SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

VETMULIN 100 mg/g Oral Granules for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each gram contains: Tiamulin hydrogen fumarate 100 mg (equivalent to tiamulin 81 mg)

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

3. PHARMACEUTICAL FORM

Oral granules

A yellowish granular material

4. CLINICAL PARTICULARS

4.1 Target species

Pig.

4.2 Indications for use (specifying the target species)

For the treatment of swine dysentery caused by *Brachyspira hyodysenteriae.*

4.3 Contraindications

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

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

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 feed 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

Do not use the product in liquid feed.

Due to the likely variability (time, geographical) in the occurrence of resistance of bacteria for tiamulin. 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.

If there is no response to treatment within 3 days, the diagnosis should be re-established.

Avoid concurrent administration of tiamulin and the ionophore products monensin, narasin and salinomycin (see section 4.8). Inform the feed supplier that tiamulin will be used, to avoid incorporating the above listed products in the feed and to avoid contamination of the feed. In case of a suspected contamination, test the feed for the presence of these ionophores before feeding. If adverse effects occur due to an interaction, stop administration of the feed immediately. Remove the contaminated feed as soon as possible and replace with uncontaminated feed.

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

Direct contact with the skin, eyes and mucous membranes should be avoided by wearing overalls, impermeable rubber gloves and safety glasses when mixing or handling the product.

In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists.
When handling the product, inhalation of the dust must be avoided by wearing a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator to European Standard EN 140 with a filter to EN 143.
Accidental ingestion should be avoided.
Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.
Wash hands after use.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician.

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

4.6 Adverse reactions (frequency and seriousness)

In rare cases, hypersensitivity to tiamulin following oral administration is reported in terms of acute dermatitis with cutaneous erythema and intense pruritus. On rare occasions erythema or mild oedema of the skin may occur in pigs following the use of tiamulin.The adverse reactions are usually 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, affected animals recover quickly. 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 containing such compounds during or for at least seven days before or after treatment with this 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 only after incorporation into feed.

The normal dose is 8.8 mg tiamulin hydrogen fumarate (equivalent to 7.1mg tiamulin base) per kg bodyweight per day during 7-10 consecutive days. Considering a feed intake of 50 grams per kg BW, this dose can be achieved by mixing 1.75 g product into 1 kg of feed (175 ppm).

Examples of g of product per animal

BW of animal	Gram of product /animal
20	1,8
25	2,2
30	2,6
35	3,1
40	3,5
45	4,0
50	4,4
60	5,3
70	6,2
80	7,0
90	7,9
100	8,8
125	11,0
150	13,2

The product should be administered to small quantities of feed for immediate consumption by individual animals. Pigs to be treated should be separated and treated individually. For treatment of larger groups, it is recommended to use tiamulin medicated premix for feeding stuff.

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

In case of an altered feed intake (weight class, age, environment) adjust the incorporation in order to guarantee an intake of 8.8 mg tiamulin hydrogen fumarate per kg per day.

In order to achieve a homogeneous intake it is recommended to use a premixture. The required amount of product can first be mixed with 10 % of the intended volume of feed. This premixture should then further be mixed homogeneously with the feed. Alternatively product can be mixed thoroughly into a part of the daily feed ratio and this can be administered prior to the feeding. It has to be ensured, that the calculated dose is completely taken up by the animals. Consideration must be given to pigs whose daily feed intake

is reduced or restricted

The required amount of product must be measured by a suitably calibrated weighing equipment.

The product should only be added to dry non-pelleted feed

If animals don't recover within 3 days after oral medication, diagnosis should be reconsidered and treatment should be changed, if necessary

The treated feed must be prepared daily just before administration to the animals.

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 effect 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.

4.11 Withdrawal period(s)

Meat and offal: 7 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 mutili*s, later renamed *Clitopilus scyphoides*.

Tiamulin is active against pathogenic mycoplasmas, against most Gram-positive microorganisms 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 properties

Tiamulin hydrogen fumarate is well absorbed from the gastrointestinal tract of pigs (85-90%) within 30 minutes. 2-4 hours (t_{max}) after the oral administration of 10 mg tiamulin hydrogen fumarate/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 hydrogen fumarate is rapidly and largely 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

Starch, pregelatinised
Wheat starch

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: 2 years.
Shelf life after first opening the immediate packaging: 3 months.
Feed to which the oral granules has been added should be replaced if not consumed within 24 hours

6.4 Special precautions for storage

Store below 25 °C. Store in a dry place. Protect from direct sunlight. Store in the original container

6.5 Nature and composition of immediate packaging

0.25 kg, 1kg, low density polyethylene bag and three-ply paper secondary bag.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product 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

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerp
Belgium

8. MARKETING AUTHORISATION NUMBER

Vm 30282/4016

9. DATE OF FIRST AUTHORISATION

28 October 2009

10. DATE OF REVISION OF THE TEXT

August 2014

PROHIBITION OF SALE, SUPPLY AND/OR USE

Prescription only medicine.

APPROVED T. NASH **15/08/14**