B.2. PROPOSAL FOR PACKAGING, LABELLING AND PACKAGE INSERT

Label-leaflet

MUTILAN 125 mg/ml ORAL SOLUTION [CZ, CY, HU, PL, PT, RO, SK]
TIAMULIN/KARIZOO 125 mg/ml ORAL SOLUTION [EL]
Tiamulin hydrogen fumarate

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

MUTILAN 125 mg/ml Oral solution [CZ, CY, HU, PL, PT, RO, SK]
TIAMULIN/KARIZOO 125 mg/ml Oral solution [EL]
Tiamulin hydrogen fumarate

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

Each ml contains:

Active substance:
Tiamulin hydrogen fumarate.....125.0mg
(corresponding to 101.4 mg tiamulin)

Excipients:
Propyl parahydroxybenzoate (E-216).....0.1mg
Methyl parahydroxybenzoate (E-218) .....0.9 mg

4. PHARMACEUTICAL FORM

Oral solution
Clear and colourless solution

5. PACKAGE SIZE

1-L bottles
5-L bottles

6. TARGET SPECIES

Pig (all categories)
Chickens (broiler, replacement pullets, layer/breeder)
Turkeys (poult (grower) and breeder)

7. INDICATIONS

Pigs

i) For the treatment of swine dysentery caused by *Brachyspira hyodysenteriae* and complicated by *Fusobacterium* spp. and *Bacteroides* spp.

ii) For the treatment of porcine respiratory disease complex (PRDC) caused by *M. hyopneumoniae* and viruses such as PRRSV and Swine Influenza virus complicated by *P. multocida and A. pleuropneumoniae.*

iii) For the treatment of pleuropneumonia caused by *A. pleuropneumoniae.*

Chickens

For the treatment and prevention of chronic respiratory disease (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae.*

Turkeys

For the treatment and prevention of infectious sinusitis and air sacculitis caused by *M. gallisepticum, M. synoviae* and *M. meleagridis.*

8. CONTRAINDICATIONS

Pigs and birds should not receive products containing monensin, narasin or salinomycin during or for at least 7 days before or after treatment with tiamulin, Severe growth depression or death may result. Refer to section 13. for information regarding interaction between tiamulin and ionophores.

Do not use in case of hypersensitivity to active substance or to any of excipients.

9. ADVERSE REACTIONS

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

Water intake may be depressed during the administration of tiamulin to birds. It appears to be concentration dependent with 0.025% tiamulin reducing intake by approximately 15%. It does not appear to have any adverse effect on overall performance of the birds or efficacy of the product; however, the water consumption should be monitored frequently, especially during hot weather.

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

10. METHOD AND ROUTE OF ADMINISTRATION

Pigs

i) Treatment of swine dysentery

The dosage is 8.8 mg tiamulin hydrogen fumarate per kg bodyweight daily administered in the drinking water of pigs for 3 to 5 consecutive days. The dose will normally be achieved at concentration of 0.006% tiamulin hydrogen fumarate (60 mg/1 litre) in drinking water.

ii) Treatment of PRDC caused by *M. hyopneumoniae* and various viruses and complicated by *P. multocida* and *A. pleuropneumoniae*.

The dosage is 15.0-20.0 mg tiamulin hydrogen fumarate per kg bodyweight daily administered for 5 to 10 consecutive days; the dose will normally be achieved at concentration of 0.012-0.018% tiamulin hydrogen fumarate (120-180 mg/1 litre) in drinking water.

iii) Treatment of pleuropneumonia caused by *A. pleuropneumoniae*.

The dosage is 20.0 mg tiamulin hydrogen fumarate per kg bodyweight daily administered for 5 consecutive days; the dose will normally be achieved at concentration of 0.018% tiamulin hydrogen fumarate (180 mg/ 1 litre) in drinking water.

Chickens

i) Treatment and prevention of chronic respiratory disease (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae* of broilers, replacement pullets and layers/breeders: the dosage is 25–30 mg per kilogram bodyweight daily administered for 3-5 consecutive days. The dose will normally be achieved at concentration of 0.020–0.025% tiamulin hydrogen fumarate (200-250 mg/1 litre).

The 0.025% concentration of tiamulin hydrogen fumarate in drinking water provides following doses according to the age of the animals:

4-week old broiler: 30 mg tiamulin hydrogen fumarate/kg bodyweight
10-week old pullet: 30 mg tiamulin hydrogen fumarate/kg bodyweight

Laying hen: 25 mg tiamulin hydrogen fumarate/kg bodyweight

Turkeys

i) Prevention of infectious sinusitis and air sacculitis caused by *M. gallisepticum, M. synoviae* and *M. meleagridis.*

Turkey poults (growers): 0.025% tiamulin hydrogen fumarate (250 mg/1 litre) in drinking water for 3 days during the first week of life and thereafter 1–3 days every 4-6 weeks according to the level of risk.

