1. NAME OF THE VETERINARY MEDICINAL PRODUCT

PROBENCIL 300 mg/ml suspension for injection for cattle and pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Procaine Benzylpenicillin …….. 300 mg

Excipients:

Sodium methyl parahydroxybenzoate (E219) …… 1.25 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suspension for injection.
White suspension.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and pigs.

4.2 Indications for use, specifying the target species

For the treatment of systemic infections in cattle and pigs caused by bacteria sensitive to penicillin

4.3 Contraindications

Do not inject intravenously.
Do not use in cases of hypersensitivity to penicillins, cephalosporins, procaine or to any of the excipients.
Do not use in case of severe renal dysfunction with anuria and oliguria.
Do not use in the presence of β-lactamase producing pathogens.
Do not use in very small herbivores such as guinea pigs, gerbils and hamsters.

4.4 Special warnings for each target species

After absorption, benzylpenicillin poorly penetrates biological membranes (e.g., blood-brain barrier) since it is ionised and poorly lipid soluble. Use of the product for treatment of meningitis or CNS infections due to e.g., *Streptococcus suis* or *Listeria monocytogenes* may not be efficacious. Furthermore, benzylpenicillin penetrates mammalian cells poorly and hence this product may have little effect in treating intracellular pathogens e.g., *Listeria monocytogenes*.

Elevated MIC values or bi-modal distribution profiles suggesting acquired resistance have been reported for the following bacteria:

- *Glaesserella parasuis*, *Staphylococcus* spp. causing MMA/PPDS, *Streptococcus* spp. and *S. suis* in pigs;
- *Fusobacterium necrophorum* causing metritis and *Mannheimia haemolytica* (only in some member states), as well as *Bacteroides* spp., *Staphylococcus chromogenes*, *Actinobacillus lignieresii* and *Trueperella pyogenes* in cattle.

Use of the veterinary medicinal product may result in a lack of clinical efficacy when treating infections caused by these bacteria.

4.5 Special precautions for use

Special precautions for use in animals

Administer by deep injection only.
The 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, farm level) epidemiological information about susceptibility of the target bacteria.
Official, national and regional 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 penicillins and cephalosporins due to the potential for cross-resistance.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Penicillin and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillin may lead to cross sensitivity to cephalosporins and vice versa. Allergic reaction to these substances may occasionally be serious.
1. Do not handle this product if you know you are sensitised or if you have been advised not to work with such preparations.
2. Handle this product with great care to avoid exposure, taking all recommended precautions.
3. If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips and eyes or difficulty with breathing are more serious symptoms and require urgent medical attention.

In case of accidental eye contact, rinse thoroughly with water.
In case of accidental skin contact wash exposed skin thoroughly with soap and water.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

4.6 Adverse reactions (frequency and seriousness)

In suckling and fattening pigs pyrexia, vomiting, shivering, listlessness and incoordination have been reported rarely, which may be caused by the release of procaine.
Systemic toxic effects have been observed in young piglets, which are transient but can be potentially lethal, especially at higher doses.
In pregnant sows and gilts a vulvar discharge which could be associated with abortion has been reported rarely.
In cattle anaphylactic reactions have been reported rarely, which may be caused by the content of povidone.

Penicillins and cephalosporins may cause hypersensitivity (allergy) following administration of the product. Allergic reactions to these substances may occasionally be serious.

In case of side effects the animal has to be treated symptomatically.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reactions)
- 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

Laboratory studies in animals have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.
The safety of the veterinary medicinal product has not been established during pregnancy and lactation. However in pregnant sows and gilts a vulvar discharge which could be associated with abortion has been reported.
Use during pregnancy and lactation only accordingly to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

The bactericidal efficacy of penicillin is counteracted by bacteriostatic medicinal products.
The effect of aminoglycosides can be enhanced by penicillins.
The excretion of benzylpenicillin is prolonged by acetylsalicylic acid.
Cholinesterase inhibitors delay the degradation of procaine.

4.9 Amounts to be administered and administration route

For intramuscular use. Shake well before use.
The recommended dosage rate is 10 mg/kg bodyweight procaine benzylpenicillin equivalent to 1 ml per 30 kg bodyweight daily. The treatment duration is 3 to 7 days..
Do not inject more than 2.5 ml per injection site in pigs.
Do not inject more than 12 ml per injection site in cattle.

The appropriate treatment duration should be chosen based on the clinical needs and individual recovery of the treated animal. Consideration should be given to the accessibility of the target tissue and characteristics of the target pathogen.

