# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Hydrotrim 500 mg/g + 100 mg/g powder for use in drinking water/milk for cattle, sheep, pigs and chickens

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

**Active substances:**

500 mg Sulfadiazine equivalent to 543.9 mg Sulfadiazine sodium
100 mg Trimethoprim

**Excipients:**

| Qualitative composition of excipients and other constituents |
|---|
| Polysorbate 80 |
| Maltodextrin |

Off-white to light beige powder.

## 3. CLINICAL INFORMATION

### 3.1 Target species

Cattle (pre-ruminant calves, sheep (pre-ruminant lambs), pigs and chickens.

### 3.2 Indications for use for each target species

Cattle (pre-ruminant calves) and sheep (pre-ruminant lambs)
Treatment and metaphylaxis of respiratory infections caused by *Mannheimia haemolytica* or *Pasteurella multocida* and infections caused by *Escherichia coli*.

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

Pigs
Treatment and metaphylaxis of respiratory infections caused by *Actinobacillus pleuropneumoniae* or *Pasteurella multocida* and infections caused by *Streptococcus suis* or *Escherichia coli*.

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

Chickens
Treatment and metaphylaxis of colibacillosis caused by *Escherichia coli*.

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

## 3.3 Contraindications

Do not use in ruminating animals.
Do not use in animals suffering from severe liver or kidney disease, oliguria or anuria.
Do not use in cases of hypersensitivity to the active substance or to 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 product in the drinking water should be adjusted to make sure that the recommended dosage is being consumed.

Pigs, cattle (pre-ruminant calves) and sheep (pre-ruminant lambs): the uptake of medication by animals may be altered as a consequence of illness. In case of insufficient water uptake, animals should be treated parenterally instead, using a suitable injectable veterinary medicinal product prescribed by the veterinarian.

## 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 sulfonamides, 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. It is particularly of importance for *E. coli* infections where high percentages of resistance are observed (see section 4.2).

Use of the veterinary medicinal 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 veterinary medicinal product deviating from the instructions given in the Summary of product characteristics (SPC) may increase the prevalence of bacteria resistant to sulfadiazine and trimethoprim and may also decrease the effectiveness of combinations of trimethoprim with other sulfonamides due to the potential for cross-resistance.

Use of the veterinary medicinal product should be in accordance with official, national and regional antimicrobial policies.

To avoid deterioration of the kidneys due to crystalluria during treatment, it should be ensured that the animal receives sufficient amount of drinking water.

This antimicrobial combination should only be used where diagnostic testing has indicated the need for simultaneous administration of each of the active substances.

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

This veterinary medicinal product contains sulfadiazine, trimethoprim and polysorbate 80, which can cause allergic reactions in some people. Hypersensitivity to sulfonamides may lead to cross reactions with other antibiotics. Allergic reactions to these substances may occasionally be serious.
People with known hypersensitivity (allergy) to sulfonamides, trimethoprim or polysorbate should avoid contact with the veterinary medicinal product.

Avoid skin and eye contact during preparation and administration. Wear personal protective equipment consisting of impervious (latex or nitrile) gloves (in compliance with Directive 89/686/EEC and EN374 norm), protective masks, eye protection and suitable protective clothing. In case of accidental contact with the eyes or skin, wash the affected area with plenty of water, and if skin rash occurs, seek medical advice immediately and show the package leaflet or the label to the physician.

This veterinary medicinal product may be harmful if ingested. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

### 3.6 Adverse events

Chickens:

| | |
|---|---|
| Very rare (<1 animal / 10,000 animals treated, including isolated reports): | Decreased drinking |
| Undetermined frequency (cannot be estimated from the available data) | Hypersensitivity reactions |

Cattle (pre-ruminant calves), sheep (pre-ruminant lambs) and pigs:

| | |
|---|---|
| Undetermined frequency (cannot be estimated from the available data) | Hypersensitivity reactions |

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

Do not use during pregnancy, lactation or lay.
Laboratory studies in rats and rabbits have shown evidence of teratogenic and foetotoxic effects.

## 3.8 Interaction with other medicinal products and other forms of interaction

Do not administer concomitantly with coccidiostats or veterinary medicinal products containing sulfonamides.

Do not associate with PABA (para-aminobenzoic acid).

Sulfonamides potentiate anticoagulants action.

## 3.9 Administration routes and dosage

In drinking water/milk (milk replacer) use (see details below for each target species).

Cattle (pre-ruminant calves) and sheep (pre-ruminant lambs):

12.5 mg of sulfadiazine and 2.5 mg of trimethoprim per kg body weight (corresponding to 25 mg of the veterinary medicinal product per kg body weight), every 12 hours for 4 to 7 consecutive days, to be dissolved in the milk replacer.

Pigs:

25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight per day (corresponding to 50 mg of the veterinary medicinal product per kg body weight per day), for 4 to 7 consecutive days, to be dissolved in drinking water.

Chickens:

25 mg of sulfadiazine and 5 mg of trimethoprim per kg body weight per day (corresponding to 50 mg of the veterinary medicinal product per kg body weight per day), for 4 to 7 consecutive days, to be dissolved in drinking water.

Guidance for preparing veterinary medicinal product solutions:
To ensure a correct dosage, body weight should be determined as accurately as possible.

The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of sulfadiazine and trimethoprim should be adjusted accordingly.

