1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Vetmulin 125 mg/ml Oral Solution for use in drinking water for pigs **(BE, BG, CZ, EL, HU, IE, NL, PL, RO, UK, ES, IT, AT, DE, PT)**

Vetmulin Vet, Oral Solution for use in drinking water for pigs (DK)

Vetmulin 101.2 mg/ml Oral Solution for use in drinking water for pigs (FR)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance 125 mg Tiamulin hydrogen fumarate (equivalent to 101.2 mg tiamulin

Excipients

Methyl parahydroxybenzoate (E218):0.90 mg
Propyl parahydroxybenzoate (E216):0.10 mg

For a full list of excipients: see section 6.1

3. PHARMACEUTICAL FORM

Oral solution for use in drinking water

Clear colourless to slightly yellow liquid.

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 or further complicated by tiamulin-susceptible *Brachyspira hyodysenteriae.*

Treatment of enzootic pneumonia and the reduction of lesions caused by tiamulin-susceptible *Mycoplasma hyopneumoniae*

4.3 Contraindications

Do not use in animals with known hypersensitivity to the active ingredient.

Do not administer products containing monensin, salinomycin ,narasin, maduramycin or other ionophores during or for at least seven days before or after treatment with the product. See also section 5.1. and 4.8.

4.4 Special warnings (for each target species)

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water, animals should be treated parenterally.

4.5 Special precautions for use

4.5.1 Special precautions for use in animals

Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies

Strategic treatment should be limited to animals where tiamulin susceptible agents have been isolated in the herd. Long term or repeated use should be avoided by improving management practice and thorough cleansing and disinfection

Severe growth depression or death may result if animals receive products containing monensin, salinomycin, narasin, maduramycin or other ionophores during or for at least seven days before or after treatment with the product. See also section 4.3 and 4.8.

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

People with known hypersensitivity to the active substance must not administer the veterinary medicinal product .

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. Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately. If accidental eye contact occurs, immediately rinse thoroughly with water. Seek medical advice if irritation persists.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

In rare cases, hypersensitivity to tiamulin following oral administration is reported in terms of cutaneous and genital erythema and pruritus. The adverse reactions are often mild and transient but in very rare cases may be serious. 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

Animals should not receive products containing monensin, salinomycin, narasin, maduramycin or other ionophores during or for at least seven days before or after treatment with the product. Severe growth depression, paralysis or death may result.

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

Cross resistance may occur between other members of macrolides or lincosamide antibiotics. Resistance to the active substance and cross resistance should be considered before the product is used.

See also section 4.3 and 4.5.1.

4.9 Amount(s) to be administered and administration route

For oral administration through the drinking water

Swine dysentery

8.8 mg tiamulin hydrogen fumarate per kg bodyweight per day (equivalent to 7ml product per 100 kg bodyweight per day) for 5 consecutive days.

Enzootic pneumonia

15-20 mg tiamulin hydrogen fumarate per kg bodyweight per day (equivalent to 12 – 16 ml product per 100 kg bodyweight per day) for 5 days.

Administration:

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:

$$\frac{\text{.....ml Vetmulin 125 mg/ml oral solution for use in drinking water per kg body weight and day} \times \text{Average body weight (kg)}}{\text{Average daily water intake (l/animal)}} = \text{....ml Vetmulin 125 mg/ml oral solution for use in drinking water per litre of drinking water}$$

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

The required doses should be measured by suitably calibrated measuring equipment. Medicated water should be refreshed every 24 hours. The uptake of consistent amounts of drinking water should be ensured by sufficient drinking facilities.

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.

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 nervous 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 signs of poisoning are observed, withdraw rapidly the medicated water and replace it with fresh water. Appropriate symptomatic treatment should be initiated.

4.11 Withdrawal period(s)

Meat and offal
5 days

5. PHARMACOLOGICAL OR IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, Pleuromutilins.

ATC Vet Code QJ01XQ01

5.1 Pharmacodynamic properties

Tiamulin hydrogen fumarate is a semi-synthetic derivative of the diterpene antibiotic pleuromutilin, produced by *Pleurotus mutilis.*

Tiamulin is bacteriostatic and inhibits protein synthesis. The product has a strong affinity for the ribosome, causing an inhibition of peptidyltransferases. As a result protein synthesis is stopped.

In vitro research has shown that resistant bacterial mutants can be created through multi step resistance. In practice, resistance in mycoplasmas has been reported rarely. Resistance against *B. hyodysenteriae* has been seen, however this spirochete remains very sensitive to tiamulin.

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 has been reported.

5.2 Pharmacokinetic properties

Following oral administration, tiamulin hydrogen fumarate is rapidly absorbed from the gastrointestinal tract of pigs (85-90%) and appears in the blood within 30 minutes. 2-4 hours (t_{max}) after the oral administration of 10 mg tiamulin/kg BW in the form of an oral solution, 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 very good distribution in the tissues with accumulation in lungs and in the colon. 30-50% of 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 of tiamulin and its metabolites 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

Disodium phosphate, anhydrous
Methylparahydroxybenzoate (E218)
Propylparahydroxybenzoate (E216)
Ethanol 96%
Purified water

6.2 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
30 months
Shelf-life after first opening the immediate packaging: 3 months
Shelf-life after dilution according to directions: 24 hours

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and composition of immediate packaging

Vetmulin 125 mg/ml is presented in a 1 litre white high density polyethylene bottle with white polypropylene tamper-evident closure sealed with white foamed disk.

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 national requirements.

7.1 MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Vm 30282/4014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1 February 2010

10. DATE OF REVISION OF THE TEXT

1 February 2010

PROHIBITION OF SALE, SUPPLY AND/OR USE

Veterinary prescription