SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

COLISTIN APSA 1,200,000 IU/g
Premix for medicated feeding stuff for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substance:
Colistin (as sulfate) 1,200,000 IU

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff
Granulated brown powder

4. CLINICAL PARTICULARS

4.1. Target species

Pig (piglet and pig for fattening).

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

4.4. Special warnings for each target species

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.

The intake of medicated feed by animals can be altered as a consequence of illness. In case of insufficient intake of feed, animals should be treated parenterally.

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 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.
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.

Official, national and regional antimicrobial policies should be taken into account when the product is used.

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

People with known hypersensitivity to polymyxins, such as colistin, or tree nuts should avoid any contact with the veterinary medicinal product.
Avoid direct contact with skin and eyes while mixing the veterinary medicinal product and handling the medicated feed. In case of contact, wash with plenty of water.
Care should be taken not to inhale any dust. 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.
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 sings that require urgent medical attention.
Do not smoke, eat or drink while handling the product.
Wash hands and any exposed skin with soap and water immediately after use.

4.6. Adverse reactions (frequency and seriousness)

No undesirable effects related to the use of colistin sulphate administered orally have been described at the recommended dose in the target species. In any event, as it is an antibiotic that acts at intestinal level, digestive alterations may appear, such as intestinal dysbiosis, accumulation of gases or mild diarrhoea.

4.7. Use during pregnancy, lactation or lay

Studies in laboratory animals (rat and mice) have not produced any evidence of embryotoxic, foetotoxic or teratogenic effects. No specific studies have been conducted in pregnant or lactating pigs. 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 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.
There is cross-resistance between colistin and polymyxin B.

4.9. Amounts to be administered and administration route

To be administered orally, in medicated feeding stuff.

The dosage is 180,000 IU of colistin/kg of bodyweight/day in feed (equivalent to 150 mg of the product/kg B.W./day) for 7 consecutive days.

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

The intake of medicated feed 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 bodyweight to be treated and the average daily feed consumption before each treatment.

The medicated feed should be the only source of feed for the animals for the entire duration of the treatment period.

To calculate the exact dosage of the veterinary medicinal product, the following formula can be used:

$$\frac{\text{150 mg of veterinary medicinal product/kg bodyweight /day} \times \text{Average pig bodyweight (kg)}}{\text{Average daily feed intake (kg/animal)}} = \text{mg of veterinary medicinal product per kg of feed}$$

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

Pelleting process of the product medicated feeds should be performed at an average temperature of 65 °C, as a maximum of 75 °C. Under normal conditions, the maximum duration time for the process should be 20 minutes.

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

Toxic signs have not been seen in pigs given twice the recommended dose (300,000 IU per kg bodyweight per day) for twice the administration period (14 days). Nevertheless, episodes of soft faeces and tympany cannot be ruled out in the event of overdose in pigs treated with colistin, which remit on interruption of treatment.

4.11. Withdrawal period

Meat and offal: 1 day

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; 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 modification of Lipid A. These modifications are associated to chromosomal mutations or transferable by plasmid MCR-1.

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 in veterinary medicine.

Of the *in vitro* study on the degree of bacterial sensitivity to Colistin of 30 strains of *Escherichia coli* isolated from swine, 90% of the strains of *Escherichia coli* were within the sensitive category.

Critical concentrations (breakpoints) of resistance:
According to the NCCLS standard:

Sensitive	MIC ≤ 6.246 µg/mL
Intermediate	MIC > 6.246 µg/mL and ≤ 16 µg/mL
Resistant	MIC > 16 µg/mL

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.

5.2. Pharmacokinetic particulars

Colistin (as sulfate) 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 soils.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Almond and hazelnut shell flour
Paraffin, light liquid
Macrogolglycerol ricinoleate (E-484)

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: 3 years.
Shelf-life after first opening the immediate packaging: 1 month.
Shelf-life after incorporation into meal and pelleted feed: 3 months.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Store in the original container.

6.5. Nature and composition of the immediate packaging

25 kg bags consisting of two sheets of kraft paper, one white calendered kraft paper layer and an internal bag of low density polyethylene of 150 gauge. The bags are thermosealed, and then sewed and bordered along the top.

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.
Pol. Industrial Agro-Reus
C/Prudence Bertrana No. 5
Reus
Tarragona
43206
Spain

8. MARKETING AUTHORISATION NUMBER

Vm 32508/4000

9. DATE OF FIRST AUTHORISATION

06 July 2016

10. DATE OF REVISION OF THE TEXT

July 2016

PROHIBITION OF SALE, SUPPLY AND/OR USE

Dispensing conditions: **Veterinary medicinal product subject to veterinary prescription**
Administration conditions: **Administration under the control or supervision of a veterinarian surgeon**

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

Approved: 06/07/2016