SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Parofor 140 mg/ml solution for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 ml:

Active substance:

Paromomycin sulfate	200 mg, equivalent to paromomycin base 140 mg or 140.000 IU of paromomycin activity

Excipients:

Methyl parahydroxybenzoate (E218)	1.0 mg
Propyl parahydroxybenzoate	0.1 mg
Sodium metabisulphite (E223)	4.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water, milk or milk replacer.
A clear yellow to amber solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (pre-ruminant calves), pigs.

4.2 Indications for use, specifying the target species

Treatment of gastro-intestinal infections caused by *Escherichia coli*.

4.3 Contraindications

Do not use in animals with hypersensitivity to paromomycin, other aminoglycosides or any of the excipients.
Do not use in cases with impaired function of the kidneys or liver.
Do not use in ruminating animals.
Do not use in turkeys due to the risk of selection for antimicrobial resistance in intestinal bacteria.

4.4 Special warnings for each target species

Cross-resistance has been shown between paromomycin and some antimicrobials in the aminoglycosides class in Enterobacterales. Use of the product should be carefully considered when susceptibility testing has shown resistance to aminoglycosides because its effectiveness may be reduced.

4.5 Special precautions for use

Special precautions for use in animals

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water/milk animals should be treated parenterally using a suitable injectable product following the advice of the veterinarian.
The use of the product should be combined with good management practices e.g. good hygiene, proper ventilation, no overstocking.
Since the product is potentially ototoxic and nephrotoxic, it is recommended to assess kidney function.
Special care should be taken when considering administration of the product to newborn animals due to the known higher gastrointestinal absorption of paromomycin in neonates. This higher absorption could lead to an increased risk of oto- and nephrotoxicity. The use of the product in neonates should be based on a benefit/risk assessment by the responsible veterinarian.
Prolonged or repeated use of the product should be avoided by improving management practices and through cleansing and disinfection.
Use of the product should be based on identification and susceptibility testing of the target pathogen(s) isolated from the animal. If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogen at farm level or at local/regional level. Use of the product should be in accordance with official, national and regional antimicrobial policies.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for crossresistance.
Aminoglycosides are considered as critical in human medicine. Consequently, they should not be used as a first line treatment in veterinary medicine.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
This product contains paromomycin, which can cause allergic reactions in some people.
People with known hypersensitivity (allergy) to paromomycin or any other aminoglycosides should avoid contact with the product.
Avoid contact with the skin and eyes.
Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product.
In the event of accidental contact with the skin or eyes, rinse with plenty of water.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Do not eat, drink and smoke when handling the product.
Do not ingest. In case of accidental ingestion, seek medical advice immediately and show the label to the physician.
Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

On rare occasions soft faeces have been observed.
Aminoglycoside antibiotics such as paromomycin can cause oto- and nephrotoxicity.
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

Laboratory studies in the rat and rabbit have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects. The use is not recommended during pregnancy.

4.8 Interaction with other medicinal products and other forms of interaction

General anaesthetics and muscle relaxing products increase the neuro-blocking effect of aminoglycosides. This may cause paralysis and apnoea.
Do not use concurrently with strong diuretics and potentially oto- or nephrotoxic substances.

4.9 Amounts to be administered and administration route

Oral use.
Pre-ruminant cattle:
For administration in milk/milk replacer.
25-50 mg paromomycin sulfate per kg BW/day (equivalent to 0.125 – 0.25 ml of product/kg BW/day).
Duration of treatment: 3-5 days.

Pigs:
For administration in drinking water.
25-40 mg paromomycin sulfate per kg BW/day (equivalent to 0.125 – 0.2 ml of product/kg BW/day).
Duration of treatment: 3-5 days.

To ensure accurate measurement of the required volume of product, suitably calibrated measuring equipment should be used.
For administration via drinking water, milk or milk replacer, the exact daily amount of product should be calculated, based on the recommended dose, and the number and weight of the animals to be treated, according to the following formula:

$$\frac{\text{ml product / kg body weight / day} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water/milk/milk replacer consumption (litre) per animal}} = \text{.... ml product per liter drinking water /milk/milk replacer}$$

To ensure a correct dosage body weight should be determined as accurately as possible.
The uptake of medicated water/milk /milk replacer depends on several factors including clinical conditions of the animals and the local conditions such as ambient temperature and humidity. In order to obtain the correct dosage, drinking water/milk/milk replacer uptake has to be monitored and the concentration of paromomycin has to be adjusted accordingly.
Medicated drinking water/milk/milk replacer and any stock solutions should be freshly prepared by carefully mixing the product in the requisite quantity of fresh potable water /milk/milk replacer every 6 hours (in milk/milk replacer) or every 24 hours (in water).

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

Paromomycin when administered orally is hardly absorbed systemically. Harmful effects due to accidental overdosing are highly unlikely.

4.11 Withdrawal period(s)

Pre-ruminant cattle
Meat and offal: 20 days
Pigs
Meat and offal: 3 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: intestinal anti-infective; antibiotics.
ATC vet code: QA07AA06.

5.1 Pharmacodynamic properties

Paromomycin belongs to the group of aminoglycoside antibiotics. Paromomycin changes the reading of messenger-RNA, which disrupts protein synthesis. The bactericidal activity of paromomycin is mainly attributed to its irreversible binding to ribosomes. Paromomycin has broad spectrum activity against numerous Gram-positive and Gram-negative bacteria, including *E. coli*.
Paromomycin acts in a concentration-dependent manner. Five mechanisms of resistance have been identified: changes of the ribosome due to mutations, reduction of permeability of bacterial cell wall or active efflux, enzymatic modification of ribosomes and inactivation of aminoglycosides by enzymes. The first three resistance mechanisms arise from mutations of certain genes on bacterial chromosomes. The fourth and fifth resistance mechanism only occurs following uptake of genetic elements coding for resistance. Paromomycin selects for resistance and cross-resistance to other aminoglycosides at a high frequency in intestinal bacteria.

Prevalence of resistance of E.coli to paromomycin seemed relatively stable between 2015 to 2020 when extrapolating MIC data for neomycin in different European countries and was around 30-40% for calves pathogens.

5.2 Pharmacokinetic properties

Following oral administration of paromomycin, hardly any absorption takes place and the molecule is eliminated unchanged via the faeces.

5.3 Environmental properties

The active ingredient paromomycin sulfate is very persistent in the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate
Sodium metabisulfite (E223)
Purified water

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: 2 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours
Shelf life after reconstitution in milk/milk replacer: 6 hours

6.4 Special precautions for storage

Product as packed for sale: do not store above 25°C.
After first opening: do not store above 25°C.
After reconstitution: there are no special restrictions on storage conditions.

6.5 Nature and composition of immediate packaging

White high density polyethylene bottle with tamper-evident screw polypropylene closure of 125 ml, 250 ml, 500 ml and 1 L.
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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

8. MARKETING AUTHORISATION NUMBER

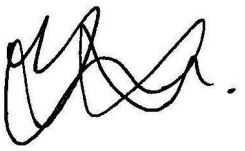
Vm 30282/4033

9. DATE OF FIRST AUTHORISATION

25 July 2017

10. DATE OF REVISION OF THE TEXT

August 2022



Approved: 04 August 2022