HUVEPHARMA®

Parofor® 70 mg/g

PAROMOMYCIN (AS SULPHATE)

Indications for use

Pre-ruminant calves:
Treatment of gastro-intestinal infections caused by ***Escherichia coli*** susceptible to paromomycin.

Origin of the molecule

Paromomycin was first isolated from culturable filtrates of *Streptomyces chrestomyceticus* and was initially named "aminosidine". Paromomycin belongs to the class of aminoglycosides with expanded spectrum, which means that it has activity against several Gram-positive as well as against many Gram-negative bacteria. Next to its antibacterial activity, the molecule also garnered widespread attention for its antiprotozoal properties. (Alejandro Grinberg, 2002; E.H. Johnson, 2000; Viu *et al.*; 2000; Grinberg et al., 2002)

Structure and activity

Paromomycin sulphate is a broad spectrum antibiotic and belongs to the group of aminoglycosides. Aminoglycosides are made up of amino groups (–NH2) attached to glycosides. The chemical structure of paromomycin and its formulation make Parofor® very stable and water-soluble (> 40g/100 ml).

Paromomycin is a cation that binds passively to negatively charged portions of the outer membranes of gram-negative bacteria and displaces cell wall Mg^{2+} and Ca^{2+} that link lipopolysaccharide molecules. The result is alteration of the cell envelope and explains the fast bactericidal activity of the molecule. In addition, paromomycin binds to the 16 rRNA of 30S subunits of ribosomes. This interaction causes termination and miscoding of protein synthesis, with subsequent bacterial cell death. This dual activity explains its rapid and broad bactericidal activity.

Product categorization and use

Parofor® water-soluble powder is for use in drinking water or milk replacer. One gram of veterinary medicinal product contains 100 mg of paromomycin sulphate (= 70 mg paromomycin as base).

Pharmacodynamics

Pharmocodynamic principles associated with paromomycin include concentration-dependent bactericidal activity.

<u>Concentration-dependent:</u> Paromomycin is rapidly bactericidal and its rate and extent of bacterial killing increases as the paromomycin concentration increases. Exposure of bacteria to a single 24-hour dose results in faster and greater extent of bactericidal activity than that noted for the same dose administered in divided doses. Clinical efficacy for infections caused by Gram-negative bacteria is increased by 50 to 90% if the C_{max}/MIC goes from 2 to 12. (Moore, 1987).

Pharmacokinetics

Paromomycin is poorly absorbed from the gastro-intestinal tract and is not inactivated by organic material, remaining in active form in the intestinal lumen. Oral application gives high concentrations in the intestinal lumen and a broad safety margin. Only unpaired gastro-intestinal motility or lesions, or ulcerations of the intestine may facilitate the absorption of the drug. Any absorbed drug is slowly excreted in the urine.

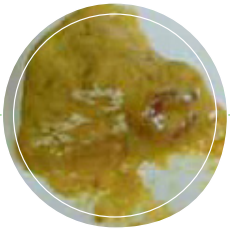
Keypoints:

1. Bactericidal.
2. Concentration-dependent activity, which means that the rate and extent of bacterial killing increases as the drug concentrations increase.

Diarrhoea in calves caused by gastro-intestinal infections

Disease

Calf diarrhoea is an extremely common event, especially in the first four weeks of life. It can cause serious economic harm: directly, through the death of calves and the cost of treatment for affected animals; and indirectly, due to retarded weight gain following the illness.



Cause

Most studies show that bovine Rotavirus, *Cryptosporidium parvum*, enterotoxigenic *Escherichia coli* and bovine Coronavirus are the major causes of diarrhoea.

Causative agent	Samples examined	% Positive samples
Rotavirus	246	32%
Cryptosporidium parvum	297	31%
Escherichia coli	171	15%
Coronavirus	252	12%

Table. Enteropathogens isolated in subjects with neonatal enteritis by the Vicenza Regional Section of the Venezie Animal Health Testing Institute between 2005 and 2007.

Diagnosis

From a clinical point of view, the key elements involved in making a clinical diagnosis are the age of onset of the diarrhoea and the characteristics of the faeces.

Etiology	Age	Faeces	Symptoms
Rotavirus	5 to 15 days	White pasty diarrhoea. Mucus	Sometimes fever
Cryptosporidium spp.	4 to 28 days	Liquid and yellowish.	Depression, dehydratation, anorexia. Fever and tenesmus possible
E. coli *ETEC	< 3 days until 14 days	Watery	Accumulation of liquid in the abdomen, fever or hypothermie possible
*AEEC and STEC	2 to 4 days	Watery, presence of mucus	Abdominal pain, dehydratation, bruxism
Coronavirus	5 to 30 days	Mucohemorrhagic enterocolitis	First depression and anorexia Severe infection: dehydration, acidose, shock and a heart failure can cause death. Also respiratory symptoms

* *ETEC: Enterotoxigenic E. coli; AEEC: Attaching and Effacing E. coli, STEC: Shiga Toxin producing E. coli*

However, in cases of neonatal gastro-intestinal infections it is always advisable to confirm the diagnosis. The BIO-X calf diagnostic kit is able to distinguish the mentioned four major causes of diarrhoea:

- Rotavirus
- *Cryptosporidium*
- *Escherichia coli* F55 (K99).
- Coronavirus

Procedure:

Step 1	Take a sample of the stool
Step 2	Dilute with the liquid contained in the bottle
Step 3	Homogenize by softly shaking
Step 4	Plunge a strip into liquid
Step 5	Wait 10 minutes and read the result

Step 1 Step 2 Step 3 Step 4 Step 5

General

Treatment:

- Is based on rehydration and the supply of buffers and energy.
- In case of a bacterial enteritis, antibiotic treatment is advised.

