1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Gabbrovet Multi 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [FR AT BE BG HR CY CZ EE DE EL HU IE IT LV LT LU NL PL PT RO SK SI ES IS UKNI]
Paromocrypto 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [DK]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Paromomycin (as sulfate): 140.0 mg
(equivalent to 140 000 IU of paromomycin activity)
(equivalent to approximately 200 mg of paromomycin sulfate)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol (E1519)	7.5 mg
Sodium metabisulfite (E223)	3.0 mg
Disodium edetate	Not applicable
Purified water	Not applicable

After dilution in water, clear colourless or light-yellow solution.
After dilution in milk, white to pale yellow liquid.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (pre-ruminant cattle and newborn calves) and pigs

3.2 Indications for use for each target species

Cattle (pre ruminant cattle):
Colibacillosis
Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin.

Cattle (newborn calves):
Cryptosporidiosis
Treatment of infections caused by diagnosed *Cryptosporidium parvum*, by reduction of diarrhoea and reduction of faecal oocyst shedding. Administration has to start within 24 hours after the onset of diarrhoea.

Pigs:
Colibacillosis
Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin.

3.3 Contraindications

Do not use in cases of hypersensitivity to paromomycin, to other aminoglycosides or to 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.

3.4 Special warnings

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

3.5 Special precautions for use

Special precautions for safe use in the target species:

The use of the veterinary medicinal 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 veterinary medicinal 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 veterinary medicinal product in calves of 5 days or less should be based on benefit-risk assessment by the responsible veterinarian.
As with any antiparasiticide, frequent and repeated use of antiprotozoals from the same class may lead to the development of resistance.
Use of the product should be in accordance with official, national and regional antimicrobial policies.

Colibacillosis
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 veterinary medicinal product following the advice of the veterinarian.
Prolonged or repeated use of the veterinary medicinal 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). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the veterinary medicinal product deviating from the given instructions may increase the prevalence of bacteria resistant to paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for cross-resistance.
Aminoglycosides are considered as critical in human medicine. Consequently, they should not be used as a first intention antimicrobial treatment in veterinary medicine.

Cryptosporidiosis
Calves should only receive the treatment upon confirmation of cryptosporidial oocysts in their faeces.
The product should only be used in individual animals.
Not for use for prophylaxis or metaphylaxis.
If applicable, antibiotic-free options should be preferred, in line with responsible use of antibiotics.
Do not use on an empty stomach. For treatment of anorexic calves, the product should be administered in half a litre of an electrolyte solution. The animals should receive enough colostrum according to good breeding practice.

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

This veterinary medicinal product contains paromomycin and benzyl alcohol, which can cause allergic reactions in some people.
People with known hypersensitivity (allergy) to paromomycin or any other aminoglycosides and/or benzyl alcohol should avoid contact with the veterinary medicinal product.
This product is slightly irritant to the eye. 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 ingest. In case of accidental ingestion, seek medical advice immediately and show the label to the physician.
Wash hands after use.
Do not eat, drink and smoke when handling the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle (pre-ruminant cattle and newborn calves) and pigs:

Rare (1 to 10 animals / 10,000 animals treated):	Soft faeces
Unknown frequencies	Aminoglycoside antibiotics such as paromomycin can cause oto- and nephrotoxicity.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy:
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.

3.8 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.

3.9 Administration routes and dosage

Oral use.
To ensure a correct dosage bodyweight should be determined as accurately as possible.

Cattle (pre-ruminant cattle):
Colibacillosis
Duration of treatment: 3-5 days.
Administration in milk/milk replacer.
Recommended dosage: 1.25 – 2.5 ml of veterinary medicinal product/10 kg BW/day, equivalent to 17500 - 35000 IU of paromomycin per kg BW/day (i.e. approximately 25-50 mg paromomycin sulfate per kg BW/day).

Cattle (newborn calves):
Cryptosporidiosis
Duration of treatment: 5 days.
Administration in milk/milk replacer or directly in the mouth using either a syringe or an appropriate device for oral administration.
Recommended dosage: 7.5 ml of veterinary medicinal product/10 kg BW/day for 5 consecutive days, i.e. 105000 IU of paromomycin per kg BW/day for 5 consecutive days (i.e. approximately 150 mg paromomycin sulfate per kg BW/day).
In case of insufficient uptake of milk, the totality of the remaining solution should be administered orally directly into the mouth of the animal.

Pigs:
Colibacillosis
Duration of treatment: 3-5 days.
Administration in drinking water.
Recommended dosage: 1.25 – 2 ml of veterinary medicinal product/10 kg BW/day, equivalent to 17500 - 28000 IU of paromomycin per kg BW/day (i.e. approximately 25-40 mg paromomycin sulfate per kg BW/day).

For the administration through the drinking water the exact daily amount of veterinary medicinal product should be based on the number of the animals to be treated, and the recommended dose calculated according to the following formula:

$$\frac{\text{ml product/ kg BW/day} \times \text{Mean bodyweight (kg) of animals to be treated}}{\text{Mean daily water consumption (litre) per animal}} = \text{ml product per litre drinking water/day/animal}$$

The uptake of medicated water 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, uptake of drinking water 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 every 6 hours (in milk/milk replacer) or every 24 hours (in water).

