ANNEX III:

LABELLING AND PACKAGE LEAFLET

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE
COMBINED LABEL AND PACKAGE LEAFLET
Composite can, securitainer and bucket

1. Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different

Marketing authorisation holder:
Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer, NL

Manufacturer responsible for the batch release:
Dopharma B.V.
Zalmweg 24
4941 VX Raamsdonksveer, NL

2. Name of the veterinary medicinal product

COLDOSTIN, 4800000 IU/g, powder for use in drinking water/milk.
Colistin sulfate

3. Statement of the active substance(s) and other ingredients

Colistin sulfate 4 800 000 IU/g

4. Pharmaceutical form

Powder for use in drinking water/milk.

White to off-white powder.

5. Package size

100 gram, 1 kg,

6. Indication(s)

Treatment and metaphylaxis of enteric infections caused by non-invasive *Escherichia coli* susceptible to colistin sulfate.
In the case of metaphylaxis, the presence of the disease in the group must be established before the product is used.

7. Contraindications

Do not use in cases of hypersensitivity to colistin sulfate or to any of the excipients.
Do not use in cases of resistance to polymyxins.
Do not use in horses, particularly in foals, since colistin sulfate, due to a shift in the gastrointestinal microflora balance could lead to the development of antimicrobial

associated colitis (Colitis X), typically associated with *Clostridium difficile*, which may be fatal.

8. Adverse reactions

None known.

If you notice any side effects, even those not already listed in this label or you think that the medicine has not worked, please inform your veterinary surgeon.

9. Target species

Cattle (calves), sheep (lambs), pigs, chickens and turkeys.

10. Dosage for each species, route(s) and method of administration

Administration route: In drinking water/milk use.

Calves, lambs and pigs:
100 000 IU of colistin sulfate per kilogram body weight i.e. 1 g of product per 48 kg body weight daily for 3-5 consecutive days.

Chickens and turkeys:
75 000 IU of colistin sulfate per kilogram body weight i.e. 1 g of product per 64 kg body weight daily for 3-5 consecutive days.

Duration of treatment should be limited to the minimum time necessary for the treatment of the disease.

11. Advice on correct administration

For the administration through the drinking water, 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:

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

To ensure a correct dosage, body weight should be determined as accurately as possible to avoid underdosing.
The uptake of medicated water depends on the physiological and clinical conditions of the animals. In order to obtain the correct dosage, the concentration of colistin sulfate has to be adjusted accordingly.
The product may be introduced via a water proportioner pump. Select the treatment dosage. Set the proportioner at the desired delivery rate. To prepare the stock solution, place the indicated quantity of product in a 10-litres container, fill with water and stir until

dissolved. The maximum recommended concentration is 250 grams of product per 10 litres of drinking water and 500 mg of product per litre of milk(replacer).
The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.
Water uptake should be monitored at frequent intervals.
After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.
For accurate dosing, use a suitably calibrated measuring device.
Medicated drinking water should be freshly prepared every 24 hours.
The medicated milk (replacer) should be used within 4 hours.
A levelled measuring spoon contains 3 grams of product.

12. Withdrawal period(s)

Withdrawal period(s):
Cattle (calves) and sheep (lambs):
Meat and offal: 1 day.

Pigs:
Meat and offal: 1 day.

Chickens and turkeys
Meat and offal: 1 day.
Eggs: zero days.

13. Special storage precautions

Store in the tightly closed, original container, in order to protect from light.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

14. Special warning(s)

Special warnings for each target species
As an adjunct to treatment, good management and hygiene practices should be introduced in
order to reduce the risk of infection and to control the potential build-up of resistance.
There is cross-resistance between colistin sulfate and polymyxin B.
Colistin sulfate exerts concentration-dependent activity against Gram-negative bacteria.
Following oral administration high concentrations are achieved in the gastrointestinal tract, i.e. the target site, due to the poor absorption of the substance. These factors indicate that a longer duration of treatment than the one indicated, leading to unnecessary exposure, is not recommended.

Special precautions for use in animals
Do not use colistin sulfate as a substitute for good management practices.
Colistin sulfate is a last resort drug in human medicine for treatment of infections caused by certain multi-drug resistant bacteria. In order to minimise any potential risk associated with widespread use of colistin sulfate, its use should be limited to treatment or treatment and metaphylaxis of diseases, and should not be used for prophylaxis.
Whenever possible, colistin sulfate should only be used based on susceptibility testing. An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.
Use of the product deviating from the instructions given in the SPC may lead to treatment failures and increase the prevalence of bacteria resistant to colistin sulfate.
In the case of newborn animals and animals with severe gastrointestinal and renal disorders, systemic exposure to colistin sulfate may be increased. Neuro- and nephrotoxic alterations may occur.

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

People with known hypersensitivity to polymyxines, such as colistin sulfate, should avoid contact with the veterinary medicinal product.
If symptoms such as rash appear after exposure, seek medical advice immediately and show the package leaflet or the label to the physician. Swelling of the face, lips or eyes or respiratory difficulties are the most serious signs which require urgent medical attention.
The product may be irritating to the eyes, skin and mucous membranes.
When handling the product direct contact of the product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
Use the product in places with suitable ventilation.
The wearing of approved dust masks (either 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), impervious gloves, overalls and safety glasses are recommended during the handling and mixing of this veterinary medicinal product.
Wash exposed skin after preparation. In case of accidental projection into the eyes, rinse abundantly with water.
Wash hands after use.
Wash your clothes daily after using the product.
Do not smoke, eat or drink when handling the product.

Pregnancy, lactation and lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay. However, colistin sulfate is poorly absorbed after oral administration; therefore, the use of colistin sulfate during pregnancy, lactation or lay should not lead to particular problems. Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

Interaction with other medicinal products and other forms of interaction

After oral administration of colistin sulfate interaction with anaesthetics and myorelaxants may not be excluded in individual cases. The combination with aminoglycosides and levamisole should be avoided. The effects of colistin sulfate may be antagonized by binary cations (iron, calcium, magnesium) and by unsaturated fatty acids and polyphosphates.

Incompatibilities

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

15. Special precautions for the disposal of unused products or waste materials, if any

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

16. Date on which the label was last approved

August 2021

17. Other information

List of pack sizes:
-Can: 1 kg
- Securitainer: 100 g, 1 kg
- Bucket: 1 kg
Not all pack sizes may be marketed.

18. The words "For animal treatment only" and conditions or restrictions regarding supply and use, if applicable

For animal treatment only - to be supplied only on veterinary prescription

19. The words "Keep out of the sight and reach of children"

Keep out of the sight and reach of children.

20. Expiry date

EXP << >>

Once opened, use by …

Shelf life after first opening the container: 3 months.
Shelf life after reconstitution in drinking water according to directions: 24 hours.
Shelf life after reconstitution in milk/milk replacer according to directions: 4 hours.

21. Marketing authorisation number(s)

Vm 28365/4010

22. Manufacturer's batch number

Batch << >>

Approved: 10/09/21