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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Metaxol 20/100 mg/ml solution for use in drinking water for pigs and chickens.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substances:
Trimethoprim 20 mg
Sulfamethoxazole 100 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
N-methyl pyrrolidone	690,8 mg
Propylene glycol	
Sodium hydroxide (for pH adjustment)	
Water, purified	

A clear, pale yellow to brownish-yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Pigs (fattening pigs) and chickens (broilers).

3.2 Indications for use for each target species

Fattening pigs:
Treatment and metaphylaxis of:
- Post-weaning diarrhoea caused by beta-haemolytic K88-positive, K99-positive or 987P *Escherichia coli* strains susceptible to trimethoprim-sulfamethoxazole.
- Secondary bacterial infections caused by *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Streptococcus* spp. and *Haemophilus parasuis* susceptible to trimethoprim-sulfamethoxazole.

Broilers:
Treatment and metaphylaxis of:
- Colibacillosis caused by *Escherichia coli* susceptible to trimethoprim-sulfamethoxazole.
- Coryza caused by *Avibacterium paragallinarum* susceptible to trimethoprim-sulfamethoxazole.

The presence of the disease in the group/flock must be established before the veterinary medicinal product is used.

3.3 Contraindications

Do not use in animals suffering from severe liver or kidney disease, oliguria or anuria.
Do not use in animals with impaired haematopoietic systems.
Do not use in cases of hypersensitivity to sulphonamides or trimethoprim or any of the excipients.

3.4 Special warnings

Severely diseased animals can have a decreased appetite and water consumption. If necessary the concentration of the veterinary medicinal in the drinking water should be adjusted to make sure that the recommended dosage is being consumed. However if the concentration of the veterinary medicinal product is increased too much, the intake of the medicated drinking water decreases for palatability reasons. Therefore water intake should be monitored regularly, especially in broilers.
In case of insufficient intake of water, pigs should be treated parenterally.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Due to the likely variability (time, geographical) in susceptibility of bacteria for potentiated sulphonamides, occurrence of resistance of bacteria may differ from country to country and even from farm to farm, and therefore bacteriological sampling and susceptibility testing are recommended. Use of the veterinary medicinal product should be based on culture and sensitivity of micro-organisms from diseased cases on farm or from recent previous experience on the farm. Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to sulfamethoxazole and trimethoprim and may also decrease the effectiveness of combinations of trimethoprim with other sulphonamides due to the potential for cross resistance. Official and local antimicrobial policies should be taken into account when the veterinary medicinal product is used.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Sulphonamides may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to sulphonamides may lead to cross reactions with other antibiotics. Allergic reactions to these substances may occasionally be serious.
Do not handle this veterinary medicinal product if you know you are sensitive to sulphonamides.
If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the physician this warning.

This veterinary medicinal product may cause skin- and respiratory irritation as well as eye damage. Personal protective equipment consisting of impermeable gloves, e.g. rubber or latex and protective glasses, should be worn when handling the veterinary medicinal product including when mixing the veterinary medicinal product with drinking water. Avoid inhalation. In the event of eye contact, rinse the eye with large amounts of clean water and, if irritation occurs, seek medical attention. In the event of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician. Wash hands and contaminated skin immediately after handling the veterinary medicinal product.

Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. The veterinary medicinal product should not be administered by pregnant women and women suspected of being pregnant. Personal protective equipment consisting of gloves should be worn when handling the veterinary medicinal product by women of childbearing age.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Pigs:

Rare (1 to 10 animals / 10,000 animals treated):	Hypersensitivity reaction.

Chickens:

Rare (1 to 10 animals / 10,000 animals treated):	Hypersensitivity reaction. Decreased drinking.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established in pigs and chickens during pregnancy, lactation, lay or in animals intended for breeding.
Laboratory studies in rabbits and rats with the excipient N-methyl pyrrolidone have shown evidence of foetotoxic effects. Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Do not combine with other veterinary medicinal products.

3.9 Administration routes and dosage

Route of administration: In drinking water use.

The veterinary medicinal product can be added directly to the drinking water to prepare a therapeutic solution at the calculated concentration, but can also be used in a concentrated stock solution by adding 200 ml of the veterinary medicinal product per litre of water and diluting this further.

