[Version 8.1,01/2017]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains:

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Granules for use in drinking water.
White or light yellow, compacted powder.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs, chickens and turkeys.

4.2 Indications for use, specifying the target species

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.

4.3 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 section 4.8 for more information regarding interaction between tiamulin and ionophores.

4.4 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.

4.5 Special precautions for use

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.

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.

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).

4.7 Use during pregnancy, lactation or lay

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.

4.8 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.

4.9 Amounts to be administered and administration route

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.

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.

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 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.

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 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.

4.11 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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use. Pleuromutilins. Tiamulin
ATC vet code: QJ01XQ01.

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.

5.1 Pharmacodynamic properties

Tiamulin hydrogen fumarate is a semi-synthetic bacteriostatic antibiotic belonging to the pleuromutilins group. The mode of action is by inhibition of bacterial proteins.
Tiamulin has a high level of in vitro activity against species of mycoplasma in pigs and birds, 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* and equivalent to 50 to 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 limitations, the in vitro susceptibility of *Lawsonia intracellularis* is difficult to test.

Resistance derives from chromosomal mutations in the 23S ribosomal RNA 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 rRNA gene affecting the peptidyl transferase centre are associated with reduced susceptibility to tiamulin in *Brachyspira* species. Mutations in the 23S rRNA gene are also associated with tiamulin resistance in *Mycoplasma* species.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin hydrogen fumarate is well absorbed in pigs (over 90%) following oral administration and widely distributed throughout the body. After a single oral dose of 10 mg and 25 mg of 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 is well absorbed in chickens after oral administration (70-95%) and reaches peak concentrations in 2-4 hours (T_{max} 2.85 hours). Following a 50 mg of tiamulin hydrogen fumarate/kg body weight single dose, the C_{max} was 4.02 µg/ml in serum by microbiological assay and after a dose of 25 mg / kg was 1.86 µg/ml. In the drinking water, a concentration of 250 ppm (0.025%) of tiamulin hydrogen fumarate provided a rolling serum level over 48 hour medication of 0.78 µg/ml (range 1.4-0.45 µg/ml) and a 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 kidneys (sites of excretion) and in the lung (30 times serum level). Excretion is mainly, via the bile (55-65%) and kidney (15-30%) as microbiologically inactive metabolites and it 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 Hydrogen Fumarate is toxic for terrestrial plants and aquatic organisms.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

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: 36 months
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution 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

Folding carton of 125 g and 1 kg with inner layer (paper/PE/Alu/HPPE).

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

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

LABORATORIOS KARIZOO, S.A.
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Spain

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10 DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.