Turkey breeders: 0.025% tiamulin hydrogen fumarate (250 mg/1 litre) in drinking water for 3-5 days every 4 weeks according to the level of risk.

ii) Treatment of infectious sinusitis and air sacculitis caused by *M. gallisepticum, M. synoviae* and *M. meleagridis.*

0.025% tiamulin hydrogen fumarate (250 mg/1 litre) in drinking water for 3-5 consecutive days.

Tiamulin hydrogen fumarate at 0.025% concentration (0.050%, i.e. 500 mg/1 litre, for 20-week old male turkeys) in drinking water will provide the the following daily doses depending on the age of the turkeys for both the above indications:

1-week old poult:	70 mg tiamulin hydrogen fumarate/kg bodyweight
4-week old poult:	50 mg tiamulin hydrogen fumarate/kg bodyweight
8-week old poult:	25-30 mg tiamulin hydrogen fumarate/kg bodyweight
20-week old poult:	20 mg tiamulin hydrogen fumarate/kg bodyweight

For the selected categories of target animal species and indications, a dilution can be made according to specified dosage in mg/kg bodyweight:

If the product will be added into large volumes of water, concentrated solution should be prepared first and then diluted to the required concentration.

Mixing 1.0 mL of product:
With 2.1 litre of water results in 0.006% solution of tiamulin hydrogen fumarate
With 1.0 litre of water results in 0.012% solution of tiamulin hydrogen fumarate
With 0.7 litre of water results in 0.018% solution of tiamulin hydrogen fumarate

Mixing 50.0 mL of product:
With 31.3 litre of water results in 0.020% solution of tiamulin hydrogen fumarate
With 25.0 litre of water results in 0.025% solution of tiamulin hydrogen fumarate
With 12.5 litre of water results in 0.050% solution of tiamulin hydrogen fumarate

Primarily the dose should be calculated from the dose as listed in mg/kg of body weight. It is necessary to adjust the dose according to the current water intake by animals and determine the bodyweight of the animals as accurately as possible to avoid underdosing

Fresh solution of tiamulin-medicated drinking water should be made up each day.
Watering systems should be checked and cleaned before using the product.

11. ADVICE ON CORRECT ADMINISTRATION

None

12. WITHDRAWAL PERIOD

Pigs
Meat and offal: 4 days

Chickens
Meat and offal: 2 days
Eggs: Zero days

Turkeys
Meat and offal: 5 days

13. SPECIAL WARNINGS, IF NECESSARY

Special precautions for use in animals
Fresh drinking water must be provided to animals after drinking medicated water.
Whenever possible, use of the product should be based on the results of susceptibility testing and information (regional, farm level) regarding current epizootological situation.
Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tiamulin.
If there is no response to treatment within 5 days, the diagnosis should be re-established.
Use of the product should be combined with the good farming practice, e.g. good zoohygiene, proper ventilation, avoiding of overstocking.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Direct contact with skin, eyes, and mucous membranes should be avoided.
Personal protective equipment consisting of protective goggles and rubber or latex gloves should be worn when handling the veterinary medicinal 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.
People with known hypersensitivity to tiamulin should handle the product with caution.
Wash hands after use.

Interaction with other medicinal products and other forms of interaction
In chickens and turkeys, in order 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), if necessary
Single oral doses of 100 mg/kg bodyweight caused hyperpnoea and abdominal discomfort in pigs. At 150 mg/kg no CNS effects were noted except for tranquillisation. At 55 mg/kg given for 14 days, a transient salivation and slight gastric irritation occurred. Tiamulin is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.
Tiamulin has a relative wide therapeutic index, with a low risk of overdose mainly due to the fact that abnormally high concentrations result in decreased water consumption and hence decreased consumption of tiamulin. LD_{50} for chicken is 1290 mg/kg bodyweight and for turkeys 840 mg/kg bodyweight.
The clinical signs of acute toxicity in chickens are – vocalization, clonic cramps and lying in a lateral position, in turkeys – clonic cramps, lateral or dorsal position, salivation and depression.
In case the symptoms of intoxication appear, remove the medicated water immediately and replace with fresh water.

Major incompatibilities
None known

14. EXPIRY DATE

EXP: {month/year}

Once opened, use by …
Shelf life after first opening the container: 6 months.
Shelf life after dilution according to directions: 24 hours.

15. SPECIAL STORAGE CONDITIONS

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

16. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.
Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

For animal treatment only.

Keep out of the sight and reach of children.

To be supplied only on veterinary prescription.

Date on which the package leaflet was last approved:

Marketing authorization number:

Batch: {number}