For prevention and control:

- It is important to decrease the exposure of calves to pathogens.
- Ensure adequate colostrum intake and supply.

Bacteria

Escherichia coli and *Salmonella*

- Restore fluid, base, glucose deficits
- Antimicrobial treatment: elements that should be taken into consideration are the following:
  - ▶ Susceptibility of the bacterium
    - ➤ Product with a Gr- spectrum
  - ▶ Level of fast action:
    - ➤ Bactericidal effect
- Concentration reached in the intestinal lumen
  - ▶ In case of sufficient water/milk intake: oral application is recommended for treatment of bacterial enteritis.
- In case of septicemia: a systemic antibiotic is advised *(Salmonella, E. coli).*

Viral

To improve the passive immunisation of calves against rota- and coronavirus, vaccination of the pregnant dam can be proposed.
Usually cows are vaccinated twice before parturition to stimulate the production of specific antibodies. This management strategy can only be successful if colostrum management as well as hygiene is improved.

Protozoa:Cryptosporidium

- Halofuginone lactate is registered for treatment of Cryptosporidium in calves at a dose rate of 100 µg/ kg bodyweight. For preventive treatment, halofuginone should be administered within 48 h after parturition, and for curative treatment, within 24 h after the onset of the clinical symptoms. Toxicity can be observed at a dose rate of 500 µg/ kg.

Mentioned in literature, although not registered:

- Prophylaxis and treatment with paromomycin sulphate is effective in preventing oocyst excretion, clinical signs and mortality. (Fayer and Ellis, 1993b; Mancassola *et al.*, 1995; Viu *et al.*, 2000)
- Sulphamidine and decoquinate have been tested with no, or limited, reduction of oocyst excretion. (Joachim *et al.*, 2003; Moore *et al.*, 2003)

TREATMENT OF ENTERITIS CAUSED BY *ESCHERICHIA COLI*

The therapy of gastrointestinal disorders focuses on locating the disease in a segment of the digestive tract and determining its cause.

In case of *Escherichia coli:*

- location: intestinal lumen

Product	Parofor®: paromomycin
Sensitivity Gr-	+++
Extended activity	+++
Fast activity	+++
Bactericidal	+++
Concentration intestine	+++

Parofor® water-soluble powder is registered for the treatment gastro-intestinal infections caused by *Escherichia coli* sensitive to paromomycin.

Recommendation for non-ruminating calves:

25-**50 mg** paromomycin sulphate/ kg bodyweight per day, for 3-**5 days.**

Keypoints of Parofor®:

- **Bactericidal activity: dual mode of action**
  - ➤ Destroying bacterial cell wall
  - ➤ Interfering with bacterial protein synthesis
- **Low oral absorption:**
  - ➤ High concentrations in the intestinal lumen
  - ➤ Safe
- **Highly active against Gr-bacteria.**

source Milk@vice

Contraindications

Do not use in animals with known 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.

Adverse reactions

In rare occasions soft faeces has been observed.
Aminoglycoside antibiotics such as paromomycin can cause phenomena such as oto- and nephrotoxicity.
If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

Special warnings

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.
Do not use in newborns (calf, piglet) due to higher absorption of paromomycin and subsequently an increased risk of oto- and nephrotoxicity.
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 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 paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for crossresistance. Paromomycin selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria.
Aminoglycosides are considered as critical in human medicine. Consequently, they should not be used as a first intention treatment in veterinary medicine.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
People with known hypersensitivity to aminoglycosides should avoid contact with the veterinary medicinal product.
Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product.
Do not eat, drink and smoke when handling the product. Wash hands after use. In case of accidental ingestion, seek medical advice immediately and show the label to the physician
When handling this product, inhalation of the dust must be avoided by wearing a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.
Use in a well-ventilated area. Avoid inhaling the powder while preparing the medicated water or milk replacer. Avoid contact with the skin and eyes. In the event of accidental contact with the skin or eyes, rinse with plenty of water and seek medical attention if irritation persists.

Amount(s) to be administered and administration route

Administration route: oral

- Non-ruminating calves: administration in milk.
  25-50 mg paromomycin sulphate/kg bodyweight/ day
- Pigs: administration in drinking water.
  25-40 mg paromomycin sulphate/kg bodyweight/ day

Duration of treatment: 3-5 days

Practical administration

For the administration through the 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:

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

Withdrawal period(s)

Meat and offal:
Calves: 20 days.
Pigs: 3 days.

Shelf life

- Shelf-life of the veterinary medicinal product as packaged for sale: 24 months.
- Shelf life after first opening the immediate packaging: 6 months.
- Shelf life after reconstitution in drinking water: 24 hours
- Shelf life after reconstitution in milk/milk replacer: 6 hours

Incompatibilities

None, as far as known

Packaging

Parofor® is packed in a block bottomed **zipped 1 kg bag.**

**Used references can be requested on demand.*
***Parofor® for use in drinking water and milk/ milk replacer brochure is following the authorized EU SPC (available at request).*
**** Indications listed above are not necessarily authorized in all countries. Please consult the local label for exact indications and posology.*

HUVEPHARMA®

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