

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.

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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 extent 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.

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The pharmacokinetic behaviour of the active substances in the plasma and milk of animals administered UBROSTAR during a pharmacokinetic study, can be summarised as follows: the mean peak plasma concentration (C_{max}) of benzylpenicillin was 14,77 ng/mL, achieved at a mean T_{max} 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. C_{max} or AUC) could be calculated from these data, but the data suggest a T_{max} 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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90 **INDICATIONS**

91 **Target species:** Cattle (at dry off)

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

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96 **CONTRAINDICATIONS**

97 Do not use in lactating cows.

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

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100 **WARNINGS and SPECIAL PRECAUTIONS**

101 **Special Warnings:**

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

104 **Special precautions for use**

105 *i) Special precautions for use in animals:*

106 Use of **UBROSTAR** should be based on susceptibility testing of the bacteria isolated from the
107 animal. If this is not possible, therapy should be based on local (regional, farm

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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

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148 **Advice on correct administration:**

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

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153 **SIDE EFFECTS**

154 None known.

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

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158 **KNOWN SIGNS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

159 Not applicable

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161 **IDENTIFICATION**

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

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165 **PRESENTATION**

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

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

170 Not all pack sizes may be marketed.

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172 **STORAGE INSTRUCTIONS**

173 Store at or below 25 °C.

174 Keep out of reach of children and uninformed persons.

175 **Disposal of unused product or waste material:**

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

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179 **REGISTRATION NUMBER**

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

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182

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

184 Boehringer Ingelheim Animal Health South Africa (Pty) Ltd

185 Suite 2, Building 4, 2nd Floor, Waterfall Corporate Campus

186 74 Waterfall Drive

187 Midrand

188 2066

189 South Africa

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191 **DATE OF THE PUBLICATION OF THE PACKAGE INSERT**

192 23 August 2022

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