PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - COMBINED LABEL AND PACKAGE LEAFLET

Package leaflet Karimulina 1000 mg/g granules for use in drinking water for pigs, chickens and turkeys

Folding carton of 125 g and 1 kg

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:

LABORATORIOS KARIZOO, S.A.
Polígono Industrial La Borda
Mas Pujades, 11-12
08140 – CALDES DE MONTBUI (Barcelona)
Spain

2. Name of the veterinary medicinal product

Karimulina 1000 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 ingredients

Each gram contains:

Active substance:
Tiamulin hydrogen fumarate 1000 mg
(equivalent to tiamulin base 809.4 mg)

White or light yellow, compacted powder.

4. Pharmaceutical form

Granules for use in drinking water.

5. Package size

125 g
1 kg

6. Indication(s)

Pigs

i) Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

ii) Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

iii) Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

iv) Treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae* including infections complicated by *Pasteurella multocida* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

v) 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 flock 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 flock must be established before the product is used.

7. Contraindications

Do not use in pigs and birds receiving veterinary medicinal products or feed additives containing polyether ionophores such as 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.
See also section *Interaction with other medicinal products and other forms of interaction* for more information regarding interaction between tiamulin and ionophores.

8. Adverse reactions

On very rare occasions erythema or mild oedema of the skin may occur in pigs following the use of tiamulin.

Chicken and turkeys: None known.

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).>

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.

Alternatively you can report via your national reporting system {national system details}.

9. Target species

Pigs, chickens and turkeys.

10. Dosage for each species, route(s) and method of administration

In drinking water use.

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

Fresh solutions of tiamulin-medicated drinking water should be made up each day.

The solubility of the product has been confirmed to be between 30.0 g/l (in hard water at 20ºC) and 5.0 g/l (in soft water at 4ºC).

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.

The calculated dose should be measured out with calibrated scales.

The dosage should be established according to the following formula:

$$\frac{\text{mg of the veterinary medicinal product per kg body weight per day} \times \text{Average body weight (kg) of animals to be treated}}{\text{Average daily water intake (litre) per animal per day}} = \text{mg of the veterinary medicinal product per litre of drinking water}$$

Pigs:
i) For the treatment of swine dysentery caused by *Brachyspira hyodysenteriae*
The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 8.8 mg of the veterinary medicinal product) / kg bw per day 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 8.8 mg of the veterinary medicinal product) / kg bw per day 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 8.8 mg of the veterinary medicinal product) / kg bw per day 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 20 mg of the veterinary medicinal product) / kg bw per day 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 20 mg of the veterinary medicinal product) / kg bw per day for 5 consecutive days.

Chickens:
Treatment and metaphylaxis of Chronic Respiratory Infections (CRD) caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*.
The dosage is 25 mg tiamulin hydrogen fumarate (equivalent to 25 mg of the veterinary medicinal product) / kg bw per day for 3 to 5 consecutive days.

Turkeys:
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 40 mg of the veterinary medicinal product) / kg bw per day for 3 to 5 consecutive days.

11. Advice on correct administration

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.

In order to avoid interactions between the polyether 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 polyether ionophores monensin, narasin and salinomycin with tiamulin, the feed mill supplying the birds should be notified that tiamulin will be used and that these anticoccicidials should not be included in the feed, nor contaminate the same.

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

12. Withdrawal period(s)

Withdrawal period(s):
Pigs
Meat and offal: 2 days (dose 8.8 mg tiamulin hydrogen fumarate/kg bw)
Meat and offal: 4 days (dose 20 mg tiamulin hydrogen fumarate/kg bw)

Chickens
Meat and offal: 2 days
Eggs: Zero days

Turkeys
Meat and offal: 6 days

13. Special storage precautions

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

Do not use this veterinary medicinal product after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

14. Special warning(s)

Special warnings for each target species:
Animals with reduced water intake and/or in a debilitated condition should be treated parenterally.

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

Special precautions for use in animals

Use of the veterinary medicinal 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.

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 in the case of oral, dermal or inhalation exposure.
Exposure by inhalation of dust, dermal contact or oral ingestion must be prevented.
Handle the product with care to avoid inhaling the powder, and contact with the skin and eyes, taking some special precautions:

- Take the necessary action to prevent the powder from spreading while the product is being handled.
- Wear gloves, overalls and goggles when handling the product or the concentrated water solution.
- Avoid contact of the product and of their concentrated water solutions with the skin and eyes.
- Do not smoke, eat or drink while handling the product.

In case of accidental eye and skin contact, rinse eyes with plenty of clean water and skin with soap and water.
In case of accidental ingestion seek medical advice and show the doctor the package leaflet or label to the physician.
People with known hypersensitivity to tiamulin should avoid contact with the veterinary medicinal product.
Wash hands after use.

Pregnancy and lactation:

The veterinary medicinal product can be used in pigs during pregnancy and lactation.

Laying birds
The veterinary medicinal product can be used in laying chickens and breeding chickens and turkeys.

Interaction with other medicinal products and other forms of interaction:
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 or feed additives containing monensin, narasin or salinomycin during or at least 7 days before and 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 as lasalocid and semduramicin, does not appear to cause any interactions; however, 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.

Overdose (symptoms, emergency procedures, antidotes):
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 tranquilisation. 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 LD_{50} 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 lying position, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

Incompatibilities:
In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

15. Special precautions for the disposal of unused product or waste materials, if any

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

16. Date on which the label was last approved

17. Other information

Package sizes:
Folding carton of 125 g
Folding carton of 1 kg

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

18. The words "For animal treatment only" and conditions or restrictions regarding supply and use, if applicable

For animal treatment only. To be supplied only on veterinary prescription.

Administration by a veterinary surgeon or under their direct responsibility.

[PL]
Wyłącznie dla zwierząt - Wydawany z przepisu lekarza – Rp.
Do podawania pod nadzorem lekarza weterynarii

19. The words "Keep out of the sight and reach of children"

Keep out of the sight and reach of children.

20. Expiry date

EXP {month/year}
Once opened use within 3 months.
Use by:

[PL]
Termin ważności (EXP)

21. Marketing authorisation number(s)

22. Manufacturer's batch number

Batch{number}

[PL]
Nr serii (Lot)