SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

COLICEN 4.000.000 UI/ml solution for use in drinking water/milk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Colistin (as sulfate) 4000000 IU

Excipients:

Benzyl alcohol (E1519) 0.010 ml

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for use in drinking water/milk

A brown –orange solution

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

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

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

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

4.3 Contraindications

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.

Do not use in case of hypersensitivity to colistin or to any of the excipients.

Do not use in case of resistance to polymyxins.

4.4 Special warnings for each target species

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

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.

Use of the product should be based on susceptibility testing and take into account official and local antimicrobials policies.

In the case of newborn animals and animals with severe gastrointestinal and renal disorders, systemic exposure to colistin 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 polymyxins, such as colistin, should avoid contact with the veterinary medicinal product.

Avoid direct contact with skin and eyes while handling the product. Impervious gloves and protective goggles must be worn while handling and dosing the product.

Wash splashes from skin immediately with soap and plenty of water.

In case of accidental eye exposure, wash with plenty of water and seek medical attention immediately and show the label to the physician.

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 or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Do not eat, drink or smoke while handling the product.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

None known.

4.7 Use during pregnancy, lactation or lay

The safety of colistin during pregnancy, lactation or lay was not investigated in target species. However, colistin is poorly absorbed after oral administration, therefore the use of colistin during pregnancy, lactation or lay should not lead to particular problems.

Use only accordingly to the benefit-risk assessment by the responsible veterinarian during these periods.

4.8 Interaction with other medicinal products and other forms of interaction

The action of colistin sulfate is inhibited by bivalent cations like Ca^{2+} and Mg^{2+}, unsaturated fatty acids and quaternary ammonium compounds.

After the oral administration of colistin sulfate, its interaction with anaesthetics and myorelaxants may not be excluded in individual cases.

Combination with other antimicrobials must be avoided.

4.9 Amounts to be administered and administration route

To be administered orally.
In drinking water/milk use
Calves, lambs, pigs: 100 000 IU of colistin per kg body weight daily for 3-5 consecutive days in drinking water or milk (replacer) in calves, equivalent to 0.25 ml of the concentrate solution per 10 kg body weight per day for 3-5 days.

Chickens and turkeys: 75 000 IU of colistin per kg body weight daily for 3-5 consecutive days in drinking water, equivalent to 18.75 ml of the concentrate solution per Ton of body weight per day for 3-5 days.

Duration of treatment should be limited to the minimum time necessary for the treatment of the disease.
Any medicated water which is not consumed within 24 hours should be discarded.
Any medicated milk which is not consumed within 3 hours should be discarded.

Direct oral administration to individual animals
The recommended daily dose should be divided into two if the product is to be administered directly into the mouth of the animal.
Prior to direct oral administration, the product should be diluted with a volume of drinking water equivalent to 2 x the volume of product concentrate to be administered.

Administration via drinking water
The intake of medicated water depends on the 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 should be made every day, immediately prior to provision.
The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period.

With the following formula, we can calculate an exact dosage:

$$\text{ml of product per liter of drinking water} = \frac{\text{ml of the product / kg b.w./ day x Average body weight (kg)}}{\text{Average daily water intake (liters) per animal}}$$

• Administration without a dosing pump:
The treatment is distributed in a tank over a period of 24 hours, for 3-5 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 per kg body weight for pigs, lambs and calves and 75 000 IU of colistin per kg body weight for chickens and turkeys.

• Administration via a dosing pump
The treatment is distributed over a period of 24 hours, for 3-5 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), if necessary
None.

4.11 Withdrawal period(s)
Calves, lambs and pigs: Meat and offal: 1 day
Not authorised for use in animals producing milk for human consumption.

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

5. PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Intestinal anti-infectives, antibiotics.
ATCvet code: QA07AA10.

5.1 Pharmacodynamic properties
Colistin is a polypeptide antibiotic belonging to the class of polymyxins.
Colistin exerts a bactericidal action on susceptible bacterial strains by disruption of their cytoplasmic membrane, leading to an alteration of the cell permeability and thus to a loss of intracellular material.
Colistin exhibits a bactericidal effect against a broad spectrum of Gram-negative bacteria among which Enterobacteriaceae, especially *Escherichia coli*.
Colistin has very little activity against Gram-positive bacteria and fungal organisms.
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.
Gram-positive bacteria, as well as some species of Gram-negative bacteria, such as *Proteus* and *Serratia*, are naturally resistant to colistin.
Resistance of *E.coli* bacteria to colistin can result from chromosomal mutations or horizontal transfer of the MCR-1 gene.

The following Minimal Inhibitory Concentrations (MIC) have been determined for colistin in European isolates of E coli . For colistin , EUCAST breakpoints are: susceptible ≤ 2 µg/ml and resistant ≥ 2 µg/ml.

Species	Bacterial pathogen	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
Chickens	E coli	0.25-2	0.5-2
Turkeys		1-2	1-8
Pigs		0.25-2	0.5
Ruminants		0.25	0.5-1

5.2 Pharmacokinetic particulars
Colistin (as sulfate) is very poorly absorbed from the gastrointestinal tract.

In serum and tissues, the concentrations of colistin are very low. In contrast, it is persistently present and in large quantities in different sections of the digestive tract.
No metabolism was observed.
Colistin is almost exclusively eliminated in the faeces.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Benzyl alcohol (E1519)
Trihydrate sodium acetate
Glacial acetic acid (for pH adjustment)
Glycerol
Purified water

6.2 Incompatibilities
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: 18 months
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution in water according to directions: 24 hours
Shelf life after dilution in milk replacer: 3 hours

6.4 Special precautions for storage
Do not store above 25 °C
Protect from light.

6.5 Nature and composition of immediate packaging
The product is presented in 1 L and 5 L white high – density polyethylene packages. The packages are sealed by a screw cap made of the same material and by induction.
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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
CENAVISA S.L.
Camí Pedra Estela s/n
43205 Reus Spain

8. MARKETING AUTHORISATION NUMBER
3458 ESP

9. DATE OF FIRST AUTHORISATION

August 5th 2016

10. DATE OF REVISION OF THE TEXT

Veterinary medicinal product subject to prescription.
Administration under control or supervision of the veterinarian.