ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

VETMULIN 101.2 mg/ml Solution for use in drinking water for pigs and laying hens [FR]
VETMULIN 125 mg/ml Solution for use in drinking water for pigs and chickens [AU, BE, BG, CY, CZ, DE, DK, EL, ES, HR, HU, IE, IT, LV, LT, NL, PL, PT, RO, SI, SK, UK]
VETMULIN [EE]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance	
Tiamulin hydrogen fumarate	125 mg
(equivalent to Tiamulin	101.2 mg)

Excipients:

Methyl parahydroxybenzoate (E218)	0.90 mg
Propyl parahydroxybenzoate	0.10 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water.
Clear, colorless to slightly yellow liquid.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs. Chickens (Laying hens).

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 (spirochaetal diarrhoea or 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.

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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.

Laying hens:
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.

4.3 Contraindications

Do not use in animals that could receive products containing 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 or to the excipients.

See section 4.8 for information regarding interaction between tiamulin and ionophores

4.4 Special warnings for each target species

Pigs with reduced water intake and/or in a debilitated condition should be treated parenterally.

Water intake may be depressed during the administration of tiamulin in birds. It appears to be concentration-dependent with 500 mg tiamulin hydrogen fumarate (equivalent to 4ml of product) in 4 litres of water reducing intake by approximately 10% and 500 mg tiamulin hydrogen fumarate (equivalent to 4 ml of 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.

4.5 Special precautions for use

Special precautions for use in animals
Use of the 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.

Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tiamulin.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
People with known hypersensitivity to tiamulin or parabens should administer the veterinary medicinal product with caution and avoid contact of medicated water with the skin.

Both the product and the diluted product in drinking water may cause hypersensitivity reactions due to contact. Avoid contact with the skin. Do not smoke, eat or drink when mixing and handling the product. Wear protective clothes and protective gloves when mixing and handling the product, and wash hands after use. In case of accidental contact with skin, rinse with plenty of clean water. Contaminated clothing should be removed.
Ingestion of the product or medicated water should be avoided.. In the event of accidental ingestion, rinse mouth with plenty of clean water and seek medical advice immediately.

4.6 Adverse reactions

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

Chickens (laying hens): 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
Can be used in pigs during pregnancy and lactation

Laying birds
Can be used in laying hens

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 containing monensin, salinomycin or narasin during or at least 7 days before or 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 lasalocid and semduramicin do not appear to cause any interaction, however the 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.

Guidance for preparing product solutions:
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.

The dosage of the product to be incorporated should be established according to the following formula:

$$\frac{\text{…. ml product per kg body weight per day} \times \text{average body weight (kg)}}{\text{water intake (litre/animal/day)}} = \text{ml of the product per litre of drinking water per day}$$

Use a sufficiently accurate commercially available device to measure the required amount of product. Only use clean containers for preparation of the medicated drinking water. Stir the medicated drinking water prepared with the product for at least 1 minute after preparation in order to assure homogeneity.
When medicating large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration. The maximum solubility of the product is 200 mL/L.

Medicated drinking water should be refreshed or replaced every 24 hours.

In order to avoid interactions between the 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, in order 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 anticoccidials 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 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.

Pigs

i) For the treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae.* The dosage is 8.8 mg tiamulin hydrogen fumarate/kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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 /kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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 /kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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/kg body weight (equivalent to 16 ml of product/100 kg body weight) administered daily for 5 consecutive days.

Chickens (laying hens)

For the treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*. the dosage is 25 mg tiamulin hydrogen fumarate/kg body weight (equivalent to 20 ml of product/100 kg body weight) administered daily for the period of 3 to 5 consecutive days.

4.10 Overdose

Pigs

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 sedation. 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.

Chickens

The LD_{50} is 1090 mg/kg body weight for chickens. 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 clinical signs of acute toxicity in chickens are vocalisation, clonic cramps and lying in a lateral position.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh unmedicated water and apply supportive, symptomatic therapy.

4.11 Withdrawal period

Pigs:

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate/ kg body weight equivalent to 7 ml of product/100 kg body weight)
Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate/ kg body weight, equivalent to 16 ml product)/100 kg body weight)

Chickens (laying hens):

Meat and offal: 2 days
Eggs: zero days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use/pleuromutilins/tiamulin
ATC Vet code: QJ01XQ01

5.1 Pharmacodynamic properties

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 shown a high level of *in vitro* activity against porcine and avian *Mycoplasma* species as well as gram-positive aerobes (streptococci and staphylococci), anaerobes (clostridia), gram-negative anaerobes (*Brachyspira hyodysenteriae*, *Brachyspira pilosicoli),* and gram-negative aerobes (*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.

