ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

APSALIQ COLISTIN 3,000,000 IU/ml
solution for use in drinking water/milk for pig, cattle, sheep, chickens and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Colistin (as sulfate) 3,000,000 IU

Excipients:
Benzyl alcohol (E-1519) 10 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water/milk.
Clear yellow solution.

4. CLINICAL PARTICULARS

4.1. Target species

Cattle (calf), sheep (lamb), pig, chicken and turkey.

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 disease in the herd should be established 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 cases 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

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

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.

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

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 animals with severe gastrointestinal and renal disorders, systemic exposure to 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 and metaphylaxis of diseases, and should not be used for prophylaxis.

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 veterinary medicinal product.

Avoid direct contact with skin and eyes while handling the product.

Personal protective equipment consisting of coveralls, gloves and safety glasses should be worn when handling the veterinary medicinal product.

If you develop symptoms following exposure such as skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

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

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.

There is cross-resistance between colistin and polymyxin B.

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 0.33 ml of the product per 10 kg body weight per day for 3-5 days.

Chicken and Turkeys: 75 000 IU of colistin per kg body weight daily for 3-5 consecutive days in drinking water, equivalent to 25 ml of the product 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/milk which is not consumed within 24 hours should be discarded.

<u>Direct oral administration to individual animals</u>

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 1.5 x the volume of product 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:

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

• Administration without a dosing pump:
The treatment is distributed in a tank over a period of 24 hours, for 3-5 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)

Cattle (calves) and Sheep (lambs)
Meat and offal: 1 day
Milk: Not authorised for use in animals producing milk for human consumption.

Pigs
Meat and offal: 1 day

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Intestinal antiinfectives, antibiotics.
ATC-vet code: QA07AA10

5.1. Pharmacodynamic properties

Colistin is a polypeptide antibiotic belonging to the polymyxin class.

Colistin 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 has a potent bactericidal action against gram negative bacteria especially enterobacteria and more particularly *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 *Serratia*.

Acquired resistance of Gram-negative enteric bacteria to colistin is rare and explained by modification of Lipid A. These modifications are associated to chromosomal mutations or transferable by plasmid MCR-1.

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, EUCAST breakpoints are: susceptible $\leq$ 2 µg/ml and resistant > 2 µg/ml. 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 the very low concentrations 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 sulphate is very persistent in soil.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Benzyl alcohol (E-1519)
Disodium edetate (E-386)
Purified water

6.2. Major 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: 3 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution according to directions: 24 hours.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Store in the original container in order to protect from light.

6.5. Nature and composition of the immediate packaging

White fluorinated high density polyethylene bottles. The bottles are closed with a blue high density polyethylene screw cap with thermosealing Aluminium / Polyethyleneterephtalate / Polyethylene discs.

Package size:
Bottle of 1 L
Bottle of 5 L

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

ANDRÉS PINTALUBA S.A.
POLÍGONO INDUSTRIAL AGRO-REUS
C/ PRUDENCI BERTRANA Nº 5
43206 - REUS (TARRAGONA)
SPAIN

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
Date of last renewal:

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