[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Coldostin, 4800000 IU/g, powder for use in drinking water/milk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:

Colistin sulfate 4 800 000 IU

Excipients:

Qualitative composition of excipients and other constituents
Lactose monohydrate
Macrogol 400

White to off-white powder.

3. CLINICAL INFORMATION

3.1 Target species

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

3.2 Indications for use for each target species

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 veterinary medicinal product is used.

3.3 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.

3.4 Special warnings

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 in section 3.9, leading to unnecessary exposure, is not recommended.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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-drugresistant 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 sufate 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 veterinary medicinal product deviating from the instructions given in the SPC may lead to treatment failures and increase the prevalence of bacteria resistant to colistin sufate. 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 veterinary medicinal product may be irritating to the eyes, skin and mucous membranes.
When handling the veterinary medicinal product direct contact of the veterinary medicinal product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided. Use the veterinary medicinal 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 veterinary medicinal product.
Do not smoke, eat or drink when handling the veterinary medicinal product.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

None known.

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 its local representative or the national competent authority via the national reporting system. See the package leaflet or label for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay.

Pregnancy and lactation:
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 according to the benefit-risk assessment by the responsible veterinarian.

3.8 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.

3.9 Administration routes and dosage

In drinking water / milk use

Dosage:

Calves, lambs and pigs:
100 000 IU of colistin sufate per kilogram body weight i.e. 1 g of veterinary medicinal 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 veterinary medicinal 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.

To ensure a correct dosage, body weight should be determined as accurately as possible.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

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

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 use of suitably calibrated measuring equipment is recommended.
The veterinary medicinal 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 veterinary medicinal product in a 10-litre container, fill with water and stir until dissolved. The maximum recommended concentration is 250 grams of veterinary medicinal product per 10 litres of drinking water and 500 mg of veterinary medicinal 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.
Medicated drinking water should be freshly prepared every 24 hours.
The medicated milk (replacer) should be used within 4 hours.

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

None known.

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 (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.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:
QA07AA10

4.2 Pharmacodynamics
Colistin sulfate exerts concentration-dependent activity against Gram-negative bacteria.
Colistin sulfate is a polypeptide antibiotic belonging to the polymyxin class.
Colistin sulfate exerts a bactericidal action on susceptible bacterial strains by disruption of the bacterial cytoplasmic membrane leading to an alteration of cell permeability and then a leakage of intracellular materials.

Colistin sulfate has a potent bactericidal action against Gram negative bacteria especially enterobacteria and more particularly *Escherichia coli*.
Colistin sulfate possesses very little activity against Gram positive bacteria and fungi.

Gram-positive bacteria are naturally resistant to colistin sulfate, as are some species of Gram-negative bacteria such as Proteus and Serratia.
Acquired resistance of Gram-negative enteric bacteria to colistin sulfate is rare and can be caused by chromosomal mutations or can be transferrable (plasmid mediated e.g. mcr genes). There is cross-resistance between colistin sulfate and polymyxin B.

The clinical breakpoints for colistin sulfate (EUCAST, 2021) for Enterobacterales are: susceptible ≤ 2 µg/ml and resistant > 2 µg/ml.

4.3 Pharmacokinetics

Colistin (as sulfate) is poorly absorbed from the gastro-intestinal tract. Following oral administration high concentrations are achieved in the gastrointestinal tract, i.e. the target site, due to the poor absorption of the substance.
In contrast to the very low concentrations of colistin sulfate in serum and tissues, high and persistent amounts are present within the different sections of the gastro intestinal tract.
No significant metabolism is observed.
Colistin sulfate is almost exclusively eliminated via the faeces.

Environmental properties
Colistin sulfate is classified as a very persistent substance in soil.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after dissolution in drinking water according to directions: 24 hours.
Shelf life after dissolution in milk/milk replacer according to directions: 4 hours.

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

- Composite can: hardboard tin provided with an inner lining of aluminium-paper (polyethylene terephthalate coated on both sides) and a seamed tin-plate bottom, closed with a tear-off aluminium membrane coated with polyethylene terephtalate on both sides and a low density polyethylene lid.
The tin contains 1 kg of veterinary medicinal product.

