Approved Package Insert

VETERINARY MEDICINE

SCHEDULING STATUS S4

PROPRIETARY NAME (and dosage form)

UBROSTAR (Dry Cow Intramammary Suspension)

COMPOSITION

Each 4,5 g intramammary syringe contains:

Penethamate hydriodide, micronized: 100 mg equivalent to 77,2 mg penethamate,

Benethamine penicillin, micronized: 280 mg equivalent to 171,6 mg penicillin,

Framycetin sulphate, micronized: 100 mg equivalent to 71,0 mg framycetin

Exipients: aluminium monostearate, hydrogenated castor oil and liquid paraffin

PHARMACOLOGICAL CLASSIFICATION

C 16.1 Intra-mammary preparations

PHARMACOLOGICAL ACTION Pharmacodynamic properties

Benethamine benzylpenicillin is the N-benzyl-2-phenylethylamine salt of benzylpenicillin, designed as a long-acting formula of benzylpenicillin. Penethamate is a prodrug from which benzylpenicillin and diethylaminoethanol are released by hydrolysis. Antibacterial activity is derived exclusively from benzylpenicillin.

The free benzylpenicillin is effective chiefly against a variety of Gram-positive pathogens, excluding β-lactamase producing staphylococci. Penicillins have a bactericidal effect on replicating bacteria by inhibiting cell wall synthesis. The bacterial activity is time dependent. Framycetin, also known as neomycin B, is a bactericidal aminoglycoside antibiotic. Inhibition of bacterial protein synthesis and presumed interference with permeability at the cell membrane play a role in effecting bacterial cell death. Its action spectrum encompasses numerous Gram-negative and some Gram-positive bacteria.

In-vivo efficacy of the combination of benzylpenicillin and framycetin has been demonstrated against: *Staphylococcus* spp., *Streptococcus* spp., *Arcanobacterium* spp., (*Corynebacterium* spp.), *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas* spp.

In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Pharmacokinetic properties

Absorption:

Penethamate penetrates the mammary glands more readily than benzylpenicillin, as it is able to pass through the lipophilic membranes. In contrast, benethamine penicillin is poorly absorbed due to its high degree of ionisation, therefore slowing down its passage through the lipophilic membranes of mammary glands. In addition, framycetin sulphate and neomycin is also poorly absorbed from the udder.

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Distribution:

Benzylpenicillin is distributed widely throughout the body, but concentrations in various fluids and tissues differ greatly. Due to their polar nature, aminoglycosides are largely excluded from most cells, the central nervous system and the eye. Approximately 60 % of benzylpenicillin in plasma is reversibly bound to albumin, while there is negligible binding of framycetin to plasma albumin.

Metabolism:

Benzylpenicillin is metabolized to some extend by hydrolysis of the β-lactam ring and the metabolites are microbiologically inactive, therefore metabolism is considered to be of little importance in the elimination of most penicillins. Aminoglycosides are generally excreted unchanged.

Elimination:

Under normal conditions, benzylpenicillin is rapidly eliminated from the body, predominately by the kidney and to a lesser extent in the bile and by other routes. Approximately 60 to 90 % of an intramuscular dose of benzylpenicillin in aqueous solution is eliminated via the urine, largely within the first hour after injection. The aminoglycosides are also excreted almost entirely by the kidney. A large fraction of a parentally administered dose is excreted unchanged during the first 24 hours with most appearing in the first 12 hours.

The pharmacokinetic behaviour of the active substances in the plasma and milk of 70 animals administered UBROSTAR during a pharmacokinetic study, can be summarised as follows: the mean peak plasma concentration (Cmax) of benzylpenicillin was 14,77 ng/mL, achieved at a mean Tmax of 22 hours, indicating slow systemic absorption. Milk concentrations of benzylpenicillin were below the limit of detection in most cows by the first post-treatment milking (approximately 12 hours), with quantifiable concentrations (1,2 – 3,5 ng/g) measured in eight of 24 cows at the first milking. Systemic absorption of framycetin was extremely low with quantifiable concentrations (55,6 – 74,8 ng/mL) measured only 12 – 24 hours, in three animals. No pharmacokinetic parameters (e.g. Cmax or AUC) could be calculated from these data, but the data suggest a Tmax of approximately 24 hours. Milk concentrations of framycetin were below detection in most cows by the first post-treatment milking (approximately 12 hours), with quantifiable concentrations (252,4 ng/g – 781,9 ng/g) measured in 11 of 24 cows at the first milking. The penicillin component of UBROSTAR will remain in the dry udder for up to 3 weeks. In the majority of cows, the framycetin components will remain in the dry udder for 10 weeks, or until calving.

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INDICATIONS

Target species: Cattle (at dry off)

For the treatment of subclinical mastitis at drying off, and the prevention of new bacterial infections of the udder during the dry period in dairy cows, caused by bacteria susceptible to penicillin and framycetin.

CONTRAINDICATIONS

Do not use in lactating cows.

Do not use in case of hypersensitivity to the active substances or any of the excipients.

WARNINGS and SPECIAL PRECAUTIONS

Special Warnings:

Where there is a risk of summer mastitis, additional management procedures, such as fly control should be considered.

Special precautions for use

i) Special precautions for use in animals:

Use of **UBROSTAR** 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.

ii) *Special precautions to be taken by the person administering the **UBROSTAR** to animals:*

Skin sensitisation may occur in persons handling **UBROSTAR**; care should be taken to avoid contact with skin.

Penicillins and cephalosporins may cause hypersensitivity following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.

1. Do not handle **UBROSTAR** if you know that you are sensitised, or if you have been advised not to work with such preparations.
2. Handle **UBROSTAR** with care (especially persons with skin damage) to avoid exposure. Wear gloves, wash hands in case of contact with skin.
3. If you develop symptoms such as a skin rash following exposure, seek medical advice and show this warning to your doctor. Swelling of the face, lips or eyes, or difficulty breathing are more serious symptoms and require urgent medical attention.

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Withdrawal period:

Meat and offal:

10 days

Milk:

If treated at least 35 days before calving, milk must not be used for 36 hours after calving.

If treated less than 35 days before calving, milk must not be used for 37 days after treatment.

PREGNANCY AND LACTATION

Pregnancy:

Can be used during pregnancy

Lactation:

Do not use during lactation

DOSAGE AND DIRECTIONS FOR USE

Intramammary administration of 100 mg penethamate hydriodide, 280 mg benethamine penicillin and 100 mg framycetin sulphate into each quarter, i.e. the contents of one syringe to be infused into each quarter immediately after last milking of a lactation

Advice on correct administration:

Before infusion, the teats should be thoroughly cleaned and disinfected, and care should be taken to avoid contamination of the injector nozzle. Following infusion, it is advisable to use a teat wipe or spray.

SIDE EFFECTS

None known.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

KNOWN SIGNS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Not applicable

IDENTIFICATION

UBROSTAR intramammary suspension is a white to off-white homogeneous sterile suspension in a plastic injector.

PRESENTATION

Pre-printed cardboard box or plastic container containing 20 or 60 single use intramammary syringes and 20 or 60 teat wipes (containing isopropanol 70 %).

Each 4,5 g syringe (white cylinder with white piston and orange cap, all made of low density polyethylene) contains 5 mL intramammary suspension.

Not all pack sizes may be marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C.

Keep out of reach of children and uninformed persons.

Disposal of unused product or waste material:

Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

REGISTRATION NUMBER

C 17/16.1/05 (Act 101/1965)

NAME AND BUSSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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