SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Coliplus 2,000,000 IU/ml Concentrate for Oral Solution for use in drinking water for Cattle, Sheep, Pigs and Chickens

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition for 1 ml:

Active substance:

Colistin (as Colistin sulfate)	2 MIU (equivalent to 83.33 mg)

Excipient(s):

Benzyl Alcohol (E1519)	10 mg
Disodium edetate	0.1 mg
Excipients qs	1 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for oral solution for use in drinking water.
Clear yellow-brown solution.

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

Treatment and metaphylaxis of gastrointestinal infections caused by non-invasive *Escherichia 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 case of hypersensitivity to polypeptide antibiotics or to any of the excipients.
Do not use in case of resistance to the polymyxin.
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

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

4.5 Special precautions for use

(i) Special precautions for use in animals

Using the veterinary medicinal product (antimicrobials) in poultry should be in accordance with Commission Regulation EC 1177/2006 and subsequent national requirements.
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.

(ii) 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.
It is recommended to wear impervious gloves when handling or administering the product.
Do not eat, drink or smoke while handling the product.
In case of accidental eye exposure, wash with plenty of water and seek medical advice immediately and show the label to the physician.
Wash hands after use.

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, lactation or lay in the target species. Use only accordingly to the risk/benefit of the veterinarian.
Using the veterinary medicinal product (antimicrobials) in poultry should be in accordance with Commission Regulation EC 1177/2006 and subsequent national requirements.

4.8 Interaction with other medicinal products and other forms of interaction

After oral administration of colistin sulphate 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 sulphate may be antagonized by binary cations (iron, calcium, magnesium) and by unsaturated fatty acids and polyphosphates.

4.9 Amounts to be administered and administration route

Dosage:

To be administered orally.
For calves, lambs and pigs the recommended dose is 100 000 IU of colistin per kilogram body weight
daily for 3-5 consecutive days. The recommended daily dose should be divided into two if the product
is to be administered directly into the mouth of the animal.
For poultry the recommended dose is 75 000 IU of colistin per kilogram body weight daily for 3-5
consecutive days.

Administration via 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 has to be adjusted accordingly. Carefully calculate the total body mass to be treated and the total 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:

$$\frac{\text{.....ml Coliplus per kg body weight and day} \times \text{Average body weight (kg)}}{\text{Average daily water intake (l/animal)}} = \text{....ml Coliplus per litre of drinking water}$$

- Administration without a dosing pump:

The treatment is distributed in a tank over a period of 24 hours, for 3 consecutive days.
Coliplus 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 IU of colistin per kg body weight. The following sequential steps should be followed:

From the dosage regimen and the total weight of animals to be treated, determine the necessary quantity of active ingredient, and deduce the necessary quantity of commercial product.
Determine the mean water consumption of the animals to be treated over 24 hours.

The following formula can be applied:

1) Calculation of product solution volume at each day (V):
   V (ml) = (Dosage per day in IU/kg b.w. x Total weight of animals to treat) / 2,000,000 IU.

2) Calculation of the quantity of drinking water to prepare (Q_{water}):
   Q_{water} (L): (Mean individual water consumption/day) x (Number of animals to be treated)

- 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. The pumped volume is constant, but the drinking frequency depends on the flow rate of the circuit. The flow rate (F) through the pump is a percentage.
If the product is administered with an automated drinking water system, we have to calculate the volume and the concentration of the stock solution. The following sequential steps should be followed:

1) Calculation of product solution volume at each distribution (V):
   V (ml) = (Dosage per day in IU/kg b.w. x Total weight of animals to treat) / 2,000,000 IU

2) Calculation of the drinking water concentration (C):
   C (ml/L) = V / Total volume of water consumed by the animals in 24 hours.

3) Calculation of the stock solution volume (V_{stock})
   V_{stock} (L) = Total volume of water consumed by the animals in 24 hours x F

4) Calculation of the stock solution concentration (Cstock):
   C_{stock} (ml/L) = C / F”

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

None.

4.11 Withdrawal period(s)

Meat and offal: Calves, Lambs, Pig and Chickens: 1 day
Eggs: Zero days
Not permitted for use in animals producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: intestinal antiinfectives, antibiotics.
ATCvet code: QA07AA10

5.1 Pharmacodynamic properties

Colistin is a polypeptide antibiotic belonging to the polymyxin class.

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.

Colistin exerts a bactericidal action on susceptible bacteria strains by disruption of the bacteria cytoplasmic membrane leading to an alteration of cell permeability and then a leakage of intracellular materials. Colistin is bactericidal and is primarily effective against a range of gram negative bacteria, such as enterobacteriaceae and in particular *Escherichia coli*. Colistin possesses virtually no activity against gram-positive bacteria and fungi.

Gram-positive bacteria are naturally resistant to colistin, as are some species of gram-negative bacteria such as *Proteus* and *Serrati.* However, acquired resistance of gram-negative enteric bacteria to colistin is rare and explained by a single step mutation.

In vitro sensibility of Colistin against *Escherichia coli* strains isolated from pigs and *Escherichia coli* strains isolated from poultry have been determined, with the following MIC_{50} and MIC_{90} values:

	MIC_{50}	MIC_{90}
Escherichia coli from pigs	0,19 µg/ml	4,0 µg/ml
Escherichia coli from poultry	0,25 µg/ml	0,38 µg/ml

According to the NCCLS standard, the critical concentration for resistance of colistin is 16 µg/ml. The sensitivity of *Escherichia coli* in cattle and sheep is similar to the sensitivity of pigs and poultry pathogens. These values were obtained in 2006.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol (E1519)
Disodium edetate
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: 2 years
Shelf-life after first opening the immediate packaging: 60 days
Shelf-life after dilution in water: 24 hours.

6.4. Special precautions for storage

Store below 25°C

6.5 Nature and composition of immediate packaging

Nature of container:
White HDPE container with tamper-evident aluminium seal and HDPE screw cap

Package sizes: 250 ml, 1 litre and 5 litres.
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 AUTHORISATION HOLDER

Divasa - Farmavic S.A.
Ctra. Sant Hipolit
Km71 PO Box 79
08503 Gurb-Vic
Spain

8. MARKETING AUTHORISATION NUMBER

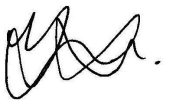
Vm 33229/4000

9. DATE OF FIRST AUTHORISATION

08 December 2010

10. DATE OF REVISION OF THE TEXT

June 2015



Approved: 01 July 2015