- Securitainer: white cylindrical polypropylene container, covered with a low-density polyethylene closure.
The securitainer contains 100 g or 1 kg of veterinary medicinal product.

- Bucket: white polypropylene square container provided with a polypropylene closure.
The bucket contains 1 kg of veterinary medicinal product.

A polystyrene measuring spoon, containing 3 grams of veterinary medicinal product per levelled measuring spoon is included.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Dopharma Research B.V.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

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 (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - <u>COMBINED LABEL AND PACKAGE LEAFLET</u>

Composite can, securitainer and bucket

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Coldostin, 4800000 IU/g, powder for use in drinking water/milk.

2. COMPOSITION

Each gram contains:

Active substance:
Colistin sulfate 4 800 000 IU

White to off-white powder.

3. PACKAGE SIZE

100 gram, 1 kg

4. TARGET SPECIES

For cattle (calves), sheep (lambs), pigs, chickens and turkeys.

5. INDICATIONS FOR USE

Indications for use

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 veterinary medicinal product is used.

6. CONTRAINDICATIONS

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.

7. SPECIAL WARNINGS

Special warnings

Special warnings:
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 safe use in the target species:
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 veterinary medicinal product deviating from the instructions given in the leaflet 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 veterinary medicinal product may be irritating to the eyes, skin and mucous membranes.
When handling the veterinary medicinal product direct contact of the veterinary medicinal product with the skin, eyes and mucous membranes and inhalation of dust particles should be avoided.
Use the veterinary medicinal 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 veterinary medicinal product.
Do not smoke, eat or drink when handling the veterinary medicinal product.

Pregnancy, lactation and lay:
The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay. 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.

Interactions 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.

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

8. ADVERSE EVENTS

Adverse events

None known.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. If you notice any side effects, even those not already listed on this label, 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 or the local representative of the marketing authorisation holder using the contact details at the end of this label, or via your national reporting system.

9. DOSAGE FOR EACH TARGET SPECIES, ROUTES AND METHOD OF ADMINISTRATION

Dosage for each species, routes 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 veterinary medicinal 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 veterinary medicinal 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.

10. ADVICE ON CORRECT ADMINISTRATION

Advice on correct administration

To ensure a correct dosage, body weight should be determined as accurately as possible.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

..... mg veterinary medicinal product per kg body weight per day	X	mean body weight (kg) of animals to be treated	=.... mg veterinary medicinal product per litre of drinking water
mean daily water consumption (litre per animal)			

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 use of suitably calibrated measuring equipment is recommended.
The veterinary medicinal 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 veterinary medicinal product in a 10-litres container, fill with water and stir until dissolved. The maximum recommended concentration is 250 grams of veterinary medicinal product per 10 litres of drinking water and 500 mg of veterinary medicinal 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.
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 veterinary medicinal product.

11. WITHDRAWAL PERIODS

Withdrawal periods
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.

12. SPECIAL STORAGE PRECAUTIONS

Special storage precautions

Keep out of the sight and reach of children.

Keep the original container tightly closed, 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. The expiry date refers to the last day of that month.

13. SPECIAL PRECAUTIONS FOR DISPOSAL

Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon how to dispose of medicines no longer required.

14. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

15. MARKETING AUTHORISATION NUMBERS AND PACK SIZES

Pack sizes
- Can: 1 kg
- Securitainer: 100 g, 1 kg
- Bucket: 1 kg

Not all pack sizes may be marketed.

16. DATE ON WHICH THE LABEL WAS LAST REVISED

Date on which the label was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

17. CONTACT DETAILS

Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:
Dopharma Research B.V.
Zalmweg 24
NL-4941 VX Raamsdonksveer
Tel. +31-162-582000
pharmacovigilance@dopharma.com

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

Local representative and contact details to report suspected adverse reactions:
{Name}
<{Address}
{Country} - {Town} {Code}>
Tel: + {Telephone number}
<{E-mail}>

18. OTHER INFORMATION

Other information

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19. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

20. EXPIRY DATE

Exp. {mm/yyyy}

Once opened, use by …

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

21. BATCH NUMBER

Lot {number}