ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton for 1 bottle of 125 ml
Outer carton for 1 bottle of 250 ml
Outer carton for 1 bottle of 500 ml
Outer carton for 1 bottle of 1 L

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

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains140.0 mg of paromomycin (as sulfate), equivalent to 140,000 IU of paromomycin activity or equivalent to approximately 200 mg of paromomycin sulfate.

3. PACKAGE SIZE

125 ml
250 ml
500 ml
1 L

4. TARGET SPECIES

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

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

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.

8. EXPIRY DATE

Exp:
For 125 ml, 250 ml, 500 ml and 1 L HDPE bottles:
Once opened, use within 6 months by __/__/__. Once diluted in drinking water, use within 24 hours. Once diluted in milk or milk replacer, use within 6 hours.

For 250 ml, 500 ml and 1 L HDPE/EVOH/HDPE bottles:
Once opened, use within 3 months by __/__/__. Once diluted in drinking water, use within 24 hours. Once diluted in milk or milk replacer, use within 6 hours.

9. SPECIAL STORAGE PRECAUTIONS

After first opening, keep the bottle tightly closed.
For 125 ml and 250 ml HDPE bottles: Do not store above 25° C.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

14. MARKETING AUTHORISATION NUMBERS

Vm 14966/3082

15. BATCH NUMBER

Lot:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Label for 1 bottle of 125 ml
Label for 1 bottle of 250 ml
Label for 1 bottle of 500 ml
Label for 1 bottle of 1 L

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

2. STATEMENT OF ACTIVE SUBSTANCES

1 ml contains140.0 mg of paromomycin (as sulfate), equivalent to 140,000 IU of paromomycin activity or equivalent to approximately 200 mg of paromomycin sulfate.

3. TARGET SPECIES

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

4. ROUTES OF ADMINISTRATION

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

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.

6. EXPIRY DATE

Exp:
For 125 ml, 250 ml, 500 ml and 1 L HDPE bottles:
Once opened, use within 6 months by __/__/__. Once diluted in drinking water, use within 24 hours. Once diluted in milk or milk replacer, use within 6 hours.

For 250 ml, 500 ml and 1 L HDPE/EVOH/HDPE bottles:

Once opened, use within 3 months by __/__/__. Once diluted in drinking water, use within 24 hours. Once diluted in milk or milk replacer, use within 6 hours.

7. SPECIAL STORAGE PRECAUTIONS

After first opening, keep the bottle tightly closed.
For 125 ml and 250 ml HDPE bottles: Do not store above 25° C.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

9. BATCH NUMBER

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET

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

2. Composition

Each ml contains:
Active substance: 140.0 mg of paromomycin (as sulfate), equivalent to 140,000 IU of paromomycin activity or equivalent to approximately 200 mg of paromomycin sulfate.
Excipients: 7.5 mg of benzyl alcohol (E1519) and 3.0 mg of sodium metabisulfite (E223).

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

3. Target species

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

4. Indications for use

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.

5. 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.

6. 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.

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.

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.

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.

Overdose:
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.

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

7. 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 product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

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).

9. Advice on correct administration

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).

10. 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.

11. Special storage precautions

Keep out of the sight and reach of children.

125 ml and 250 ml HDPE bottles:
Do not store above 25°C.
500 ml and 1-litre HDPE bottles:
This veterinary medicinal product does not require any special storage conditions.
250 ml, 500 ml and 1-litre HDPE/EVOH/HDPE bottles:
This veterinary medicinal product does not require any special storage conditions.
All presentations:
After first opening, keep the bottle tightly closed.

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

All presentations:
Shelf life after dilution in drinking water: 24 hours.
Shelf life after dilution in milk or milk replacer: 6 hours.

Do not use this veterinary medicinal product after the expiry date which is stated on the container after "Exp". The expiry date refers to the last day of that month.

12. Special precautions for disposal

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.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

MA: 14966/3082
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.

15. PID LINK (Do not print heading)

[The following statement must be included where reference to the European Union Product Database is included on the product information. This statement is relevant to both UK(GB) and UK(NI) products:]

Find more product information by searching for the 'Product Information Database' on www.gov.uk.

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

Ceva Sante Animale
8 rue de Logrono
33500 Libourne
France

Manufacturer responsible for batch release:
Ceva Santé Animale, Z.I. Très le Bois, 22600 Loudéac, France

17. Other information

Pharmacodynamic properties
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.

Pharmacokinetic particulars
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.

Gavin Hall
Approved: 11 November 2025