B.1. SUMMARY OF PRODUCT CHARACTERISTICS

1. 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]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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) 0.9mg

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution
Clear and colourless solution

4. CLINICAL PARTICULARS

4.1. Target species

Pigs (all categories)
Chickens (broiler, replacement pullet, layer/breeder)
Turkeys (poult (grower) and breeder)

4.2. Indications for use, specifying the target species

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.*

4.3. 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 4.8. for information regarding interaction between tiamulin and ionophores.
Do not use in case of hypersensitivity to active substance or to any of excipients.

4.4. Special warnings for each target species

In order to avoid interaction between tiamulin and the incompatible ionophores monensin, narasin and salinomycin in pigs, please ensure that these active substances are not included in the feed and do not contaminate the feed.

Concurrent use of tiamulin and ionophore anticoccidial maduranicin can result in a mild to moderate growth depression in chickens. Such situation is temporary and under normal conditions it remits spontaneously within 3-5 days after stopping the tiamulin therapy. This phenomenon probably does not occur in case of lasalocid or semduramicin ionophores.

4.5. Special precautions for use

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.

4.6. Adverse reactions (frequency and seriousness)

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.

4.7. Use during pregnancy, lactation or lay

Tiamulin can be used in pigs during pregnancy and lactation.

Tiamulin may be used in laying and breeding birds as it has been shown to have no adverse effects on egg production, fertility or hatchability in chickens and turkeys.

4.8. 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.

4.9. Amounts to be administered and administration route

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 dosage as listed in mg/kg of bodyweight. 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.

4.10. 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.

4.11. Withdrawal period

Pigs
Meat and offal: 4 days

Chickens
Meat and offal: 2 days
Eggs: Zero days.

Turkeys
Meat and offal: 5 days

5. PHARMACOLOGICAL PROPERTIES

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

Tiamulin is bacteriostatic semi-synthetic antibiotic belonging to the pleuromutilin group and acts at the ribosomal level by inhibiting bacterial protein synthesis.

5.1. Pharmacodynamic properties

Tiamulin has been shown to possess a high level of in-vitro activity against porcine and avian mycoplasmas and also against gram-positive aerobes (streptococci and staphylococci) and anaerobes (clostridia) and gram-negative anaerobes (*Brachyspira hyodysenteriae, Bacteroides* spp. *and Fusobacterium* spp.) and gram-negative aerobes (*Actinobacillus pleuropneumoniae*). Tiamulin is not effective against *Enterobacteriaceae* family, e.g. salmonellas or *Escherichia coli*.

Antimicrobial susceptibility of bacteria to tiamulin:

Susceptibility of the target microorganisms isolated from pigs to tiamulin:

Species (no. of isolates)	MIC range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
B. hyodysenteriae (92)[1]	≤0.008-64	0.25	4.0
Bacteroides vulgatus	0.25-1.0	-	-
F. necrophorum	0.39	-	-
A. pleuropneumoniae (129)[2]	0.25–16.0	8.0	8.0
P. multocida (332)[3]	8–32	16	32
M. hyopneumoniae (43)[4]	≤0.004-0.062	0.016	0.031
M. hyosynoviae (18)[5]	0.0025–0.1	0.005	0.025

Data: [1] 2008 (DE, ES, UK, IE); [2] 2009 (BE, DK, FR, DE, NL, PL, ES, UK); [3] 2007-2011 (CZ); [4] 2008 (ES, UK); [5] 1997 (FR, DE, DK)

Susceptibility of the target microorganisms isolated from chickens and turkeys to tiamulin:

Species (no. of isolates)	MIC range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
M. gallisepticum (32)[6]	≤0.004–>256	0.008	1.0
M. synoviae (21)[7]	≤0.004–0.5	0.125	0.25
M. meleagridis[8]	0.0025–3.13	0.1	0.25

Data: [6] 2008 (NL, ES, UK); [7] 2008 (NL, UK); [8] 2002

Tiamulin has been shown to act at the 70S ribosome level and the primary binding site is on the 50S subunit and the secondary site lies on the spot where the 50S and 30S subunits join. It inhibits microbial protein synthesis by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.
A bactericidal concentration can be achieved, however, it is 50-100 times higher than the bacteriostatic concentration.

