SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Colixyme 22.5 MIU/g powder for use in drinking water

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g contains

Active substance:

Colistin (as sulfate) 22.5 MIU

Excipients:

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for use in drinking water

White or almost white powder

4. CLINICAL PARTICULARS

4.1 Target species

Cattle (calves) and pigs, chicken, and turkeys.

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of enteric infections caused by non-invasive *E. coli* susceptible to colistin.

The presence of the disease in the herd should be established before metaphylactic treatment.

4.3 Contraindications

Do not use in cases of known hypersensitivity to colistinor to any of the excipients.

Do not use in case of resistance to polymyxins.

Do not use in horses, particularly in foals, since colistin, 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.

4.4 Special warnings for each target species

Severely diseased animals have a different drinking pattern and must consequently be treated parenterally.

Colistin 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 4.9, leading to unnecessary exposure, is not recommended.

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."

4.5 Special precautions for use

Special precautions for use in animals

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.

In the case of newborn animals and of animals with severe gastrointestinal and renal disorders the absorption of colistin may be increased. Neuro- and nephrotoxic alterations may occur.

Do not use colistin as a substitute for good management practices.

Colistin 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, its use should be limited to treatment or treatment and metaphylaxis of diseases, and should not be used for prophylaxis.

Whenever possible, colistin should only be used based on susceptibility testing.

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."

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

People with known hypersensitivity to polymyxins, such as colistin, should avoid contact with the product.

Personal protective equipment consisting of gloves and protective goggles should be worn when handling and dosing the veterinary medicinal product.

When handling the product, avoid all direct contact with skin and eyes, as well as inhaling the powder.
Wash hands following use. Wash your clothes daily after using the product.
Use the product in places with suitable ventilation.
Do not smoke, eat or drink while handling the product.
If symptoms such as rash appear after exposure, seek medical attention and present these warnings. Swelling of face, lips or eyes, and difficulty breathing are serious signs that require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

None known

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation.
Use only accordingly to the benefit-risk assessment by the responsible veterinarian.

4.8 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 neuromuscular blocking action of muscle relaxants (tubocurare, suxamethonium, pancurare, galamine) are potentiated by Colistin increasing the risk of respiratory failure. 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.
There is cross-resistance between colistin and polymyxin B.

4.9 Amounts to be administered and administration route

In drinking water use.
Calves and pigs: 100 000 IU of colistin/kg body weight daily for 3-5 consecutive days (equivalent to 4,44 mg product/kg BW/day for 3-5 days).

Chicken and turkeys:. 75 000 IU of colistin/kg body weight daily for 3-5 consecutive days (equivalent to 3,33 mg product/kg BW/day for 3-5 days).

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

The intake of medicated water depends on the physiological and clinical condition of the animals. In order to obtain the correct dosage, the concentration of colistin has to be adjusted accordingly. Carefully calculate the average body weight to be treated and the average daily water consumption before each treatment.

Medicated water must be renewed every 24 hours. The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.

Use the following formula in order to calculate the quantity of the product (mg) that should be incorporated per litre drinking water:

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

Administration without a dosing pump:

The treatment is distributed in a tank over a period of 24 hours, for 3 consecutive days.

The product is added to a volume of the drinking water corresponding to the volume consumed by the animals over the treatment period (24 hours) to achieve a dose of 100 000 IU of colistin/kg body weight for calves and pigs and 75 000 IU of colistin/kg body weight for poultry.

Administration via a dosing pump:

The treatment is distributed over a period of 24 hours, for 3 consecutive days.

A dosing pump is used to add a stock solution at a pre-determined concentration to the drinking water.

4.10 Overdose (symptoms, emergency procedures, antidotes)

In case of overdose, transitory digestive problems appear, such as softening of the faeces and mild bloat. Sings of neurotoxicity and nephrotoxicity may also appear.

4.11 Withdrawal period(s)

Calves and pigs

Meat and offal: 1 day

Chickens and turkeys

Meat and offal: 1 day

Eggs: zero days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: intestinal antiinfectives, antibiotics

ATC vet code **QA07 AA10**

5.1 Pharmacodynamic properties

'Colistin sulfate is a polypeptide antibiotic belonging to the polymyxins class; activity has been shown against non-invasive *Escherichia coli*.

Colistin exerts a bactericidal action on susceptible bacteria strains by disruption of the bacterial cytoplasmic membrane leading to an alteration of cell permeability and then a leakage of intracellular materials.

Acquired resistance of Gram –negative enteric bacteria to colistin is rare and explained by a single step mutation. Cross-resistance has been reported between the different polymyxins and is complete with polymyxin B. No cross-resistance has been reported between colistin and antibiotics of other groups.

Colistin 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.

For colistin sulfate, EUCAST clinical breakpoints (01/2020) for Enterobacterales are: susceptible ≤ 2 µg/ml and resistant ≥ 2 µg/ml. It should be noted that MIC determination should be performed using the broth microdilution method.

5.2. Pharmacokinetic particulars:

Colistin is poorly absorbed from the gastro-intestinal tract. In contrast to very low concentration of colistin 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 is almost exclusively eliminated via the faeces.

Environmental properties:

The active ingredient colistin sulfate is very persistent in soils.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Major Incompatibilities

Divalent cations (calcium, magnesium, manganese)

Unsaturated fatty acids.

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

6.3 Shelf-life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years

Shelf-life after first opening of the immediate packaging:

6150 MIU bag : 28 days

615 MIU and 1020 MIU sachets: use immediately

Shelf life after dilution according to directions: 24 hours.

6.4 Special precautions for storage

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

6.5 Nature and composition of immediate packaging

Bag and sachets of low density polyethylene/aluminium/ polyester with thermo-sealing closing system.

<u>Pack sizes:</u>

Bag of 6150 MIU containing 273,06 g of product

Cardboard box with 20 sachets of 615 MIU containing 27,3 g of product

Cardboard box with 20 sachets of 1020 MIU containing 45,28 g of product

Not all pack sizes may be marketed.

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

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

7. MARKETING AUTHORIZATION HOLDER

ANDERSEN S.A.
Avda. de la Llana 123
Polígono Industrial "La Llana"
08191 Rubí (Spain)

8. MARKETING AUTHORIZATION NUMBER:

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT:

PROHIBITION OF SALE, SUPPLY AND/OR USE

To be supplied only on veterinary prescription.
Administration by a veterinary surgeon or under their direct responsibility