1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Ubrolexin intramammary suspension for lactating dairy cows

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 g (12 ml) intramammary syringe contains:

Active substances:
200 mg cefalexin (equivalent to 210 mg cefalexin monohydrate)
100 000 I.U. kanamycin monosulfate

Excipients:

Qualitative composition of excipients and other constituents
Paraffin, yellow soft
Paraffin, liquid

Off-white smooth oily paste.

3. CLINICAL INFORMATION

3.1 Target Species

Cattle (lactating cows).

3.2 Indications for use for each target species

Treatment of clinical mastitis in lactating dairy cows for bacteria susceptible to the combination of cefalexin and kanamycin such as *Staphylococcus aureus* (see section 4.1), *Streptococcus dysgalactiae*, *Streptococcus uberis* and *Escherichia coli*.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances, or to any of the excipients.
Do not use in non-lactating cattle.
Do not use in the case of known resistance of cefalexin and/or kanamycin.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:
The veterinary medicinal product should be used for treatment of clinical mastitis only.

Use of the 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 and farm level) epidemiological

information about susceptibility of the target bacteria as well as by taking into account official national antimicrobial policies.

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to cefalexin and kanamycin and may decrease the effectiveness of treatment with other cephalosporins or aminoglycosides due to the potential for cross-resistance.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion, or skin contact. Hypersensitivity to penicillins may lead to cross sensitivity to cephalosporin and vice versa. Allergic reactions to these substances may occasionally be serious.
People with known hypersensitivity to cefalexin and kanamycin should avoid contact with the veterinary medicinal product.
Take all recommended precautions. Handle this veterinary medicinal product with great care to avoid exposure by accidental contact with the skin. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product. Wash exposed skin after use.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the package leaflet or the label to the physician. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

None known.

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 the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Laboratory studies in animals have not produced any evidence of teratogenic effects. Field studies in dairy cows have not produced any evidence of a teratogenic, foetotoxic or maternotoxic effects. Can be used during pregnancy. Can be used during lactation.

3.8 Interaction with other medicinal products and other forms of interaction

In general, combination with bacteriostatic antimicrobials should be avoided. In case of resistance to cefalexin, cross-resistance with other cephalosporins is likely to occur.
In case of resistance to kanamycin, cross-resistance occurs between kanamycin, neomycin and paromomycin. A one way resistance with streptomycin is known.

3.9 Administration routes and dosage

Intramammary use.

Treat the infected quarter(s) twice, leaving an interval of 24 hours between treatments. Use the contents of one syringe (containing 200 mg cefalexin as monohydrate and 100,000 I.U. kanamycin as monosulphate) per quarter per treatment. Each syringe is for single use only.

Before infusion, the udder should be milked out completely, the teat should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the injector nozzle.

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

No available data.

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

Not applicable.

3.12 Withdrawal periods

Meat and offal: 10 days.
Milk: 5 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ51RD01

4.2 Pharmacodynamics

The veterinary medicinal product is a combination consisting of cefalexin and kanamycin at ratio 1.5 : 1. Cefalexin represents a first generation cephalosporin and belongs to the class of ß-lactam antibiotics. It provides a mainly time-dependent antibacterial activity against Gram-positive pathogens by inhibiting the synthesis of the bacterial peptidoglycan cell wall.

Kanamycin belongs to the class of aminoglycosides and provides bactericidal activity against gram-negative pathogens and against *Staphylococcus aureus*. Kanamycin provides mainly a concentration-dependent antibacterial activity through inhibition of bacterial protein synthesis and reduction of translation fidelity at ribosomal level.

The combination of cefalexin and kanamycin showed a bactericidal mode of action against *Staphylococcus aureus, Streptococcus dysgalactiae, Streptococcus uberis* and *Escherichia coli.* The effect of cefalexin and kanamycin in combination is mainly time-dependent.

Minimum inhibitory concentration, checkerboard analysis, kill kinetic and post antibiotic effect data demonstrate an advantage of the combination by broadening the activity spectrum and by showing synergistic antibacterial activity: the effect of cefalexin is enhanced by kanamycin and vice versa.

Further, the combination produces a larger suppression of bacterial growth (post antibiotic effect) against all target mastitis pathogens compared with the individual compounds.

Staphylococcus aureus has the potential to evade the immune system and establish deep-seated infection in the mammary gland. Thus, as is the case for other intramammary veterinary medicinal products, bacteriological cure rates in the field are expected to be low.

In vitro studies have demonstrated that isolates (2002-2004 and 2009-2011) of *S. aureus* are susceptible to the combination of active substances.

In vitro studies demonstrate that isolates of *S. agalactiae* (collected in 2004) and coagulase-negative staphylococci (collected in 2004 and 2009-2011) are susceptible to the combination of active substances.

Three mechanisms of resistance to cephalosporin are known: reduced permeability of the cell wall, enzymatic inactivation and absence of specific penicillin binding sites. Exogenous ß-lactamase production is the main method for *Staphylococcus aureus* and other Gram-positives bacteria to inactivate cephalosporins. Genes for ß-lactamases are found in both, chromosomes and plasmids, and may be moved by transposons. Gram-negative bacteria express low levels of species specific ß-lactamases within the periplasmic space, which contributes to resistance by hydrolysis of susceptible cephalosporins.
Resistance to kanamycin can be either chromosomal or plasmid-mediated. The clinical resistance to aminoglycosides is mainly caused by plasmid-specified enzymes, which are found in the periplasmic space of the bacteria. The enzyme binds to the aminoglycoside and prevents it binding to the ribosome and thus aminoglycoside can no longer inhibit protein synthesis.
The occurrence of co-resistance, induced by specific enzyme systems that are encoded for resistance, is particularly family specific for the ß-lactams and aminoglycosides. There are incidences of multiple resistances, and this is mainly due to the way in which a resistance gene is transferred either by transposons or integrons to plasmids, which then encode for resistance to both the ß-lactams and aminoglycosides.

4.3 Pharmacokinetics

After intramammary infusion on two consecutive days at 24-hour intervals the absorption and distribution of both active ingredients in the blood stream were fast but limited.
Kanamycin plasma concentrations reached a C_{max} of 0.504 and 1.024 µg/ml after the first and second dose respectively at T_{max} of six and four hours respectively. Plasma cefalexin levels reached 0.85 to 0.89 µg/ml two hours after administration.

The available metabolism data indicate that both parent substances, cefalexin and kanamycin, are the major compounds with antimicrobial activity.

Following intramammary administration of the veterinary medicinal product, cefalexin and kanamycin were mainly excreted via milk during milking. The highest concentrations of kanamycin A in milk were detected 12 hours after the first dose, with concentrations ranging between 6360 to 34500 µg/kg. Kanamycin A concentrations peaked again after the second dose administration with residues detected in the range of 3790 to 22800 µg/kg. The highest concentrations of cefalexin in milk were detected at 36 hours, with concentrations ranging between 510 µg/kg and 4601µg/kg.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

None known.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

5.3 Special precautions for storage

The veterinary medicinal product does not require any special storage conditions.

5.4 Nature and composition of immediate packaging

Cardboard box with 10 or 20 single use intramammary syringes and 10 or 20 disinfecting towels (containing isopropanol 70 %).
Each 10 g syringe contains 12 ml intramammary suspension and consists of a barrel with plunger and sealed sterile tip, all made of low density polyethylene.
Not all pack sizes may be marketed.

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

Boehringer Ingelheim Vetmedica GmbH

7. MARKETING AUTHORISATION NUMBER(S)

VPA10454/016/001

8. DATE OF FIRST AUTHORISATION

26/10/2007

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

09/09/2025

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).