Fattening pigs:
5 mg trimethoprim and 25 mg sulfamethoxazole per kg body weight a day, for 4-7 days. This corresponds to 1 ml of the veterinary medicinal product per 4.0 kg body weight per day.
Based on the recommended dose, daily water consumption, and the number and weight of the pigs to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\text{Mean body weight (kg) of pigs to be treated}}{\text{Mean daily water consumption (litre) per pig} \times 4.0} = \text{xx ml veterinary medicinal product per litre drinking water}$$

Broilers:
7.5 mg trimethoprim and 37.5 mg sulfamethoxazole per kg body weight a day, for 3 days. This corresponds to 1 ml of the veterinary medicinal product per 2.67 kg body weight per day.
Based on the recommended dose, daily water consumption, and the number and weight of the birds to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\text{Mean body weight (kg) of birds to be treated}}{\text{Mean daily water consumption (litre) per bird} \times 2.67} = \text{xx ml veterinary medicinal product per litre drinking water}$$

To ensure a correct dosage, the body weight and water consumption should be determined as accurately as possible.
The daily amount is to be added to the drinking water such that all medication will be consumed in 24 hours. Medicated drinking water and stock solutions should be freshly prepared every 24 hours.
During the treatment period animals should not have access to water sources other than the medicated

water. However, it should be ensured that animals always have sufficient water available. After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of active substance. The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of the veterinary medicinal product may need to be adjusted accordingly.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In chickens an acute overdose will likely not occur because the birds will be reluctant to drink the strongly concentrated drinking water (too bitter taste if above 2 litres of the veterinary medicinal product per 1000 litres drinking water). Chronic overdose in chickens will result in a strongly diminished water- and feed intake and retarded growth.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Pigs: Meat and offal: 8 days.
Chickens: Meat and offal: 5 days.
Not for use in birds producing or intended to produce eggs for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01EW11

4.2 Pharmacodynamics

Trimethoprim and sulfamethoxazole have a broad spectrum of activity against gram-positive and gram-negative bacteria including *Streptococcus* spp. *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Haemophilus parasuis*, *Avibacterium paragallinarum* and *E. coli in vitro*.
Sulphonamides block the conversion of para-aminobenzoic acid to dihydrofolic acid. Its effect is bacteriostatic.
Trimethoprim inhibits dihydrofolic acid reductase, which converts dihydrofolic into tetrahydrofolic acid.
The effect of trimethoprim is bacteriostatic and in combination with sulphonamides it is bactericidal. Sulphonamides and trimethoprim thus cause a successive blockage of two enzymes that play an important role in the metabolism of bacteria and protozoa. Their effect is synergistic.

Bacterial resistance to trimethoprim and to sulphonamides can be mediated via 5 main mechanisms: (1) changes in the permeability barrier and/or efflux pumps, (2) naturally insensitive target enzymes, (3) changes in the target enzymes, (4) mutational or recombinational changes in the target enzymes, and (5) acquired resistance by drug-resistant target enzymes.

4.3 Pharmacokinetics

Following oral administration, trimethoprim and sulfamethoxazole are rapidly and almost completely absorbed from the gut. The bioavailability of sulfamethoxazole is slightly higher than that of trimethoprim. It is distributed to all tissues except the brain. The highest concentrations can be found in the lungs, the liver and the kidneys.

Sulphonamides are metabolised in various ways. The degree of acetylation, hydroxylation and glucuronidation depends, among other things, on the species and age of the animal. Trimethoprim is

metabolised to a large extent in the liver. Important metabolic pathways are O-methylation, N-oxidation in the ring structure and alpha hydroxylation. Sulfamethoxazole and trimethoprim are primarily excreted through the kidneys.

Environmental properties
Trimethoprim is persistent in soils.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 1 year.
Shelf life after dilution or reconstitution according to directions: 24 hours.

5.3 Special precautions for storage

Do not freeze.

5.4 Nature and composition of immediate packaging

HDPE bottle of 1 litre, closed with a tamper proof HDPE screw cap.
HDPE container of 5 litres, closed with tamper proof HDPE screw cap.
Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Eurovet Animal Health B.V.

7. MARKETING AUTHORISATION NUMBER

VPA 10989/066/001

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 08 July 2016

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

12/10/2023

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).