In European isolates of *Brachyspira hyodysenteriae* collected between 1990 and 2012 the minimum inhibitory concentration (MICs) ranged from ≤0.016 µg/ml to >16 µg/ml, with MIC_{50} of ≤0.063 µg/ml to 4 µg/ml and MIC_{90} of ≤0.016 µg/ml to >16 µg/ml.

In European isolates of *Brachyspira pilosicoli* the MICs ranged from (citation from 2006-2008-2012) ≤0.008-64 µg/ml, with MIC_{50}s of ≤0.062 µg/ml up to 0.125 µg/ml and MIC_{90}s of 0.25 µg/ml up to 8 µg/ml.

Susceptibility testing of *Lawsonia intracellularis* is challenging since this is an obligate intracellular organism. The tiamulin MIC data determined for the available EU *Lawsonia* strains were (citation from 2017) all below the estimated ileal tiamulin contents of 0.63 µg/ml.

In European isolates tiamulin was highly active against *Mycoplasma hyopneumoniae*, with MIC_{50} of 0.016 µg/ml, MIC_{90} of 0.062 µg/ml, and a MIC range of 0.002-0.125 µg/ml (citation from 2014).

In newer European strains (2005-2013) and older global isolates (before 1997) MIC ranges were similar for *Mycoplasma gallisepticum* ranging from 0.001 – 0.037 µg/ml with MIC_{50}s of 0.001 and 0.008 µg/ml and MIC_{90}s of 0.025 and 0.031 µg/ml. No resistant strains were found. For *Mycoplasma synoviae* MICs ranged from 0.05 to 0.5 µg/ml with MIC_{50}s of 0.1 µg/ml and a MIC_{90} of 0.25 µg/ml.

5.2 Pharmacokinetic properties

Pigs

Tiamulin hydrogen fumarate is well absorbed in the pig (over 90%) following oral administration and widely distributed through the body. Following a single oral dose of 10 mg and 25 mg 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 (laying hens)

Tiamulin hydrogen fumarate is well absorbed in chickens (70-95%) after oral administration and reaches peak concentrations in 2-4 hours (T_{max} 2.85 hours). Following a 50 mg tiamulin hydrogen fumarate/kg body weight single dose the C_{max} was 4.02 µg/ml in serum by microbiological assay and after a 25 mg/kg dose it was 1.86 µg/ml. In drinking water the 250 ppm (0.025%) tiamulin hydrogen fumarate concentration provided a rolling serum level over a 48 hour medication period of 0.78 µg/ml (range 1.4-0.45 µg/ml) and 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 kidney (sites of excretion) and in the lung (30 times serum level). Excretion is mainly via the bile (55-65%) and kidney (15-30%) as mainly microbiologically inactive metabolites and is quite rapid, 99% of the dose within 48 hours.

5.3 Environmental properties

Tiamulin only degrades slowly in soils and may accumulate over years.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate
Disodium phosphate anhydrous
Ethanol 96%
Water for injection

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 as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after dilution in drinking water according to directions: 24 hours

6.4 Special precautions for storage

Store in the original container in order to protect from light.

6.5 Nature and composition of immediate packaging

The product is presented in:

- 1 litre high density polyethylene (HDPE) bottle closed with polypropylene (PP) screw cap and low density polyethylene (LDPE) seal disc.
- 5 litre high density polyethylene (HDPE) jar, closed with HDPE ribbed cap with a tamper-evident ring

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 AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerp
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

11. . PROHIBITION OF SALE, SUPPLY AND/OR USE

To be completed in accordance with national requirements after conclusion of the DC phase.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

Bottle of 1 L
Can of 5 L

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

VETMULIN 101.2 mg/ml Solution for use in drinking water for pigs and laying hens [FR]
VETMULIN 125 mg/ml Solution for use in drinking water for pigs and chickens [AU, BE, BG, CY, CZ, DE, DK, EL, ES, HR, HU, IE, IT, LV, LT, NL, PL, PT, RO, SI, SK, UK]
VETMULIN [EE]
Tiamulin hydrogen fumarate

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:

Active substance
Tiamulin hydrogen fumarate 125 mg
(equivalent to tiamulin 101.2 mg)

Excipients:
Methyl parahydroxybenzoate (E218) 0.90 mg
Propyl parahydroxybenzoate 0.10 mg

3. PHARMACEUTICAL FORM

Solution for use in drinking water

4. PACKAGE SIZE

1 Litre
5 Litre

5. TARGET SPECIES

Pigs and chickens (laying hens).

