SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

DISENTIN 125 mg/ml Oral solution [CZ, HU, PL, RO, SK, EL]
MAYMULINA 125 mg/ml Oral solution [ES, PT]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tiamulin hydrogen fumarate.....125.0mg

Excipients:
Propyl parahydroxybenzoate.....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 (broilers, pullets, laying hens and breeding birds)
Turkeys (poult and breeding turkeys)

4.2. Indications for use, specifying the target species

Pigs

i) Treatment of pig dysentery caused by strain of *Brachyspira hyodysenteriae* and complicated by strains of *Fusobacterium* spp. and *Bacteroides* spp.

ii) Treatment of porcine respiratory disease complex (PRDC) caused by *M. hyopneumoniae* and viruses such as PRRS and flu in pigs complicated by *P. multocida and A. pleuropneumoniae* bacteria.

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

Chickens

Treatment and prevention of chronic respiratory diseases (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae.*

Turkeys

Treatment and prevention of infections sinusitis and air sacculitis caused by *M. gallisepticum, M. synoviae* and *M. meleagridis.*

4.3. Contraindications

Do not use monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. This may result in severe growth depression or death.

4.4. Special warnings for each target species

In order to avoid interaction with the incompatible ionophores monensin, narasin and salinomycin in pigs, please ensure that these active agents are not included in the feed and that there was no contamination of the feed with these agents.

Concurrent use of Tiamulin and ionophores anticoccidium of 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 of stopping the tiamulin therapy. It would appear that this does not happen with ionophores lasalocid or semduramicin.

4.5. Special precautions for use

Special precautions for use in animals
Freshly medicated water must be prepared daily. Watering equipment should be inspected and cleaned prior to addition of the product.
Whenever possible, use of the product should be based on the results of susceptibility testing and take into account the epidemiological information on resistance (regional, farm level) and national policies with respect to use of antimicrobials.
Use of the product deviating from the information given within SPC can cause increase of 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

Avoid contact with skin, eyes and mucous membranes.
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.
In case of accidental ingestion, seek medical advice immediately and show the 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)

Occasionally erythema and other hypersensibilty reactions can occur in pigs.
In these cases symptomatologic therapy is indicated.

While administering tiamulin to poultry, the consumption of water may fall. This depends on the concentration: the 0.0125% concentration of tiamulin may result in 10% lower consumption of water, while the concentration of 0.025% may decreases the consumption by 15%. No negative effects on the overall condition of the poultry or the overall effectiveness of the product are to be expected; however, the water consumption should be monitored frequently, especially during hot weather.

4.7. Use during pregnancy, lactation or lay

The product is suitable for use in pigs during pregnancy and lactation.

Tiamulin can be used for laying hens and breeding birds, no adverse effects have been shown on production of eggs, fertility or hatchability in chickens or turkeys.

4.8. Interaction with other medicinal products and other forms of interaction

In order to prevent interaction of incompatible ionophores monensin, narasin and salinomycin in pigs, it should be ensured that these effective agents are not contained in the feed and that there was no contamination of the feed with these agents.

For chickens and turkeys, to avoid interactions between the incompatible ionophores monensin, narasin and salinomycin and tiamulin, the feed mill supplying the birds 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 dysentery in pigs

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

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

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

Chickens

i) Prevention of chronic respiratory diseases (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae*.

Broilers: 0.0125%-0.025% tiamulin hydrogen fumarate (125 mg-250 mg/1 litre) in drinking water for 3 days during first week of life and thereafter for 1-2 days every 3-4 weeks, according to risk.

Replacement pullets: 0.0125%-0.025% tiamulin hydrogen fumarate (125 mg-250 mg/1 litre) in drinking water for 3 days during the first week of life, thereafter 1-2 days every 4-6 weeks according to the level of risk.

Laying and breeding hens: 0.0125%-0.025% tiamulin hydrogen fumarate (125 mg-250 mg/1 litre) in drinking water for 3 days every 4 weeks from the start of laying according to the level of risk.

ii) Treatment of chronic respiratory diseases (CRD) and air sacculitis caused by *M. gallisepticum* and *M. synoviae* in broilers, replacement pullets, layers and breeding hens. Tiamulin hydrogen fumarate 0.025% (250 mg/1 litre) in drinking water during 3-5 days.

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

4-week old broiler:	30 mg/kg of bodyweight
10-week old pullets:	30 mg/kg of bodyweight
Laying hen:	25 mg/kg of 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.

Turkeys 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.*

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

Tiamulin hydrogen fumarate in 0.025% concentration in drinking water will provide the following daily dosage depending on the age of the turkey:

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

Mixing 2.0 ml of product with 1 litre of water results in 0.025% solution of tiamulin hydrogen fumarate and mixing 1.0 ml of the product with 1 litre of water results in 0.0125% tiamulin hydrogen fumarate solution.

If adding the product into large volumes of water, please start by preparing a concentrated solution and then dilute it to the required concentration.

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

4.10. Overdose (symptoms, emergency procedures, antidotes), if necessary

Single oral doses of 100 mg/kg bodyweight in pigs caused hyperpnoea and abdominal discomfort. 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 ptosis.

Should the symptoms of intoxication appear, remove the medicated water immediately and replace it 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 of antibiotics and acts at the ribosomal level to inhibit bacteria protein synthesis.

5.1. Pharmacodynamic properties

Tiamulin has shown a high level of in-vitro activity against porcine and avian mycoplasma 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 sensitivity to Tiamulin:

Strain	MIC range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
B. hyodysenteriae	0.3-3.8	0.3	1.7
Bacteroides vulgatus	0.25-1.0	-	-
F. necrophorum	0.39	-	-
A. pleuropneumoniae	3.0-10.0	5.0	6.0
P. multocida	1.9-31.2	-	-
M. hyopneumoniae	0.08-0.34	0.06	0.20
M. gallisepticum	0.0005-0.25	0.001	0.025
M. synoviae	0.05-0.5	0.1	0.25
M. meleagridis	0.025-3.13	0.1	0.25

Despite the fact that clinically important resistance to tiamulin needs the combination of mutations, the MIC range can vary (geographically, with time) and therefore current status of susceptibility/resistance should be considered prior the use of the product.

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 where the 50S and 30S subunits join. It inhibits microbial protein production by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.
A bactericide concentration can be achieved, however this is 50-100 times higher than the bactreriostatic concentration.

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, according to the microbiology tests, C_{max} values were 1.03 µg/ml and 1.82 µg/ml 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 of 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 assay

Chickens

Following oral administration, tiamulin is well absorbed in chickens (70 – 95 %) reaching the maximum concentration in 2-4 hours (Tmax 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 after 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 rolling 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% that value 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; with administration of 25 mg/kg serum concentration is 1.46 µg/ml. These levels were reached about 2-4 hours after administration. For turkeys breeders with the 0.025% dosage of tiamulin, the average level in serum was 0.36 µg/ml (range 0.22-0.5 µg/ml). Tiamulin in eggs was concentrated similarly to chickens.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

6.2. 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 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.

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

[CZ, HU, PL, RO, SK, EL]:
VETPHARMA ANIMAL HEALTH, S.L.
Les Corts, 23
08028 – BARCELONA
Spain

[ES, PT]:
LABORATORIOS MAYMÓ, S.A.
Vía Augusta, 302
08017 – BARCELONA
Spain

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

PROHIBITION OF SALE, SUPPLY AND/OR USE
Not applicable.