The use of suitably calibrated measuring equipment is recommended.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{\text{mg veterinary medicinal product/kg body weight/day} \times \text{average body weight (kg) of animals to be treated}}{\text{average daily water intake (l/animal)}} = \text{mg veterinary medicinal product per litre of drinking water/milk replacer}$$

Prepare the solution with fresh tap water (or milk replacer for cattle (pre-ruminant calves)) immediately before use. Milk replacer should be prepared prior to the addition of the veterinary medicinal product. The solution should be vigorously stirred for 5 minutes. Medicated milk replacer should be consumed immediately after preparation. Water uptake should be monitored at frequent intervals during medication. The medicated drinking water should be the sole source of drinking water for the treatment duration. Any medicated drinking water which is not consumed within 24 hours should be discarded. After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

The maximum solubility of the veterinary medicinal product is 1g/L. During dissolution, the solution should be stirred for at least 2 minutes. Solutions should be checked visually for complete dissolution.
For stock solutions and when using a proportioner, take care not to exceed the maximum solubility. Adjust flow rate settings of the dosing pump according to concentration of the stock solution and water intake of the animals to be treated.

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

Sulfonamides overdose causes renal toxicity. In this case, the administration of the veterinary medicinal product has to be stopped.

### 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

Cattle (pre-ruminant calves)
Meat and offal: 12 days.

Sheep (pre-ruminant lambs)
Meat and offal: 12 days.

Pigs
Meat and offal: 12 days.

Chickens
Meat and offal: 12 days.
Not for use in birds producing or intended to produce eggs for human consumption.

# 4. PHARMACOLOGICAL INFORMATION

## 4.1 ATCvet code: QJ01EW10

## 4.2 Pharmacodynamics

Trimethoprim and sulfadiazine have a broad spectrum of activity against gram-positive and gram-negative bacteria including *Streptococcus suis, Pasteurella multocida, Actinobacillus pleuropneumoniae, Mannheimia haemolytica* and *E. coli in vitro*. Sulfonamides block the conversion of para-aminobenzoic acid to dihydrofolic acid. Their effect is bacteriostatic.

Trimethoprim inhibits dihydrofolic acid reductase, which converts dihydrofolic into tetrahydrofolic acid.

The effect of trimethoprim in combination with sulfonamides is bactericidal. Sulfonamides and trimethoprim thus cause a successive blockage of two enzymes that play an important role in the metabolism of bacteria. Their effect is synergistic and time dependent.

Bacterial resistance to trimethoprim and to sulfonamides 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.

A summary of available susceptibility data of *E. coli* from the Vetpath IV (years 2015 and 2016) and from the 2019 Resapath program report is presented below.

Susceptibility data presented showed high levels of resistance among *E. coli* isolated from pigs (39% classified as susceptible in the VetPath IV data - n=333 - and 51% in Resapath data - n= 1834).

For cattle (pre-ruminant calves), the VetPath IV data (n=230) showed a susceptibility of 70%, while in the Resapath program for cattle (pre-ruminant calves) (n=4148) and sheep (pre-ruminant lambs) (n=334), the percentage of susceptibility was 60% and 61%, respectively.

For chickens and turkeys, data taken from the VetPath IV program (n=65) showed a susceptibility of *E. coli* of 83%.

## 4.3 Pharmacokinetics

The pharmacokinetic properties of sulfadiazine and trimethoprim are species dependent. With continuous administration in the drinking water, the steady-state concentrations are achieved in approximately 2 days.

Overall, sulfadiazine has almost complete and rapid oral absorption with very persistent plasma rates and oral bioavailability ranging between 80 to 90%. Its binding to plasma proteins varies between 28 to 80%, according to the species (28%

pigs, 49% cattle (pre-ruminant calves), 80% chickens). It presents a wide distribution in most tissues and organs in all species. Sulfadiazine is metabolised in the liver, and mainly excreted in the urine.

Trimethoprim is rapidly and well absorbed following oral administration with oral bioavailability ranging from 80 to 90%. Approximately 30% to 60% of trimethoprim is bound to plasma proteins, in percentages that vary according to the species (49% pigs, 57% cattle (pre-ruminant calves), 77% chickens) and it presents a wide distribution in most tissues and organs in all species. Tissue concentrations, especially in lungs, liver and kidneys are often higher than the corresponding plasma concentrations. Trimethoprim is likely metabolised in the liver, and mainly excreted in the urine. The elimination rate of trimethoprim is generally faster than the one of sulfadiazine in all species.

**Environmental properties**
Trimethoprim is persistent in soils.

## 5. PHARMACEUTICAL PARTICULARS

### 5.1 Major incompatibilities

Do not add to drinking water treated with sodium hypochlorite at 5 ppm.

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: 30 months.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dissolution in drinking water according to directions: 24 hours.
Shelf life after dissolution in milk replacer according to directions: 1 hour.

### 5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

### 5.4 Nature and composition of immediate packaging

100 g pillow sachet and 1 kg resealable block-bottom zipped sachet made of polyethylene/aluminium/polyethylene terephthalate laminate.

### 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

Huvepharma NV

## 7. MARKETING AUTHORISATION NUMBER

Vm 30282/3003

## 8. DATE OF FIRST AUTHORISATION

03 October 2023

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

October 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*).

Approved 03 October 2023