SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substances:

Trimethoprim	20 mg
Sulfamethoxazole	100 mg

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs (fattening pigs) and chickens (broilers).

4.2 Indications for use, specifying the target species

Fattening pigs:
Treatment and metaphylaxis of:
- Post weaning diarrhoea caused by ß-haemolytic K-88positive, K99- positive or 987P *Escherichia coli* strains.
- Secondary bacterial infections caused by *Pasteurella multocida*, *Actinobacillus pleuropneumoniae*, *Streptococcus spp.* and *Haemophilus parasuis*.

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 product is used.

4.3 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 case of known hypersensitivity to sulphonamides or trimethoprim or any of the excipients.

4.4 Special warnings for each target species

Severely diseased animals can have a decreased appetite and water consumption. If necessary the concentration of the veterinary medicinal product in the drinking water should be adjusted to make sure that the recommended dosage is being consumed. However if the concentration of the 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 uptake of water, pigs should be treated parenterally.

4.5 Special precautions for use

Special precautions for use in animals

Due to the likely variability (time or geographically) 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 product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the 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. Use of the product should be in accordance with official, national and regional antimicrobial policies.

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 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 product may cause skin- and respiratory irritation as well as eye damage.
Impermeable gloves, e.g. rubber or latex and protective glasses, should be worn when handling the product.
Avoid inhalation. Wash hands and contaminated skin immediately after handling the product.
In the event of eye contact, rinse the eye with large amounts of clean water and, if irritation occurs, seek medical attention.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
The excipient N-methylpyrrolidone (NMP) may damage unborn children; therefore, women of child bearing age must be very careful to avoid exposure via spillage onto the skin when administering the product. If you are pregnant, think you may be pregnant or are attempting to conceive, you should not administer the product.

Other precautions

Manure from animals treated with this product may cause toxic effects to plants after spreading onto land. This risk can be reduced by avoiding too frequent and repeated use of the product.

4.6 Adverse reactions (frequency and seriousness)

A diminished water intake in chickens may occur occasionally.
Hypersensitivity reactions can occur rarely (more than1 but less than 10 animals in 10,000 animals).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay.
Laboratory studies in rats conducted with trimethoprim have shown evidence of teratogenicity at higher doses than recommended therapeutic ones.
Laboratory studies with the excipient N-methylpyrrolidone in rabbits and rats have shown evidence of teratogenic, foetotoxic, maternotoxic and reprotoxic effects.

4.8 Interaction with other medicinal products and other forms of interaction

Do not combine with other veterinary medicinal products.

4.9 Amounts to be administered and administration route

In drinking water use.

The 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 per day, for 4-7 consecutive days. This corresponds to 1 ml of the veterinary medicinal product per 4.0 kg body weight per day.

Broilers:
7.5 mg trimethoprim and 37.5 mg sulfamethoxazole per kg body weight per day, for 3 consecutive 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 animals to be treated, the exact daily amount of the veterinary medicinal product required can be calculated according to the following formula:

$$\frac{\text{…ml product/ kg body weight/day} \times \text{mean body weight (kg) of animals to be treated}}{\text{mean daily water consumption (litre) per animal}} = \text{… ml product per litre of drinking water}$$

Body weight and water consumption should be determined as accurately as possible to ensure administration of the correct dose. 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 uptake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of the veterinary medicinal products has to be adjusted accordingly.

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

In chickens an acute overdose is unlikely to 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.

4.11 Withdrawal period

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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, combinations of sulphonamides and trimethoprim.

ATCvet-code: QJ01EW11

5.1 Pharmacodynamic properties

Sulphonamides block the conversion of para-aminobenzoic acid to dihydrofolic acid. Their activity is bacteriostatic.
Trimethoprim inhibits dihydrofolic acid reductase, which converts dihydrofolic into tetrahydrofolic acid. The activity of trimethoprim is bacteriostatic and in combination with sulphonamides it is bactericidal.
Sulphonamides and trimethoprim thus cause a successive blockade of two enzymes that play an important role in the metabolism of bacteria. Their effect is synergistic.

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.

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.

5.2 Pharmacokinetic properties

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.
Sulfonamides are metabolised in various ways. The degree of acetylation, hydroxylation and glucuronidation depends on, among other things, the species and the age of the animal. Trimethoprim is metabolised to a large extent in the liver. Major 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

The mixture of sulfamethoxazole and trimethoprim shows to have phytotoxic effects on terrestrial plants.
Trimethoprim is persistent in soils.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

N-methylpyrrolidone
Propylene glycol,
Sodium hydroxide (for pH adjustment),
Water, purified

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 of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours.

6.4 Special precautions for storage

Do not refrigerate or freeze. Protect from frost.

6.5 Nature and composition of immediate packaging

- High-density polyethylene bottles with low-density polyethylene screw cap containing 1 litre of product;
- High-density polyethylene jerrycan with high-density polyethylene screw cap containing 5 litres of product.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products 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

Dopharma Research B.V.
Zalmweg 24
4941 VX Raamsdonksveer
The Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 28365/4011

9. DATE OF THE FIRST AUTHORISATION

22 August 2017

10. DATE OF REVISION OF THE TEXT

July 2022

Approved 06 July 2022