

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Vetmulin 100 g/kg premix for medicated feeding stuff for pigs, chickens, turkeys and rabbits

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each kg contains tiamulin hydrogen fumarate 100 g (equivalent to tiamulin 81 g).

Excipients:

For a full list of excipients: see section 6.1.

3 PHARMACEUTICAL FORM

Premix for medicated feeding stuff.

A yellowish free-flowing granular material.

4 CLINICAL PARTICULARS

4.1 Target Species

Pigs

Chickens (broiler, replacement pullet, layer/breeder)

Turkeys (poult (grower) and breeder)

Rabbits

4.2 Indications for use, specifying the target species

Pigs

For the treatment and metaphylaxis, when the disease is present at herd level, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the herd should be established before use.

For the treatment of colitis caused by *Brachyspira pilosicoli*

For the treatment of ileitis caused by *Lawsonia intracellularis*

For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens

For the treatment and metaphylaxis, when the disease is present at herd level, of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae* susceptible to tiamulin. The presence of the disease in the herd should be established before use.

Turkeys

For the treatment and metaphylaxis, when the disease is present at herd level, of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae* susceptible to tiamulin. The presence of the disease in the herd should be established before use.

Rabbits

For the treatment and metaphylaxis, when the disease is present at herd level, of epizootic rabbit enterocolitis (ERE) caused by pathogens susceptible to tiamulin. The presence of the disease in the herd should be established before use.

4.3 Contraindications

Do not use in cases of known hypersensitivity to the active substances or 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 seven days before or after treatment with the product. Severe growth depression or death may result.

See 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 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.

In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage

4.5 Special precautions for use

4.5.1 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, the use of the product should be based on bacteriological sampling and susceptibility testing, taking 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.

Inform the feed supplier that tiamulin will be used, to avoid incorporating of ionophore products containing monensin, narasin and salinomycin 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.

4.5.2 Special precautions for the 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.

Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.

Wash hands after use.

Accidental ingestion should be avoided. 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 to pigs is reported in terms of acute dermatitis with cutaneous erythema and intense pruritus. 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

Can be used in pigs during pregnancy and lactation.
 Can be used in laying and breeding chickens and turkeys.
 Can be used in rabbits 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, animals should not receive products containing such compounds during or for at least seven days before or after treatment with this product. Severe growth depression, ataxia, paralysis or death may result. Tiamulin may lessen the antibacterial activity of beta-lactam antibiotics, whose action is dependent on bacterial growth.

4.9 Amounts to be administered and administration route

For oral administration only after incorporation in medicated feed.
 The uptake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin should be adjusted using the following formula:

$$\text{Kg premix/tonne} = \frac{\text{Dose rate (mg/kg)} \times \text{mean bodyweight (kg)}}{\text{Mean feed intake (kg)} \times \text{premix strength (mg/g)}}$$

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

Pigs

Treatment of Swine Dysentery caused *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*.

Dosage: 5 – 10 mg tiamulin hydrogen fumarate (equivalent to 4.05 – 8.1 mg tiamulin base) / kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 – 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Metaphylaxis of Swine Dysentery caused by *B. hyodysenteriae*

Dosage: 2.0 mg tiamulin hydrogen fumarate (equivalent to 1.62 mg tiamulin base) / kg bodyweight daily administered for 2 to 4 weeks. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected.

Metaphylaxis with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*

Dosage: 7.5 mg tiamulin hydrogen fumarate (equivalent to 6.075 mg tiamulin base) / kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*

Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate (equivalent to 4.05 – 8.1 mg tiamulin base) / kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed, providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Chickens (broiler, replacement pullet, laying and breeding hens)

Treatment and metaphylaxis of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.

Dosage - Treatment and metaphylaxis: 25 mg tiamulin hydrogen fumarate (equivalent to 20.25 mg tiamulin base) / kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected.

Turkeys (young poults, breeding turkeys)

Treatment and metaphylaxis of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.

Dosage - Treatment and metaphylaxis: 40 mg tiamulin hydrogen fumarate (equivalent to 32.4 mg tiamulin base) / kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected.

Metaphylaxis with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* and *M. meleagridis* and then as an aid in the metaphylaxis strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The metaphylaxis strategy should include efforts to eliminate the infection from the parent generation.

Rabbits

Treatment of Epizootic Rabbit Enterocolitis (ERE) and metaphylaxis of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.

Dosage: 3 mg tiamulin hydrogen fumarate (equivalent to 2.43 mg tiamulin base) / kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 - 3 days after clinical signs have resolved. Metaphylaxis should be administered during 3 – 4 weeks from the first week after weaning.

Medicated feed may be pelleted using a pre-conditioning step for 5 minutes at a temperature not exceeding 75°C.

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

Pigs: A single oral dose of 100 mg/kg BW caused hyperpnoea and abdominal discomfort in pigs. At a dose of 150 mg/kg the only effect on the central nervous system was lethargy. A dose of 55 mg/kg for 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.

Chickens and turkeys: The LD₅ for chickens is 1290 mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.

If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

4.11 Withdrawal Period(s)

Pigs

Metaphylaxis (at 2.0 mg/kg bodyweight): Meat and offal: 1 day.

Treatment (at 5-10 mg/kg bodyweight): Meat and offal: 6 days.

Chickens

Meat and offal: 1 day.

Eggs: Zero days.

Turkeys

Meat and offal: 4 days.

Rabbits

Meat and offal: Zero days.

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

ATC Vet Code: QJ01XQ01

Pharmacotherapeutic group: antibacterials for systemic use, pleuromutilins.

5.1 Pharmacodynamic properties

Tiamulin is a bacteriostatic semi-synthetic antibiotic belonging to the pleuromutilin group of antibiotics and acts at the ribosomal level to inhibit bacterial protein synthesis.

Tiamulin has shown *in-vitro* activity against a wide range of bacteria including *Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*, *Lawsonia intracellularis* and *Mycoplasma* spp.

Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S 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.

Mechanisms responsible for resistance development in *Brachyspira* spp to the pleuromutilin class of antibiotics are considered to be based on mutations at the ribosomal target site. Clinically relevant resistance to tiamulin requires combinations of mutations around the tiamulin binding site. Resistance to tiamulin may be associated with decreased susceptibility to other pleuromutilins.

5.2 Pharmacokinetic properties

Pigs:

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%).

Chickens

Tiamulin is well absorbed in chickens (70-95%) after oral administration.

Tiamulin distributes widely through the body and has been shown to concentrate in the liver and kidney (sites of excretion) and in the lung (30 times serum level). Excretion is mainly via the bile (55-65%) and kidney (15-30%) as mainly microbiologically inactive metabolites and is quite rapid, 99% of the dose within 48 hours.

Turkeys

In turkeys serum levels of tiamulin are similar to chickens. In breeders on 0.025% tiamulin the average serum level was 0.36 µg/ml (range 0.22-0.5 µg/ml).

Rabbits

There are no pharmacokinetic data available for rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pregelatinised starch

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

Shelf life after incorporation into meal or pelleted feed: 3 months

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

Polyethylene/paper bag of 5 kg and 20 kg.

Polyethylene/aluminium/polyethylene terephthalate bag of 1 kg.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Huvepharma N.V.
Uitbreidingstraat 80
2600 Antwerpen
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

VPA 10782/005/002

9 DATE OF THE FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20th February 2009

Date of last authorisation: 19th February 2014

10 DATE OF REVISION OF THE TEXT

June 2015