

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Cubarmix Equi 400 mg/g + 80 mg/g oral powder for horses (AT, BE, DE, ES, HU, IE, IT, NL, PL, RO, UK(NI))

Trisulmix Equi 400 mg/g + 80 mg/g oral powder for horses (FR)

Cubarmix Vet 400 mg/g + 80 mg/g oral powder for horses (DK, SE)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substances:

Sulfadiazine: 400 mg

Trimethoprim 80 mg

Excipients:

Qualitative composition of excipients and other constituents
Vanilla flavour
Lactose monohydrate

White to cream coloured powder.

3. CLINICAL INFORMATION

3.1 Target species

Horses.

3.2 Indications for use for each target species

Treatment of infections caused by micro-organisms susceptible to the combination of sulfadiazine and trimethoprim, such as infections of the upper respiratory tract and wound infections.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substances (or any other sulfonamide) or to any of the excipients.

Do not use in horses with severe liver parenchymal damage or kidney damage.

Do not use in horses with blood dyscrasias or cardiac arrhythmias.

3.4 Special warnings

In case of infections involving purulent conditions, trimethoprim-sulfonamides combinations are not recommended due to a diminished efficacy under such conditions.

Cross-resistance has been shown between sulfadiazine and other sulfonamides. Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to combinations of trimethoprim with other sulfonamides because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:

The use in horses under 1 year old should be avoided.

Throughout the treatment, animals should have free access to drinking water to avoid possible crystalluria.

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 should be in accordance with official, national and regional antimicrobial policies.

Narrow spectrum antibiotic therapy with a lower risk of antimicrobial resistance selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

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

This veterinary medicinal product may cause hypersensitivity reactions following inhalation, ingestion or skin contact. Hypersensitivity to sulfonamides may lead to cross reactions with other antibiotics. Allergic reactions to sulfonamides may occasionally be serious. People with known hypersensitivity to sulfadiazine (or other sulfonamides) or trimethoprim should avoid contact with the veterinary medicinal product.

The veterinary medicinal product may be harmful in case of accidental ingestion including hand-to-mouth contact, inhalation or accidental contact with unprotected skin and eyes. This veterinary medicinal product may cause irritation to skin, eyes and respiratory system.

Care should be taken not to inhale any dust and contact with skin and eyes should be avoided. Take care to avoid accidental ingestion, especially by children.

Personal protective equipment consisting of rubber gloves, goggles and a dust mask (disposable half-mask respirator conforming to EN149 or a non-disposable respirator EN140 with a filter EN143) should be worn when mixing or handling the veterinary medicinal product. Do not smoke, eat or drink while handling the veterinary medicinal product. The veterinary medicinal product should be stored at a safe place out of the reach and site of children.

In case of skin or eyes contact, rinse immediately with plenty of water.

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

Wash hands after use.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Horses:

Common (1 to 10 animals / 100 animals treated):	Digestive tract disorder (e.g. loose stool, diarrhoea, colitis) ¹
Undetermined frequency (cannot be estimated from the available data)	Hypersensitivity reaction (e.g. urticaria) Inappetence Hepatic disorder Renal disorder, renal tubular disorder ² Haematologic effects (e.g. anaemia, thrombocytopenia, or leucopenia) Haematuria, crystalluria

¹ Treatment should be discontinued and symptomatic treatment initiated, if needed.

² tubular obstruction

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 or immediate packaging for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy or lactation in mares.

Pregnancy:

Laboratory studies in rats and rabbits have shown evidence of teratogenic effects at dosages that were above the therapeutic dosages.

Do not use during pregnancy.

Lactation:

When administered to lactating females, small amounts of trimethoprim and sulfadiazine are present in the maternal milk.

The use is not recommended during lactation.

3.8 Interaction with other medicinal products and other forms of interaction

Potentiated sulfonamides used in conjunction with alpha₂-adrenoceptor agonists like detomidine are known to be able to cause fatal arrhythmias in the horse.

Do not administer concurrently with para-aminobenzoic acid (PABA). Local anaesthetics from the group of para-aminobenzoic acid esters (procaine, benzocaine, tetracaine) can locally inhibit the effect of sulfonamides.

3.9 Administration routes and dosage

In feed use.

The recommended dose per administration is 30 mg combined active ingredients per kg body weight, meaning 25 mg sulfadiazine and 5 mg trimethoprim per kg body weight or 62.5 mg veterinary medicinal product/kg body weight (equivalent to 12.5 g powder per 200 kg of BW) administered once daily for 5 days.

