1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Entemulin 450 mg/g granules for use in drinking water for pigs, chickens and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

Active substances:
Tiamulin hydrogen fumarate …450 mg (corresponds to 365 mg of tiamulin base)

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

3. PHARMACEUTICAL FORM

Granules for use in drinking water.
White crystalline small granules.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs, chickens (broilers, pullets, layers and breeders), turkeys (fattening and breeding birds).

4.2 Indications for use,specifying the target species

Pigs
i) Treatment of swine dysentery caused by sensitive strains of *Brachyspira hyodysenteriae* and complicated by *Fusobacterium* spp. and *Bacteroides* spp.
ii) Treatment of porcine respiratory disease (PRDC) caused by *M. hyopneumoniae* and viruses such as PRRS and swine influenza, and complicated by *P. multocida* and *A. pleuropneumoniae*.
iii) Treatment of pleuropneumonia caused by *A. pleuropneumoniae*.
Chickens
Prevention and treatment of chronic respiratory disease (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae*.
Turkeys
Prevention and treatment of infectious sinusitis and air sacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.

4.3 Contraindications

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

4.4 Special warnings for each target species

In order to avoid interactions between tiamulin and the incompatible ionophores monensin, narasin and salinomycin, veterinarian and farmer should be notified that this substances not be included in the feed or contaminate the feed.

Concomitant use of tiamulin and the ionophore anticoccidial 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. This interaction does not appear to occur with the ionophores lasalocid or semduramicin.

4.5 Special precautions for use

Special precautions for use in animals

The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water animals should be, where appropriate, treated parenterally.
After the consumption of the medicated drinking water, the animals should be provided with fresh drinking water.
Use of the product should be based on susceptibility testing and should take into account official national and regional policies with respect to the use of antibiotics.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tiamulin.
Unjustified repeated or prolonged use of the product should be avoided and good management practices e.g. good hygiene, proper ventilation, no overstocking should be followed to improve health status of the herd/flock.
If no clinical response to treatment is observed within five days, the treatment should be discontinued and the diagnosis and therapy should be reassessed.

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

When mixing direct contact with the skin, eyes and mucous membranes should be avoided.
Personal protective equipment consisting of safety glasses, mask (disposable respirator in compliance with European standard EN149 or non-disposable respirator in compliance with European standard EN140 fitted with a filter compliant to EN143 standard) and rubber or latex gloves when handling or mixing the product.
In case of accidental contact with skin or mucous membranes, rinse affected area immediately with plenty of water and remove contaminated clothing, which is in direct contact with the skin.
In case of accidental contact with eyes, rinse the eye immediately with plenty of fresh water. If irritation occurs seek medical advice and show the package leaflet or the label to the physician.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
People with known hypersensitivity to tiamulin should handle the product with caution.

Wash hands with soap and water after use.

4.6 Adverse reactions (frequency and seriousness)

On rare occasions erythema or mild oedema of the skin may occur in pigs following the use of tiamulin hydrogen fumarate.
Water intake may be depressed during the administration of tiamulin hydrogen fumarate to birds. It appears to be concentration dependent with 0.025% tiamulin hydrogen fumarate reducing intake by approximately 15%, while with 0.0125% tiamulin hydrogen fumarate the intake is reduced by 10%. It does not appear to have any adverse effect on overall performance of the birds or efficacy of the product, but water intake should be monitored frequently, especially in hot weather.

4.7 Use during pregnancy, lactation or lay

The product can be used during pregnancy and lactation in pigs.
The product can be used in laying and breeding birds as it has been shown to have no adverse effects on egg production, fertility and hatchability in chickens and turkeys.

4.8 Interaction with other medicinal products and other forms of interaction

In pigs, to avoid interaction between tiamulin and tiamulin-incompatible ionophores monensin, salinomycin and narasin, it should be verified that these substances were not included in the feed or contaminated the feed.
In chicken and turkey, to avoid interactions between tiamulin and the incompatible ionophores monensin, narasin and salinomycin, the feed mill supplying the feed should be notified that tiamulin will be used and that these products 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 water medication immediately and replace with fresh water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

4.9 Amounts to be administered and administration route

Pigs
i) Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* and complicated by *Fusobacterium* spp. and *Bacteroides* spp.
The dosage is 8.8 mg tiamulin hydrogen fumarate / kg bw daily, administered in drinking water to pigs for 3-5 consecutive days, depending on the severity and duration of infection. The dose is usually achieved at a concentration of 0.006% tiamulin hydrogen fumarate.
ii) Adjuvant therapy of PRDC caused by *M. hyopneumoniae* and viruses and complicated by *P. multocida* and *A. pleuropneumoniae*.
The dosage is 15.0 to 20.0 mg of tiamulin hydrogen fumarate / kg bw for 5-10 consecutive days. The dose is usually achieved at a concentration of 0.012% - 0.018% tiamulin hydrogen fumarate in drinking water.
iii) Treatment of pleuropneumonia caused by *A. pleuropneumoniae*.
The dosage is 20.0 mg tiamulin hydrogen fumarate / kg bw for 5 consecutive days. The dose is usually achieved at a concentration of 0.018% tiamulin hydrogen fumarate in drinking water.