If no distinct clinical response is seen within 3 days, redetermine the diagnosis and change the treatment if necessary.

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.

The cap may be safely punctured up to 50 times.

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

In the case of overdose, central nervous symptoms and/or convulsions may occur.

4.11 Withdrawal periods

Pigs
Meat and offal: 6 days for treatment duration 3-5 days.
8 days for treatment duration 6-7 days.

Cattle:
Meat and offal: 6 days for treatment duration 3-5 days.

8 days for treatment duration 6-7 days.
Milk: 96 hours (4 days).

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Beta-lactamase-sensitive penicillins
ATC vet code: QJ01CE09

5.1 Pharmacodynamic properties

Procaine benzylpenicillin is a β-lactam antibiotic that is included in the group G natural penicillins, for exclusively parenteral administration and of reduced spectrum.

It has a fundamentally bactericidal action against most Gram-positive bacteria and a limited number of Gram-negative bacteria, including the following microorganisms in its spectrum of action:

Gram-positive bacteria: *Trueperella pyogenes, Erysipelothrix rhusiopathiae, Listeria spp., Staphylococcus spp.* (non-penicillinase producing) and *Streptococcus spp.*
Gram-negative bacteria: *Pasteurella multocida* and *Mannheimia haemolytica*.

Mechanism of action: It exerts its effect on multiplying bacteria blocking the biosynthesis of the bacterial wall. It is fixed by covalent binding after opening of the β-lactam nucleus on certain enzymatic proteins PBP (transpeptidase).

Resistance: some microorganisms become resistant by R plasmid-mediated production of β-lactamases, which break the β-lactam ring of the penicillins, making them inactive.

Enterobacterales, *Bacteroides fragilis*, most *Campylobacter* spp., *Nocardia* spp. and *Pseudomonas* spp. as well as beta-lactamase–producing *Staphylococcus* spp. are resistant.

Clinical breakpoints for penicillins based on European Committee on Antimicrobial Susceptibility Testing, version 8.1, 2018:

Bacterial groups	**MIC breakpoint (µg/ml)**	
	Susceptible	**Resistant**
Listeria spp.	S≤1	R>1
Pasteurella multocida	S≤0.5	R>0.5
Staphylococcus spp.	S≤0.125	R>0.125
Streptococcus spp.	S≤0.25	R>0.25

In the case on *Mannheimia haemolytica, Trueperella pyogenes, Erysipelothrix rhusiopathiae* no breakpoints have been determined.

The following Minimum Inhibitory Concentrations (MIC) have been determined for benzylpenicillin in target bacterias isolated from diseased animals according to European Committee on Antimicrobial Susceptibility Testing, version 8.1, 2018:

Organisms	**MIC range (µg/ml)**	**MIC_{90} (µg/ml)**
Listeria spp.	≤ 1-1	≤0.5
Mannheimia haemolytica	ND	ND
Pasteurella multocida	≤ 0.5-0.5	≤0.25
Staphylococcus spp.	≤ 0.125-0.125	ND
Streptococcus spp.	≤ 0.25-0.25	ND
Trueperella pyogenes	ND	ND

Erysipelothrix rhusiopathiae	ND	ND

ND: not determined.

5.2 Pharmacokinetic particulars

In pigs after a single intramuscular dose of 10 mg/kg body weight (bw), maximum plasma concentrations of 2.78 µg/mL were reached after 1 hour; the terminal elimination half-life (t½) was 2.96 hours.

In cattle after a single intramuscular dose of 10 mg/kg body weight (bw), maximum plasma concentrations of 0.65 µg/mL were reached after 2 hours; the terminal elimination half-life (t½) was 5.91 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lecithin
Sodium methyl parahydroxybenzoate (E219)
Sodium citrate
Disodium edetate
Povidone
Carmellose sodium
Citric acid monohydrate
Water for injections

6.2 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 28 days at 2 ºC-8 ºC.

6.4. Special precautions for storage

Store in a refrigerator (2 ºC-8 ºC).
Keep the vial in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

100 ml and 250 ml colourless polyethylene terephthalate (PET) bottles with type I bromobutyl rubber stoppers and flip-off caps.

Pack sizes:
Carton box with 1 vial of 100 ml
Carton box with 1 bottle of 250 ml

Not all pack sizes may be marketed.

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

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

MEVET S.A.U.

8. MARKETING AUTHORISATION NUMBER(S)

VPA22009/001/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/05/2019

10. DATE OF REVISION OF THE TEXT

28/03/2024

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.