

Summary of Product Characteristics

1 NAME OF THE VETERINARY MEDICINAL PRODUCT

Tialin 250 mg/ml solution for use in drinking water for pigs, chickens and turkeys

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains:

Active substance:

Tiamulin hydrogen fumarate 250.0 mg
equivalent to 202.4 mg of tiamulin

Excipients:

Ethanol 96% 200.0 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Target Species

Pigs, chickens (pullets, breeders, layer hen) and turkeys (breeders, layer hen).

4.2 Indications for use, specifying the target species

Pigs

- Treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin.
- Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin.
- Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin.
- Treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin.
- Treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

The presence of the disease in the herd must be established before the product is used.

Chickens

Treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae* susceptible to tiamulin.

The presence of the disease in the herd must be established before the product is used.

Turkeys

Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis* susceptible to tiamulin.

The presence of the disease in the herd must be established before the product is used.

4.3 Contraindications

Do not use in pigs and birds that could receive products containing monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Do not use in cases of hypersensitivity to the active substance or to the excipient. See section 4.8 for information regarding interaction between tiamulin and ionophores.

4.4 Special warnings for each target species

Pigs with reduced water intake and/or in a debilitated condition should be treated parenterally.

The water intake of birds should be monitored at frequent intervals during treatment, especially in hot weather, because water intake may be depressed during the administration of tiamulin. This appears to be a concentration-dependent effect and does not appear to have any adverse effect on the overall performance of the birds or efficacy of the veterinary medicinal product. 500 mg tiamulin hydrogen fumarate in 4 litres of water may reduce intake by approximately 10% and 500 mg tiamulin hydrogen fumarate in 2 litres of water by 15% in chickens. In turkeys, this effect is more marked, with approximately a 20% reduction observed and therefore it is recommended not to exceed a concentration of 500 mg tiamulin hydrogen fumarate in 2 litres of the drinking water.

4.5 Special precautions for use

Special precautions for use in animals

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria. In some European regions, an increasing proportion of *Brachyspira hyodysenteriae* isolates from clinical cases demonstrate significantly reduced in vitro susceptibility to tiamulin.

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tiamulin.

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

This product may cause skin and eye irritation. When mixing, direct contact with the skin and eyes should be avoided by wearing impermeable rubber gloves and safety glasses.

In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists.

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

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

On very rare occasions erythema or mild oedema of the skin may occur in pigs following the use of tiamulin hydrogen fumarate. Apathy and death may result.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports)

4.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:

Can be used in pigs during pregnancy and lactation.

Laying birds:

Can be used in laying chickens and in breeding chickens and turkeys.

4.8 Interaction with other medicinal products and other forms of interactions

Tiamulin has been shown to interact with ionophores such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

If signs of an interaction do occur, stop both the administration of tiamulin-medicated drinking water and also the administration of ionophore-contaminated feed immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Concomitant use of tiamulin and the divalent ionophore anticoccidials lasalocid and semduramicin do not appear to cause any interaction, however the concomitant use of maduramicin may lead to a mild to moderate growth depression in chickens. The situation is transient and recovery normally occurs within 3 - 5 days following withdrawal of tiamulin treatment.

4.9 Amounts to be administered and administration route

In drinking water use.

The product should be administered using suitably calibrated equipment.

Guidance for preparing product solutions:

When medicating large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration.

The product is soluble and stable from low concentration up to maximum concentration of the product of 500 ml/L (1:1 dilution) in water of at least 4° C.

Fresh solutions of tiamulin-medicated drinking water should be made up each day. Any medicated drinking water remaining from the previous day should be discarded.

To ensure the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin has to be adjusted accordingly.

Make sure the animals do not have access to non-medicated water during the period when the medicated water is given.

After the end of the medication period the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

In order to avoid interactions between the ionophores and tiamulin, the veterinarian and farmer should check that the feed label does not state that it contains salinomycin, monensin and narasin.

For chickens and turkeys, in order to avoid interactions between the incompatible ionophores monensin, narasin and salinomycin and tiamulin, the feed mill supplying the birds feed should be notified that tiamulin will be used and that these anticoccidials should not be included in the feed or contaminate the feed.

The feed should be tested for the ionophores prior to use if there is any suspicion that contamination of the feed might occur.

If an interaction does occur, stop tiamulin medication immediately and replace with fresh drinking water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

The dosage of the product to be incorporated should be established according to the following formula:

$$\frac{\text{Dose (ml product per kg body weight per day)} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (litre) per animal per day}} = \text{___ ml product per litre of drinking water}$$

Pigs

i) For the treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 0.035 ml solution)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

ii) For the treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 0.035 ml solution)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

iii) For the treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 0.035 ml solution)/kg body weight administered daily in the drinking water of pigs for 5 consecutive days.

iv) For the treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 0.08 ml solution)/kg body weight administered daily for 5 consecutive days.

v) For the treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 0.08 ml solution)/kg body weight administered daily for 5 consecutive days.

Chickens

For the treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*.

The dosage is 25 mg tiamulin hydrogen fumarate (equivalent to 0.1 ml solution)/kg body weight administered daily for the period of 3 to 5 consecutive days.

Turkeys

For the treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis*.

The dosage is 40 mg tiamulin hydrogen fumarate (equivalent to 0.16 ml solution)/kg body weight administered daily for the period of 3 to 5 consecutive days.