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

After administration of 1X, 2X and 3X the recommended dose for the treatment of cryptosporidiosis (150, 300 and 450 mg of paromomycin sulfate/kg) during 3 times the recommended duration (15 days), in newborn calves (5-13 days) histopathological kidney abnormalities has been observed in some calves. These abnormalities can be observed in calves without any treatment however a nephrotoxicity related to the treatment cannot totally be ruled out.
At 3X the recommended dose, administration to newborn calves induced a slight loss of appetite, reversible at the end of the treatment period. The decrease of the milk consumption had a limited impact on the body weight gain.

At 5X the recommended dose, administration to newborn calves induced severe inflammation of the gastrointestinal tract and necrozing inflammation of the urinary bladder. Repeated overdose (at 5X) may be associated with death.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Cattle (pre-ruminant cattle and newborn calves):
- Colibacillosis: Dosage: 25-50 mg/kg/day for 3 to 5 days. Meat and offal: 20 days
- Cryptosporidiosis: Dosage: 150 mg/kg/day for 5 days. Meat and offal: 110 days

Pigs: Meat and offal: 3 days

Due to the accumulation of paromomycin in the liver and kidneys, any repeated courses of treatment during the withdrawal period should be avoided.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QA07AA06

4.2 Pharmacodynamic

Colibacillosis
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-dependant manner. Five mechanisms of resistance have been identified: changes of the ribosomes 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 chromosome. The fourth and fifth resistance mechanism only occurs following uptake of mobile genetic elements coding for resistance. Paromomycin selects for resistance and cross-resistances at high frequency against a variety of other aminoglycosides among intestinal bacteria. Prevalence of resistance of *E. coli* to paromomycin was relatively stable between 2002 to 2015 and around 40% for bovine pathogens and 10% for porcine pathogens.

Cryptosporidiosis
Paromomycin has antiprotozoal activity, although its mechanism of action is unclear. In *in vitro* studies using HCT-8 and Caco-2 cell lines inhibitory activity against *C. parvum* was observed. Resistance of cryptosporidia to paromomycin has not been described to date. Nevertheless, the use of aminoglycosides is associated with the occurrence of bacterial resistance. Paromomycin may select for cross-resistance to other aminoglycosides.

4.3 Pharmacokinetic

The bioavailability of paromomycin when administered as a single oral dose of 150 mg paromomycin/kg bodyweight to 8 - 10 days old calves was 3.23 %.

With regard to the absorbed fraction, the mean peak plasma concentration (C_{max}) was 4.148 ± 3.106 mg/l, the median time to attain the peak plasma concentration (T_{max}) was 4.75 hours (2-12 h) and the mean terminal half-life ($t_{1/2}$) was about 10 hours. The main part of the dose is eliminated unchanged in the faeces while the absorbed fraction is excreted almost exclusively in urine as unchanged paromomycin.
Paromomycin displays age-related pharmacokinetics, with the greatest systemic exposure occurring in newborn animals.

Environmental properties

The active ingredient paromomycin binds strongly to soil and is very persistent in the environment.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale in high density polyethylene (HDPE) bottles:
- 125 ml: 1 year
- 250 ml: 18 months
- 500 ml: 2 years
- 1 L: 3 years

Shelf-life of the veterinary medicinal product as packaged for sale in high density polyethylene/ ethylene vinyl alcohol/ high density polyethylene (HDPE/EVOH/HDPE) bottles:
- 250 ml: 6 months
- 500 ml: 6 months
- 1 L: 6 months

Shelf life after first opening the immediate packaging :
- high density polyethylene (HDPE) bottles : 6 months
- high density polyethylene/ ethylene vinyl alcohol/ high density polyethylene (HDPE/EVOH/HDPE) bottles: 3 months

<u>All presentations</u>:
Shelf life after dilution in drinking water: 24 hours
Shelf life after dilution in milk or milk replacer: 6 hours

5.3 Special precautions for storage

<u>125 ml and 250 ml HDPE bottles:</u>
Do not store above 25°C.

<u>500 ml and 1-litre HDPE bottles:</u>
This veterinary medicinal product does not require any special storage conditions.

<u>250 ml, 500 ml and 1-litre HDPE/EVOH/HDPE bottles:</u>
This veterinary medicinal product does not require any special storage conditions.

<u>All presentations:</u>

After first opening, keep the bottle tightly closed.

5.4 Nature and composition of immediate packaging

Nature of container:

- White high density polyethylene (HDPE) bottles, with a polypropylene (PP) screw cap and a polyvinylchloride (PVC) or a low density polyethylene (LDPE) seal
  125, 250, 500 ml and 1 L bottles

or

- White high density polyethylene/ ethylene vinyl alcohol/ high density polyethylene (HDPE/EVOH/HDPE) bottles with a high density polyethylene (HDPE) screw cap and a polyethylene terephtalate/ polyethylene/ polyethylene foam/ polyethylene/ polyethylene terephtalate (PET/PE/LDPE foam/PE/PET) seal
  250, 500 ml and 1 L bottles

- Polypropylene (PP) dosing device of 30 ml graduated every 5 ml

Pack sizes:
Cardboard box containing 1 plastic bottle of 125 ml
Cardboard box containing 1 plastic bottle of 250 ml
Cardboard box containing 1 plastic bottle of 500 ml
Cardboard box containing 1 plastic bottle of 1 L
For each listed pack size, a 30 ml dosing device is joined.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater.
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Detailed information on this veterinary medicinal product is available in the Union Product Database.