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PACKAGE LEAFLET

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

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:

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

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each gram of white crystalline small granules for use in drinking water contains 450 mg of tiamulin hydrogen fumarate (equivalent to 365 mg of tiamulin base).

4. INDICATION(S)

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*.

5. 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.

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6. ADVERSE REACTIONS

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.

If you notice any serious effects or other effects not mentioned in this leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

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

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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

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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

<i>Concentration of tiamulin in drinking water</i>	<i>Liters of water per 100 g of the product</i>	<i>Grams of the product per 100 L drinking water</i>
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		

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	23	250	138.9	
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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.

9. ADVICE ON CORRECT ADMINISTRATION

When large volumes of medicated water are needed, a concentrated solution should be first prepared, then diluted to the final concentration. Fresh solutions of tiamulin-medicated drinking water should be made up each day.

10. WITHDRAWAL PERIOD

Pigs

Meat and offal: 4 days.

Chickens:

Meat and offal: 2 days;

Eggs: zero days.

Turkeys:

Meat and offal: 5 days.

11. SPECIAL STORAGE PRECAUTIONS

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Keep out of the sight and reach of children.

This veterinary medicinal product does not require any special storage conditions. Do not use after the expiry date stated on the label.

Shelf-life after first opening the container.: 4 months

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

12. SPECIAL WARNING(S)

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 these 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.

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.

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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.

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.

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.

Overdose (symptoms, emergency procedures, antidotes):

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 therapeutic 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.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

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14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

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.

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