Add 1g of product to 7.5 liters of water for a solution of 0.006% tiamulin hydrogen fumarate; add 1 g of product to 3.75 liters of water for a solution of 0.012% tiamulin hydrogen fumarate; add 1 g of product to 2.5 liters of water for a solution of 0.018% tiamulin hydrogen fumarate.

When large volumes of medicated water are needed, a concentrated solution should be first prepared (with maximal concentration of 50-60 g product/L water), then diluted to the final concentration. Fresh solutions of tiamulin-medicated drinking water should be made up each day.

Chickens
i) Prevention of chronic respiratory diseases (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae*.
Broilers: 0.0125% - 0.025% tiamulin hydrogen fumarate in drinking water for 3 days in the first week of life, and then 1-2 days every 3-4 weeks depending on risk.
Replacement pullets: 0.0125% - 0.025% tiamulin hydrogen fumarate in drinking water for 3 days in the first week of life, and then 1-2 days every 4-6 weeks depending on risk.
Laying hens and breeding hens 0.0125% tiamulin hydrogen fumarate in drinking water for 3 days every 4 weeks from the beginning of laying period depending on risk.

ii) Treatment of chronic respiratory diseases (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae* in replacement broilers, laying hens and breeding hens. Tiamulin hydrogen fumarate 0.025% in drinking water for 3-5 days.
Tiamulin hydrogen fumarate at a concentration of 0.025% in drinking water provides the following dosage of tiamulin depending on the age of animals:
Broilers 4 weeks old: 30 mg / kg body weight
Pullets 10 weeks old: 30 mg / kg body weight
Layers: 25 mg / kg body weight

The following table is intended as a guide for the prevention and treatment of poultry

Concentration of tiamulin in drinking water	*Liters of water per 100 g of the product*	*Grams of the product per 100 L drinking water*
0.025%	*180*	*55.6*
0.0125%	*360*	*27.8*

	Age of birds in weeks	Amount of drinking water in litres per day	The product (in grams)	Final concentration in %
Prophylaxis	1	18	5	0.0125
	4	60	27.5	0.02
	6	80	35	0.02
	9	110	50.6	0.02
Therapy	4	60	33.3	0.025
	6	80	44.4	
	8	100	55.6	
	10	120	66.7	
	12	140	77.8	
	14	160	88.9	
	16	180	100	
	18	200	111.1	
	20	220	122.2	
	23	250	138.9	

Turkeys
i) For prevention of infectious sinusitis and air sacculitis caused by *Mycoplasma gallisepticum, Mycoplasma meleagridis* and *Mycoplasma synoviae*.
Production (broiler) turkeys: 0.025% tiamulin in drinking water, for 3 days in the first week of life, followed by 1-3 days at 4-6 weeks intervals, depending on risk.
Breeding turkeys: 0.025% tiamulin in drinking water, for 3-5 days at 4 weeks intervals, depending on risk.
ii) For the treatment of infectious sinusitis and air sacculitis caused by *Mycoplasma gallisepticum, Mycoplasma meleagridis* and *Mycoplasma synoviae*.
Production turkeys: 0.025% tiamulin in drinking water, for 3-5 days
Tiamulin hydrogen fumarate at a concentration of 0.025% in drinking water provides the following dosages depending on the age of animals:
- 1 week old poults: 70 mg/kg
- 4 weeks poults: 50 mg/kg
- 8 weeks poults: 25-30 mg/kg
- 20 weeks poults: 20 mg/kg.

Add 1.1g of product to 2 liters of water for 0.025% solution of tiamulin hydrogen fumarate. Add 1.1g of product to 4 liters of water for 0.0125% solution of tiamulin hydrogen fumarate.

When large volumes of medicated water are needed, a concentrated solution should be first prepared (with maximal concentration of 50-60 g product/L water), then diluted to the final concentration. Fresh solutions of tiamulin-medicated drinking water should be made up each day.

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 has a relatively high therapeutic index in pigs. The minimum lethal dose has not been established in pigs.

In poultry, tiamulin has a high theraputic index. The probability of overdose is reduced, as water consumption is limited, and the intake of tiamulin is reduced if abnormally high concentrations are administered.
The LD50 for chickens is 1290 mg/kg and for turkeys 840 mg/kg bodyweight.
Clinical signs of acute toxicity in chickens are - vocalization, clonic seizures and lateral recumbency.
In turkeys signs of acute toxicity include clonic seizures, lateral or dorsal recumbency, salivation and dullness.
If signs of acute intoxication do occur immediately remove the medicated water and replace it with fresh unmedicated water.