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

In drinking water use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

Pigs

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate/ kg body weight equivalent to 7 ml of product/100 kg body weight)
Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate/ kg body weight, equivalent to 16 ml product)/100 kg body weight)

Chickens (laying hens):

Meat and offal: 2 days
Eggs: Zero days

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP: {mm/yy}
Shelf-life after first opening the immediate packaging: 3 months
Once opened, use by: ….
Shelf-life after dilution in drinking water: 24 hours

11. SPECIAL STORAGE CONDITIONS

Store in the original container in order to protect from light.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot:

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

VETMULIN 101.2 mg/ml Solution for use in drinking water for pigs and laying hens [FR]
VETMULIN 125 mg/ml Solution for use in drinking water for pigs and chickens [AU, BE, BG, CY, CZ, DE, DK, EL, ES, HR, HU, IE, IT, LV, LT, NL, PL, PT, RO, SI, SK, UK]
VETMULIN [EE]

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation
Huvepharma NV
Uitbreidingstraat 80
2600 Antwerpen
Belgium

Manufacturer responsible for batch release
Biovet JSC
39 Petar Rakov Str.
4550 Peshtera
Bulgaria

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

VETMULIN 101.2 mg/ml Solution for use in drinking water for pigs and laying hens [FR]
VETMULIN 125 mg/ml Solution for use in drinking water for pigs and chickens [AU, BE, BG, CY, CZ, DE, DK, EL, ES, HR, HU, IE, IT, LV, LT, NL, PL, PT, RO, SI, SK, UK]
VETMULIN [EE]

Tiamulin hydrogen fumarate

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

Solution for use in drinking water.
Clear, colourless to slightly yellow liquid.

Each ml contains:

Active substance	
Tiamulin hydrogen fumarate	125 mg
(equivalent to Tiamulin	101.2 mg)
Excipients:	
Methyl parahydroxybenzoate (E218)	0.90 mg
Propyl parahydroxybenzoate	0.10 mg

4. INDICATION(S)

The presence of the disease in the herd must be established before the product is used.

In pigs

For the treatment of Swine Dysentery caused by tiamulin susceptible *Brachyspira hyodysenteriae*.
For the treatment of Porcine Colonic Spirochaetosis (spirochaetal diarrhoea or colitis) caused by tiamulin susceptible *Brachyspira pilosicoli.*
For the treatment of Porcine Proliferative Enteropathy (ileitis) caused by tiamulin susceptible *Lawsonia intracellularis*.
For the treatment and methapylaxis of Enzootic pneumonia caused by tiamulin- susceptible *Mycoplasma hyopneumoniae,* including infections complicated by tiamulin-susceptible *Pasteurella multocida*.

In chickens (laying hens)

For the treatment and methaphylaxis of Chronic Respiratory Disease caused by tiamulin-susceptible *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by tiamulin-susceptible *Mycoplasma synoviae.*

5. CONTRAINDICATIONS

Do not use in animals that could receive products containing 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 or excipients.

See section 12 for information regarding interaction between tiamulin and ionophores

6. ADVERSE REACTIONS

Pigs: In very rare cases, erythema or mild oedema of the skin (skin reactions) may occur in treated pigs.

Chickens (laying hens): 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)

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon

7. TARGET SPECIES

Pigs and chickens (laying hens).

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

In drinking water use

Pigs

i) For the treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae.* The dosage is 8.8 mg tiamulin hydrogen fumarate/kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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 /kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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 /kg body weight (equivalent to 7 ml of product/100 kg body weight) administered daily in the drinking water of pigs 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/kg body weight (equivalent to 16 ml of product/100 kg body weight) administered daily for 5 consecutive days.

Chickens (laying hens)

For the treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*. the dosage is 25 mg tiamulin hydrogen fumarate/kg body weight (equivalent to 20 ml of product/100 kg body weight) administered daily for the period of 3 to 5 consecutive days.

9. ADVICE ON CORRECT ADMINISTRATION

Administration:

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 actual body weight, the water consumption, the clinical condition of the animals, the environment and the age of the animal. In order to obtain the correct dosage, the concentration of tiamulin should be adjusted accordingly. Follow the instructions below to calculate the required daily amount of product:

$$\frac{\text{. …. ml product per kg body weight per day} \times \text{average body weight (kg)}}{\text{water intake (litre/animal/day)}} = \text{ml of the product per litre of drinking water per day}$$

Use a sufficiently accurate device to obtain the required volume of product. Use clean containers for preparation of the medicated drinking water. Stir the medicated drinking water prepared with the product for at least 1 minute after preparation in order to assure homogeneity. When medicating

large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration. The maximum solubility of the product is 200 mL/ L
Medicated drinking water should be refreshed or replaced every 24 hours.

