1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Vetmulin 450 mg/g granules for use in drinking water for pigs. (All MS except FR)

Vetmulin 364 mg/g granules for use in drinking water for pigs. (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each gram contains tiamulin hydrogen fumarate 450.0 mg (equivalent to tiamulin 364.2 mg) (All MS except FR)

Each gram contains 364.2 mg tiamulin as 450.0 mg Tiamulin hydrogen fumarate (FR only)

Excipients: For a full list of excipients: see section 6.1

3. PHARMACEUTICAL FORM

Granules for use in drinking water,

White to pale yellow granules

4. CLINICAL PARTICULARS

4.1 Target species

Pigs

4.2 Indications for use (specifying the target species)

For the treatment of swine dysentery caused by tiamulin-susceptible *Brachyspira hyodysenteriae*.
For the treatment of enzootic pneumonia caused by tiamulin-susceptible *Mycoplasma hyopneumoniae.*

The presence of the disease in the herd should be established before use.

4.3 Contraindications

Do not use in animals with known hypersensitivity to the active ingredient or to any of the excipients.

Do not use in case of resistance to tiamulin.

Do not administer products containing ionophores such as monensin, salinomycin or narasin during or for at least 7 days before or after treatment with the product.

See also section 4.8.

4.4 Special warnings (for each target species)

The uptake of medication by animals can be altered as a consequence of illness. For animals with a reduced water intake, treat parenterally using an appropriate injectable product.
Long term or repeated use should be avoided by improving management practice and thorough cleansing and disinfection.

4.5 Special precautions for use

Special precautions for use in animals

Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for tiamulin, the use of the product should be based on bacteriological sampling and susceptibility testing and take into account official and local antimicrobial policies. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tiamulin and may decrease the effectiveness of treatment with other pleuromutilins due to the potential for cross-resistance.

Strategic treatment should be limited to animals where tiamulin susceptible agents have been isolated in the herd.

Special precautions for the person administering the veterinary medicinal product to animals

When mixing, direct contact with the skin and mucous membranes should be avoided. Accidental ingestion should be avoided. Wear overalls, safety glasses, mask and impervious gloves when handling or mixing the product. Wash affected parts if skin contact occurs. If accidental eye contact occurs, immediately rinse thoroughly with water.

Seek medical advice if irritation persists. Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.

People with known hypersensitivity to tiamulin should avoid contact with the veterinary medicinal product.

4.6 Adverse reactions (frequency and seriousness)

On rare occasions, hypersensitivity to tiamulin following oral administration is reported in terms of increased salivation, mild oedema, acute dermatitis with cutaneous erythema and intense pruritus. The adverse reactions are often mild and transient but on very rare occasions may be serious and can lead to apathy or death. If these typical side effects occur, stop treatment immediately and clean animals and pens with water. Normally, the animals recover fast thereafter. Symptomatic treatment such as electrolyte therapy and an anti-inflammatory therapy may be useful.

4.7 Use during pregnancy, lactation or lay

The product can be used during pregnancy and lactation.

4.8 Interaction with other medicinal products and other forms of interaction

Tiamulin is known to produce clinically important – often lethal – interactions with ionophore antibiotics, including monensin, narasin, salinomycin. Therefore, pigs should not receive products such compounds during or for at least 7 days before and after treatment with the product. Severe growth depression or death may result.

Tiamulin may lessen the antibacterial activity of beta-lactam antibiotics whose action is dependent on bacterial growth..

4.9 Amount(s) to be administered and administration route

For oral administration through the drinking water. The uptake of medicated water depends on the clinical condition of the animals, the environment, the age and the kind of feed provided. In order to obtain the correct dosage, the concentration of tiamulin has to be adjusted accordingly. Use suitably calibrated weighing equipment to weigh the necessary amount of product .

Swine dysentery caused by *Brachyspira hyodysenteriae*:
8.8 mg tiamulin hydrogen fumarate per kg bodyweight per day for 5 consecutive days.

Enzootic pneumonia caused by *Mycoplasma hyopneumoniae*
15-20 mg tiamulin hydrogen fumarate per kg bodyweight per day for 5 days.