Resistance mechanisms in *Brachyspira* spp. to pleuromutilins are based on development of mutations within the ribosomal binding site.

Clinically important resistance to tiamulin is associated with the combination of mutations around the tiamulin binding site. Resistance to tiamulin may be associated with reduced susceptibility to other pleuromutilins.

5.2. Pharmacokinetic particulars

Pigs

Following oral administration in pigs, tiamulin is well absorbed (over 90%) and rapidly distributed into the whole body. Following single oral dose of 10 mg and 25 mg doses of tiamulin per kg of bodyweight, C_{max} values were 1.03 µg/mL and 1.82 µg/mL according to the microbiology tests, respectively, and T_{max} was 2 hours for both doses. The concentration in lungs, which are the target tissue, was shown as well as concentration in liver where it is metabolized and excreted (70-85%) into bile, the remainder is excreted through kidneys (15-30%). Non-absorbed and non-metabolised tiamulin passes down the intestines to the colon, where it concentrates.

Concentration in water	**Calculated daily dose of tiamulin mg/kg bodyweight**	**Tiamulin activity (µg/mL)**		
		Lungs	*Tonsils*	*Intestine content*
60 ppm	6.2	1.11	a	2.16
120 ppm	13.2	4.26	a	5.59
180 ppm	20.9	8.5	2.5	18.58

a=below limit of sensitivity of the assay

Chickens

Following oral administration, tiamulin is well absorbed in chickens (70–95%) reaching the maximum concentration in 2-4 hours (T_{max} 2.85 hours). Following single oral dose of 50 mg/kg bodyweight, C_{max} as determined by serum microbiology tests was 4.02 µg/mL, and following administration of 25 mg/kg bodyweight it was 1.86 µg/kg. In 8-week poults, 0.025% concentration of tiamulin in drinking water resulted in average serum level of 0.78 µg/mL during the 48-hour period of medication (range of 1.4-0.45 µg/mL), and with 0.0125% concentration of tiamulin in drinking water average serum level was 0.38 µg/mL (range 0.65-0.2 µg/mL). Protein binding was about 50% (range 45-52%).

Tiamulin is distributed to the whole body and concentrations in liver and kidneys (excretion points) and lungs (30x the serum level) and eggs have been shown. The excretion is mainly through bile (55-65%) and kidneys (15-30%) mostly as microbiologically inactive metabolites, it is relatively fast with 99% of the dose within 48 hours.

Turkeys

The levels of tiamulin in serum are lower with single oral dose at 50 mg/kg bodyweight, the maximum concentration in serum being 3.02 µg/mL; after administration of 25 mg/kg, serum concentration is 1.46 µg/mL. These levels were reached about 2-4 hours after administration. After the 0.025% dosage of tiamulin, the average level in serum was 0.36 µg/mL (range 0.22-0.5 µg/mL) in turkey breeders. Tiamulin was concentrated in eggs similarly to chickens.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Propyl parahydroxybenzoate (E-216)
Methyl parahydroxybenzoate (E-218)
Citric acid monohydrate
Disodium phosphate dihydrate
Ethanol (96%)
Purified water

6.2. Major incompatibilities

None known

6.3. Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 6 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

White high-density polyethylene bottles of 1-L and 5-L capacity. Bottles are closed with a polyethylene screw cap with induction sealing. Each bottle is supplied with a device suitable for measuring volumes within 10 and 75 ml.
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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

LABORATORIOS KARIZOO, S.A.
Pol. Ind. La Borda, Mas Pujades 11-12
08140 Caldes de Montbui (Barcelona)
Spain

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

FURTHER INFORMATION
To be supplied only on veterinary prescription.