In order to avoid interactions between the ionophores and tiamulin, the veterinarian and farmer should check with the feed mill that the feed does not contain salinomycin, monensin and narasin.
For chickens, in order 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 anticoccidials 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 have occurred.
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 salinomycin, monensin or narasin.

10. WITHDRAWAL PERIOD(S)

Pigs:

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate/ kg body weight equivalent to 7 ml of product/100 kg body weight)
Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate/ kg body weight, equivalent to 16 ml product/100 kg body weight)

Chickens (laying hens):

Meat and offal: 2 days
Eggs: Zero days

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Store in the original container in order to protect from light.

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.
Shelf life as packaged for sales: 3 years.
Shelf life after first opening the immediate packaging: 3 months
Shelf life after dilution in drinking water: 24 hours

12. SPECIAL WARNING(S)

Special warnings for each target species
Water intake may be depressed during the administration of tiamulin in birds. Water intake should be monitored at frequent intervals, especially in hot weather.
Pigs with reduced water intake and/or in a debilitated (weak) condition should be treated parenterally (intravenously or intramuscularly).

Special precautions for the use in animals

Use of the 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.

Use of the product deviating from the instructions of the package leaflet may increase the prevalence of bacteria resistant to tiamulin.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

People with known hypersensitivity to tiamulin or parabens should administer the veterinary medicinal product with caution.

Both the product and the diluted product in drinking water may cause hypersensitivity reactions due to contact. Avoid contact of both the product and medicated water with the skin. Do not smoke, eat or drink when handling the product. Wear protective clothes and gloves when mixing and handling the product, and wash hands after use. In case of accidental contact with skin, rinse with plenty of clean water. Contaminated clothing should be removed.

Ingestion of the product or medicated water should be avoided. In the event of accidental ingestion, rinse mouth with plenty of clean water and seek medical advice immediately.

Pregnancy and lactation

Can be used in pigs during pregnancy and lactation.

Lay

Can be used in laying chickens

Interaction with other medicinal products and other forms of interaction:

Severe growth depression, ataxia, paralysis (lameness) or death may result from the interaction of tiamulin with ionophores such as monensin, salinomycin and narasin. Animals should not receive products containing monensin, salinomycin or narasin during or at least 7 days before or after treatment with tiamulin. If signs of an interaction do occur, stop both the administration of tiamulin-medicated drinking water and 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. Simultaneous use of tiamulin and lasalocid or semduramicin do not appear to cause any interaction. Simultaneous use of maduramicin and tiamulin 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.

Overdose (symptoms, emergency procedures, antidotes)

In pigs, single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight caused hyperpnoea and abdominal discomfort. At a dose of 150 mg tiamulin hydrogen fumarate/kg body weight, the only effect on the central nervous system was sedation. A dose of 55 mg tiamulin hydrogen fumarate/kg body weight during 14 days caused a transient salivation and a mild irritation of the stomach. Tiamulin hydrogen fumarate has an adequate therapeutic index in the pig (meaning that the dose that has a therapeutic effect is much lower than the dose causing toxicity), and therefore a minimum lethal dose for pigs has not been established.

The LD_{50} (the dose at which 50% of a tested chicken population died after a specified test duration) in chickens, is 1090 mg/kg body weight. Tiamulin hydrogen fumarate has a relatively high therapeutic index in birds. The likelihood of an overdose is low as water intake and hence

tiamulin hydrogen fumarate intake is reduced if abnormally high doses are given. The clinical signs of acute toxicity in chickens are: vocalisation, clonic cramps and lying in a lateral position. If signs of poisoning occur, rapidly remove the medicated water and replace it with fresh unmedicated water. Appropriate symptomatic treatment should be initiated.

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

Other information
Tiamulin only degrades slowly in soils and may accumulate over years.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

To be completed nationally

15. OTHER INFORMATION>

The product is presented in 1 litre high density polyethylene (HDPE) bottles closed with polypropylene (PP) screw cap and low density polyethylene (LDPE) seal disc and 5 litre high density polyethylene (HDPE) jars, closed with HDPE ribbed cap with a tamper-evident ring.

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.