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

Single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg tiamulin hydrogen fumarate/kg body weight no central nervous system effects were noted except for tranquillisation. At 55 mg tiamulin hydrogen fumarate/kg body weight given daily for 14 days, a transient salivation and slight gastric irritation occurred. Tiamulin hydrogen fumarate is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.

Regarding poultry, there is a relatively high therapeutic index with tiamulin hydrogen fumarate and the likelihood of an overdose is considered remote especially as water intake and hence tiamulin hydrogen fumarate intake is reduced if abnormally high concentrations are given. The LD50 is 1090 mg/kg body weight for chickens and 840 mg/kg body weight for turkeys.

The clinical signs of acute toxicity in chickens are – vocalisation, clonic cramps and lying in a lateral position, and in turkeys – clonic cramps, lateral or dorsal position, salivation and ptosis.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

4.11 Withdrawal period(s)

Pigs

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate (equivalent to 0.035 ml solution)/kg body weight)

Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate (equivalent to 0.08 ml solution)/kg body weight)

Chickens

Meat and offal: 2 days

Eggs: Zero days

Turkeys

Meat and offal: 6 days

5 PHARMACOLOGICAL or IMMUNOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterial for systemic use, pleuromutilins, tiamulin.
ATC vet code: QJ01XQ01.

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 a high level of *in vitro* activity against porcine and avian *Mycoplasma* species as well as gram-negative anaerobes (*Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*), and gram-negative aerobes (*Actinobacillus pleuropneumoniae* and *Pasteurella multocida*).

Tiamulin has been shown to act at the 70S ribosome level and the primary binding sites are on the 50S subunit. It appears to inhibit microbial protein production by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.

Bactericidal concentrations can be reached but vary according to the bacterium. It can be as little as two times the MIC for *Brachyspira hyodysenteriae* and *Actinobacillus pleuropneumoniae* but as high as 50 - 100 times the bacteriostatic level for *Staphylococcus aureus*. The MIC distribution for tiamulin against *Brachyspira hyodysenteriae* is bimodal, suggesting reduced susceptibility of some strains to

tiamulin. Due to technical constraints the susceptibility of *Lawsonia intracellularis* is difficult to test *in vitro*.

Resistance derives from chromosomal mutations in the 23S rRNA and *rplC* genes. These chromosomal mutations emerge relatively slowly and in a stepwise fashion and are not transferred horizontally. In addition, resistance genes can be located on plasmids or on transposons like the *vga* genes and the *cfr* gene. This type of resistance is transferable between bacteria and bacterial species. The mechanism of antimicrobial resistance varies according to the bacterial species.

Mutations in the ribosomal protein L3 gene and 23S ribosomal RNA gene affecting the peptidyl transferase centre are associated with reduced susceptibility to tiamulin in *Brachyspira* species. Mutations in the 23S ribosomal RNA gene are also associated with tiamulin resistance in *Mycoplasma* species.

5.2 Pharmacokinetic particulars

Pigs

Tiamulin hydrogen fumarate is well absorbed in the pig (over 90%) following oral administration and widely distributed through the body. Following a single oral dose of 10 mg and 25 mg tiamulin hydrogen fumarate/kg body weight the C_{max} was 1.03 µg/ml and 1.82 µg/ml in serum respectively by microbiological assay and the T_{max} was 2 hours for both. It has been shown to concentrate in the lung, polymorphonuclear leucocytes and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Serum protein binding is approximately 30%. Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon. Colon contents concentrations of tiamulin have been estimated at 3.41 µg/ml following administration of tiamulin hydrogen fumarate at 8.8 mg/kg body weight.

Chickens

Tiamulin hydrogen fumarate is well absorbed in chickens (70-95%) after oral administration and reaches peak concentrations in 2-4 hours (T_{max} 2.85 hours). Following a 50 mg tiamulin hydrogen fumarate/kg body weight single dose the C_{max} was 4.02 µg/ml in serum by microbiological assay and after a 25 mg/kg dose it was 1.86 µg/ml. In drinking water the 250 ppm (0.025%) tiamulin hydrogen fumarate concentration provided a rolling serum level over a 48 hour medication period of 0.78 µg/ml (range 1.4-0.45 µg/ml) and at 125 ppm (0.0125%), 0.38 µg/ml (range 0.65-0.2 µg/ml) in eight-week old chickens. Serum protein-binding was approximately 45%. It 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 hydrogen fumarate are lower with a 50 mg tiamulin hydrogen fumarate/kg body weight single dose giving a C_{max} of 3.02 µg/ml in serum, and 25 mg/kg giving 1.46 µg/ml. These were achieved at about 2-4 hours after dosing. In breeders on 0.025% tiamulin hydrogen fumarate the average serum level was 0.36 µg/ml (range 0.22-0.5 µg/ml). Serum protein-binding was approximately 50%.

5.3 Environmental Properties

Tiamulin is very persistent in soils.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%
Citric acid monohydrate
Disodium phosphate dihydrate
Water purified

6.2 Major 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 dilution or reconstitution according to directions: 24 hours.

6.4 Special precautions for storage

Do not freeze.

6.5 Nature and composition of immediate packaging

White opaque high density polyethylene bottle of 1 liter with transparent graduated scale closed with white opaque low density polyethylene screw-cap.
White opaque high density polyethylene container of 5 liters closed with white opaque high density polyethylene screw-cap.

Not all pack sizes may be marketed.

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

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

Dechra Regulatory B.V.
Handelsweg 25
5531 AE Bladel
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

VPA22622/019/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 July 2018

10 DATE OF REVISION OF THE TEXT

January 2019