fluoropolymer coated rubber type I (Ph. Eur.) stopper, secured with an aluminium cap.

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

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

VPA10989/071/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd February 2018

10 DATE OF REVISION OF THE TEXT