The uptake of medicated water depends on the actual body weight, the water consumption, the clinical condition of the animals, the environment, the age and the kind of feed provided. In order to obtain the correct dosage, the concentration of tiamulin should be calculated, as follows:

$$\frac{\text{…. mg of the product per kg body weight and day} \times \text{Average body weight (kg)}}{\text{Average daily water intake (l/animal)}} = \text{....mg of the product per litre of drinking water}$$

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

The product can be added directly to the required volume of drinking water or a concentrated solution can be prepared to be diluted to the final concentration afterwards. The maximum solubility of the product is 10 gram/liter.

Fresh solution should be made up each day and other sources of drinking water should be prevented. Do not use rusty recipients for preparing the solutions.

To avoid formation of resistance by consumption of tiamulin in sub therapeutic doses, the watering equipment has to be cleaned adequately at the end of treatment.

If there is no response to treatment within 3 days, the diagnosis should be re-considered and treatment should be changed, if necessary. Water intake should be monitored at frequent intervals during medication.

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

A single oral dose of 100 mg/kg BW caused hyperpnoea and abdominal complaints in pigs. At a dose of 150 mg/kg the only effects on the central nerve system was lethargy. A dose of 55 mg/kg during 14 days caused increased salivation and a mild irritation of the stomach. Tiamulin hydrogen fumarate has a relatively high therapeutic index in pigs. The minimum lethal dose has not been established in pigs.

If suspected adverse reactions do occur due to overdose, the medication should be discontinued and appropriate symptomatic treatment should be initiated.

4.11 Withdrawal period(s)

Meat and offal: 5 days

5. PHARMACOLOGICAL OR IMMUNOLOGICAL PROPERTIES

ATC Vet Code: QJ01XQ01

Pharmacotherapeutic group: Antibacterials for systemic use, Pleuromutilins

5.1 Pharmacodynamic properties

Tiamulin hydrogen fumarate is a semi-synthetic diterpene antibiotic pleuromutilin, produced by *Pleurotus mutilis,* later renamed *Clitopilus scyphoides.*
Tiamulin is active against pathogenic mycoplasmas, against some Gram-positive organisms and anaerobes.

Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the ribosome level and the primary binding site is on the 50S subunit and possibly a secondary site where the 50S and 30S subunits join. It appears to inhibit microbial protein production by producing biochemical inactive initiation complexes, which prevent elongation of the polypeptide chain

Research has shown that resistant bacterial mutants can be created through multi step resistance. Horizontal transferable resistance has also been described (eg. *vga* genes & *cfr* gene). In practice, resistance in mycoplasmas has been reported rarely. Resistance against *B. hyodysenteriae* has been seen, and can vary geographically.
If response to treatment of dysentery with the product is poor, then the possibility of resistance must be considered.
Cross resistance between tiamulin and tylosin tartrate has been reported: micro-organisms that are resistant for tiamulin, are also resistant for tylosin tartrate, but not vice versa. Transferable resistance mechanism (cfr) can cause cross-resistance to lincosamides, streptogramines (A) and phenicols (florfenicol).

Resistance in *Brachyspirae hyodysenteriae* can be caused by a point mutation in the 23S rRNA gene and/or the ribosomal protein L3 gene..

5.2 Pharmacokinetic particulars

Tiamulin is well absorbed from the gastrointestinal tract of pigs. 2-4 hours (t_{max}) after the oral administration of 10 mg tiamulin/kg BW, a C_{max} of 1 µg/ml was measured. An oral administration of 25 mg/kg gave a C_{max} of 1.82 µg/ml. There is a very good distribution in the tissues. There is accumulation in lungs and in the colon. 30-50% of the tiamulin is bound to serum proteins.

Tiamulin is rapidly metabolised in the liver (hydroxylation, de-alkalysation, hydrolysis). At least 16, biologically inactive metabolites have been identified. The excretion is through the bile and faeces (70-85%). The remainder is excreted through the urine (15-30%).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Lactose monohydrate

6.2 Incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution or reconstitution according to directions: 24 hours

6.4 Special precautions for storage

Do not refrigerate or freeze.
Store in original container.

6.5 Nature and composition of immediate packaging

Block bottomed zipped 1 kg bag Polyethylene terephthalate/aluminium/low density Polyethylene

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7.1 MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80

2600 Antwerpen
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE