[Version 9,03/2022]

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Karimulina 101.2 mg/ml solution for use in drinking water for rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Tiamulin (as hydrogen fumarate) 101.2 mg
(equivalent to 125.0 mg of tiamulin hydrogen fumarate)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Propyl parahydroxybenzoate (E-216)	0.1mg
Methyl parahydroxybenzoate (E-218)	0.9mg
Citric acid monohydrate (E330)	
Disodium phosphate dihydrate	
Ethanol (96%)	
Purified water	

Clear and colourless solution for use in drinking water.

3. CLINICAL INFORMATION

3.1 Target species

Rabbits

3.2 Indications for use for each target species

Reduction of mortality due to epizootic enteropathy in association with infections caused by *Clostridium perfringens*.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use with monensin, narasin or any other ionophores.

3.4 Special warnings

Clostridium perfringens being only one of many causal factors of epizootic rabbit enteropathy, it is essential to improve zootechnical factors.
Start treatment as soon as a first case of mortality due to enteropathy caused by *Clostridium perfringens* is confirmed.

Cross-resistance has been shown between pleuromutilins, oxazolidinones, phenicols, streptogramin A and lincosamides. Use of tiamulin should be carefully considered when susceptibility testing has shown resistance to pleuromutilins, oxazolidinones, phenicols, streptogramin A and lincosamides because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Before installing a treatment, the management and sanitary conditions at the farm should be evaluated against the risk of an outbreak of the disease. Treatment should be initiated in case of historical cases of epizootic enteropathy in the herd and as soon as a death is confirmed.
Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.
Use of the product should be in accordance with official, national and regional antimicrobial policies.
An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
People with known hypersensitivity to the active substance should avoid contact with the veterinary medicinal product.
When mixing, direct contact with the skin and mucous membranes should be avoided. Accidental ingestion should be avoided.
Personal protective equipment consisting of overalls, safety glasses and impervious gloves should be worn when handling or mixing the veterinary medicinal product.
Accidental inhalation should be avoided.
Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately. If accidental eye contact occurs, immediately rinse thoroughly with clean water. Seek medical advice if irritation persists.
After exposure if symptoms such as a cutaneous rash appear, seek medical advice.
In case of accidental ingestion, seek medical advice.
Wash hands after use.

Special precautions for the protection of the environment:
Due to environmental risk linked to tiamulin residues, the veterinary medicinal product should only be used when the farming method allows the manure from treated animals to be diluted once with manure from untreated animals.
Tiamulin is very persistent in soil.
Tiamulin is toxic for terrestrial plants and cyanobacteria.

3.6 Adverse events

Rabbits

Undetermined frequency	Decreased drinking (slight and transient).

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See section “Contact details” of the package leaflet.

3.7 Use during pregnancy, lactation or lay

Laboratory studies in rabbits have shown evidence of a foetotoxic and maternotoxic effects from 55 mg/kg.
Do not use in pregnant rabbits.

3.8 Interaction with other medicinal products and other forms of interaction

Tiamulin interacts with monensin and narasin or any other ionophores and may result in signs indistinguishable from an ionophore toxicosis. Rabbits should not receive products containing monensin, narasin or any other ionophores during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

3.9 Administration routes and dosage

Oral use.
16 mg of tiamulin per kg body weight per day, for 10 days in drinking water, which is equivalent to 16 ml of solution per 100 kg body weight per day, for 10 days.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

$$\frac{0.16 \times \text{mean body weight (kg) of animals to be treated}}{\text{mean daily water intake (litre per animal)}} = \text{ml product per litre of drinking water}$$

To ensure a 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 animal. In order to obtain the correct dosage the concentration of veterinary medicinal product in water has to be adjusted accordingly. Monitor water intake at frequent intervals during medication.
The use of suitably calibrated weighing equipment is recommended if part of containers is used.
The medicated water should be made freshly every day and any medicated water not consumed within 24 hours should be discarded appropriately.
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.
If there is no response to treatment within 5 days, the diagnosis should be re-established.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

From 5 times of the recommended dose, a slight decrease of food consumption was observed in females.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Meat and offal: 2 days

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01XQ01

4.2 Pharmacodynamics

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 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.
Resistance derives from chromosomal mutations in the 23 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 (conferring cross-resistance between pleuromutilins, oxazolidinones, phenicols, streptogramin A and lincosamides). This type of resistance is transferable between bacteria and bacterial species. The mechanism of antimicrobial resistance varies according to the bacterial species.

4.3 Pharmacokinetics

After repeated oral administration of 16 mg of tiamulin per kg for 10 consecutive days, steady state is rapidly reached and no excessive accumulation of tiamulin was observed in the plasma or in the digestive tract.

Environmental properties

Tiamulin is very persistent in soil.
Tiamulin is toxic for terrestrial plants and cyanobacteria.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale (1-L bottle): 4 years.
Shelf life of the veterinary medicinal product as packaged for sale (5-L barrel): 30 months.
Shelf life after first opening the immediate packaging: 6 months.
Shelf life after dilution according to directions: 24 hours.

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

White high-density polyethylene containers containing 1 L and 5 L of product, with a high-density polyethylene screw cap with induction sealing.

Pack sizes
1 bottle of 1 L
1 barrel of 5 L

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste. Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

This veterinary medicinal product should not enter water courses as tiamulin may be dangerous for cyanobacteria and other aquatic organisms.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

LABORATORIOS KARIZOO, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation:

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

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

{Containers of 1L and 5L}

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Excipients:

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Methyl parahydroxybenzoate (E-218) 0.9 mg

Clear and colourless solution for use in drinking water.

3. PACKAGE SIZE

Container of 1L and 5L.

4. TARGET SPECIES

Rabbits.

5. INDICATIONS FOR USE

Indications for use
Reduction of mortality due to epizootic enteropathy in association with infections caused by *Clostridium perfringens*.

6. CONTRAINDICATIONS

Contraindications
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use with monensin, narasin or any other ionophores.

7. SPECIAL WARNINGS

Special warnings

Special warnings:

Clostridium perfringens being only one of many causal factors of epizootic rabbit enteropathy, it is essential to improve zootechnical factors.

Start treatment as soon as a first case of mortality due to enteropathy caused by *Clostridium perfringens* is confirmed.

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When mixing, direct contact with the skin and mucous membranes should be avoided. Accidental ingestion should be avoided.

Personal protective equipment consisting of overalls, safety glasses and impervious gloves should be worn when handling or mixing the veterinary medicinal product.

Accidental inhalation should be avoided.

Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately. If accidental eye contact occurs, immediately rinse thoroughly with clean water. Seek medical advice if irritation persists.

After exposure if symptoms such as a cutaneous rash appear, seek medical advice.

In case of accidental ingestion, seek medical advice.

Wash hands after use.

Special precautions for the protection of the environment:

Due to environmental risk linked to tiamulin residues, the veterinary medicinal product should only be used when the farming method allows the manure from treated animals to be diluted once with manure from untreated animals.

Tiamulin is very persistent in soil.

Tiamulin is toxic for terrestrial plants and cyanobacteria.

Pregnancy:

Laboratory studies in rabbits have shown evidence of a foetotoxic and maternotoxic effects from 55 mg/kg. Do not use in pregnant rabbits.

Interactions with other medicinal products and other forms of interaction:

Tiamulin interacts with monensin and narasin or any other ionophores and may result in signs indistinguishable from an ionophore toxicosis. Rabbits should not receive products containing monensin, narasin or any other ionophores during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

Overdose:
From 5 times of the recommended dose, a slight decrease of food consumption was observed in females.

Special restrictions for use and special conditions for use:
Not applicable

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

8. ADVERSE EVENTS

Adverse events

Rabbits

Undetermined frequency	Decreased drinking (slight and transient).

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed on this label, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details on this label, or via your national reporting system {national system details}.

9. DOSAGE FOR EACH TARGET SPECIES, ROUTES AND METHOD OF ADMINISTRATION

Dosage for each species, routes and method of administration
Oral use.
16 mg of tiamulin per kg body weight per day, for 10 days in drinking water, which is equivalent to 16 ml of solution per 100 kg body weight per day, for 10 days.

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The intake of medicated water depends on the clinical condition of the animal. In order to obtain the correct dosage the concentration of veterinary medicinal product in water has to be adjusted accordingly. Monitor water intake at frequent intervals during medication.

10. ADVICE ON CORRECT ADMINISTRATION

Advice on correct administration
The use of suitably calibrated weighing equipment is recommended if part of containers is used.
The medicated water should be made freshly every day and any medicated water not consumed within 24 hours should be discarded appropriately.

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. If there is no response to treatment within 5 days, the diagnosis should be re-established.

11. WITHDRAWAL PERIODS

Withdrawal periods
Meat and offal: 2 days

12. SPECIAL STORAGE PRECAUTIONS

Special storage precautions

Keep out of the sight and reach of children.
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 after Exp. The expiry date refers to the last day of that month.

13. SPECIAL PRECAUTIONS FOR DISPOSAL

Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste. Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.
Ask your veterinary surgeon how to dispose of medicines no longer required.

14. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Classification of veterinary medicinal products
Pharmacotherapeutic group: Antibacterials for systemic use. Pleuromutilins. Tiamulin
ATC vet code: QJ01XQ01.

15. MARKETING AUTHORISATION NUMBERS AND PACK SIZES

EU/0/00/000/000

Pack sizes
1 bottle of 1 L
1 barrel of 5 L
Not all pack sizes may be marketed.

16. DATE ON WHICH THE LABEL WAS LAST REVISED

Date on which the label was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

17. CONTACT DETAILS

Contact details

Marketing authorisation holder and manufacturer responsible for batch release and contact details to report suspected adverse reactions:
LABORATORIOS KARIZOO, S.A.
Pol. Ind. La Borda, Mas Pujades 11-12
08140 Caldes de Montbui (Barcelona)
Spain
Telf. +34 93 865 41 48

18. OTHER INFORMATION

Other information
Not applicable

19. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

20. EXPIRY DATE

Exp

Shelf life after first opening the immediate packaging: 6 months
Shelf life after dilution according to directions: 24 hours

21. BATCH NUMBER

Lot