To ensure a correct dosage, body weight should be determined as accurately as possible.

The use of suitably calibrated weighing equipment is recommended.

Mix with a small quantity of feed. It is recommended that other feed be withdrawn until medicated feed has been consumed.

The veterinary medicinal product is to be administered only for the treatment of individually fed animals.

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

In case of an overdose loose faeces or diarrhoea may be observed. This is generally self-limiting, but treatment should be discontinued and if needed symptoms can be treated symptomatically e.g. fluid therapy in case of dehydration.

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

Meat and offal: 6 months.

Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet-code:

QJ01EW10

4.2 Pharmacodynamics

Sulfadiazine (SDZ) belongs to the group of sulfonamide chemotherapeutics, trimethoprim (TMP) belongs to the diaminopyrimidines.

Sulfadiazine inhibits the incorporation of para-aminobenzoic acid into folic acid and trimethoprim inhibits the enzyme dihydrofolate reductase which converts dihydrofolic acid into tetrahydrofolic acid. TMP and SDZ act together synergistically as a time-dependent antimicrobial with a double-blockade in the synthesis of purines which are required for DNA synthesis.

TMP-SDZ combinations have a broad bactericidal action against many gram-positive and gram-negative aerobic bacteria, but a limited bactericidal action against anaerobic bacteria.

Bacterial resistance to trimethoprim and to sulfonamides can be mediated via five main mechanisms: changes in the permeability barrier and/or efflux pumps, naturally insensitive target enzymes, changes in the target enzymes, mutational or recombinational changes in the target enzymes, and acquired resistance by drug-resistant target enzymes. Cross resistance has been shown between the combination SDZ/TMP and combinations of TMP with other sulfonamides. Spread of the resistance genes of TMP/SDZ is mainly chromosomal-, plasmid- and transposon-encoded.

Sulfonamide resistance genes are linked chromosomally (*folP* genes) or extrachromosomally, e.g. to integron 1 (*sul1* genes) and plasmids (*sul2* genes). The result of the expression of these genes is a change in the structure of the dihydropteroate synthetase enzyme so that sulfonamides lose their ability to bind and the mechanism of their action is disrupted. There is mutual cross-resistance in the sulfonamide group.

TMP resistance genes (*dfr* genes) are linked chromosomally or extrachromosomally, e.g. on integrons 1 and 2 or on transposons. Extrachromosomal *dfr* genes are divided into two subgroups. More than 30 *dfr* genes are currently described. Their action is manifested by a change in the structure of the dihydrofolate reductase enzyme and its sensitivity to trimethoprim. Chromosomally linked resistance is manifested either by overproduction of dihydrofolate reductase or loss of function of the thymidylate synthase enzyme.

4.3 Pharmacokinetics

At the recommended dosage for horses of 30 mg of active substances (meaning 25 mg sulfadiazine and 5 mg trimethoprim) per kg body weight mean maximum plasma concentrations of approximately 16.8 mg of sulfadiazine/L and 1.9 mg of trimethoprim/L are obtained after a median 2.6 and 0.9 hours, respectively. The plasma half-life for sulfadiazine is 7.7 hours and for trimethoprim 2.7 hours.

Both substances are metabolized in the liver; sulfadiazine by acetylation and glucuronidation and trimethoprim by hydroxylation and glucuronidation. Excretion takes place mainly via the kidneys, only to a lesser extent via faeces.

Environmental properties

Trimethoprim is persistent in soil.

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:

- Container: 3 years.
- Sachet: 2 years.

Shelf life after first opening the immediate packaging:

- Container: 3 months.
- Sachet: use immediately.

Shelf life after mixing into the feed: use immediately.

5.3 Special precautions for storage

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

Store in the original package in order to protect from light.

5.4 Nature and composition of immediate packaging

Container: white cylindrical polypropylene container, covered with a low-density polyethylene lid.

The container contains 500 g or 800 g of veterinary medicinal product.

Sachet: single use, white, heat sealed, 4 layer sachet with a inner layer of coextrusion copolymere+PE. The sachets contain 12.5 g, 37.5 g or 50 g of veterinary medicinal product.

Pack sizes:

- Sachets of 12.5 g packed in a carton box containing 15 or 100 sachets.
- Sachets of 37.5 g packed in a carton box containing 5, 10 or 100 sachets.
- Sachets of 50 g packed in a carton box containing 5, 10 or 100 sachets.

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

Dopharma Research B.V.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

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

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>).