4.11 Withdrawal period(s)

Pigs
Meat and offal: 4 days.

Chickens:
Meat and offal: 2 days;
Eggs: zero days.

Turkeys:
Meat and offal: 5 days.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, Pleuromutilins
ATCvet code: QJ01XQ01

Tiamulin is a semi-synthetic bacteriostatic antibiotic belonging to the group of pleuromutilins and acts at ribosomal level by inhibition of protein synthesis in bacteria

5.1 Pharmacodynamic properties

Tiamulin showed a high level of activity *in vitro* against mycoplasmas of pigs and birds as well as against Gram-positive aerobic (staphylococci and streptococci) and anaerobes (clostridia) and Gram-negative anaerobes (*Brachyspira hyodysenteriae, Bacteroides* spp. and *Fusobacterium* spp.) and aerobic gram-negative bacteria (*Actinobacillus pleuropneumoniae*). Tiamulin is not effective against representatives of *Enterobacteriaceae*, such as *Salmonella* or *Escherichia coli*.

Antimicrobial spectrum of tiamulin

Organism	**MIC range (µg/ml)**	**MIC_{50} (µg/ml)**	**MIC_{90}90 (µg/ml)**
B. hyodysenteriae	0.3 – 3.8	0.3	1.7
Bacteroides vulgatus	0.25 – 1.0	-	-
F. necrophorum	0.39	-	-
A. pleuropneumoniae	3.0 – 10.0	5.0	6.0
P. multocida	1.9 – 31.2	-	-
M. hyopneumoniae	0.08 – 0.34	0.06	0.20
M. gallisepticum	0.0005 – 0.25	0.001	0.025
M. synoviae	0.05 – 0.5	0.1	0.25
M. meleagridis	0.025 – 3.13	0.1	0.25

It has been shown that tiamulin acts at the 70S ribosome subunit 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 biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.
Bactericidal concentrations can be obtained at more than 50-100 times the bacteriostatic levels.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin is well absorbed in pigs (over 90%) after oral administration, and widely distributed throughout the body. Following a single oral dose of 10 mg and 25 mg of tiamulin / kg bodyweight Cmax was 1.03 µg / ml and 1.82 µg / ml by microbiological test and Tmax was 2 hours for both doses. Concentration was demonstrated in the lungs, which is the target tissue and the liver, where it is metabolized and excreted (70-85%) in bile, and the remainder is excreted through the kidneys (15-30%). Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon and concentrates there.

Concentration in drinking water	**Daily dose of tiamulin (mg/kg bodyweight)**	**Tiamulin activity (µg/ml)**		
		Lungs	*Tonsils*	*Colon content*
60 ppm	6.2	1.11	a	2.16
120 ppm	13.2	4.26	a	5.59
180 ppm	20.9	8.5	2.5	18.58

a = < below the limit of susceptibility of test

Chickens
Tiamulin is well absorbed in chickens (70-95%) after oral administration and reaches maximum concentration after 2-4 hours (Tmax 2.85 h). After a single dose of 50 mg/kg bodyweight, Cmax was 4.02 µg/ml in serum and 1.86 µg/ml after 25 mg/kg, respectively. In drinking water, after a 48 hours treatment, 0.025% tiamulin a serum concentration of 0.78 µg/ml (between 1.4-0.45 µg/ml) was determined and 0.38 µg/ml serum after 0.0125% tiamulin, in 8 weeks chickens.
Protein binding was about 50% (between 45-52%)
Tiamulin is widely distributed 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%) predominately in forms of microbiologically inactive metabolites and is relatively fast, 99% of the dose is excreted within 48 hours.

Turkeys
In turkeys serum levels of tiamulin are lower after a single dose of 50 mg and 25 mg per kg body weight, with the peak serum concentrations of 3.02 µg / ml and 1.46 µg / ml, respecticvely. These

levels were achieved 2-4 hours after administration. In breeders dosed with 0.025% tiamulin, mean serum level was 0.36 µg / ml (range from 0.22 to 0.5 µg / ml). Tiamulin is concentrated in the eggs, similar to chickens.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

6.2 Incompatibilities

None known.

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: 4 months
Shelf-life after dilution or reconstitution according to directions: 24 hours

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

PET/AL/LDPE bag containing 1 kg, 5 kg or 10 kg of granules. The bag is heat-sealed after filling.
Paper/Paper/HDPE bag containing 1 kg, 5 kg or 10 kg of granules. The bag is sewed after filling.
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

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

1.3.1	Tiamulin hydrogen fumarate
SPC, Labeling and Package Leaflet	CZ

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.