ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE VETERINARY MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State / EEA	Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Novartis Animal Health GmbH. , Biochemiestrasse 10, 6250 Kundl AUSTRIA	Denagard Novartis 100 g/kg Arzneimittelvormischung zur Herstellung von Fütterungsarzneimitteln für Schweine	Premix	100g/kg	Pigs	Oral
Austria	Novartis Animal Health GmbH. , Biochemiestrasse 10, 6250 Kundl AUSTRIA	Denagard Novartis 20 g/kg Arzneimittelvormischung zur Herstellung von Fütterungsarzneimitteln für Schweine	Premix	20g/kg	Pigs	Oral
Austria	Novartis Animal Health GmbH. , Biochemiestrasse 10, 6250 Kundl AUSTRIA	Tiamutin 20 g/kg Arzneimittelvormischung zur Herstellung von Fütterungsarzneimitteln für Schweine	Premix	20g/kg	Pigs	Oral
Belgium	VMD nv Leo Aerden Hoge Mauw 900, 2370 Arendonk BELGIUM	Tiamutin 10% gemedicineerd voormengsel	Premix	100mg/g	Pigs	Oral
Cyprus	Novartis Animal Health Inc., Basle, SWITZERLAND	Denagard 10%	Premix	100mg/g	Pigs	Oral
Czech Republic	Novartis Animal Health d.o.o., Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% premix ad us.vet.	Premix	100mg/g	Pigs Chickens Turkeys	Oral

Czech Republic	Novartis Animal Health d.o.o., Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 2% premix ad us.vet.	Premix	20mg/g	Pigs Chickens Turkeys	Oral
France	Novartis Sante Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Denagard prémélange tiamuline 16.2 pneumonie volaille - porc	Premix	16.2mg/g	Pigs Turkeys Chickens	Oral
France	Novartis Sante Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Denagard prémélange tiamuline 6.5 enterite porc enterocolite lapin	Premix	6.5mg/g	Rabbits Pigs	Oral
Germany	Novartis Tiergesundheit GmbH Zielstattstr. 40, 81379 München GERMANY	Denagard 10% AMV	Premix	100g/kg	Pigs	Oral
Greece	Premier Shukuroglou Hellas S.A Mesogion Av 198, 15561 Holargos GREECE	Denagard 2%	Premix	20mg/g	Pigs	Oral
Greece	Premier Shukuroglou Hellas S.A Mesogion Av 198, 15561 Holargos GREECE	Denagard 10%	Premix	100mg/g	Pigs	Oral
Hungary	Novartis Animal Health d.o.o. Verovskova 57, 1000 Ljubljana SLOVENIA	Denagard 10 % gyógypremix A.U.V.	Premix	100mg/g	Pigs	Oral

Ireland	Novartis Animal Health Ireland Ltd., Industrial Park, Cork Road, Waterford IRELAND	Tiamutin 2%	Premix	20mg/g	Pigs	Oral
Ireland	Novartis Animal Health Ireland Ltd., Industrial Park, Cork Road, Waterford IRELAND	Tiamutin 80%	Premix	800mg/g	Pigs	Oral
Italy	Novartis Animal Health S.P.A Largo Umberto Boccioni, 1 21040 Origlio (Varese) ITALY	Denagard 10% Premix	Premix	100mg/g	Pigs Chickens Turkeys	Oral
Italy	Novartis Animal Health S.P.A Largo Umberto Boccioni, 1 21040 Origlio (Varese) ITALY	Denagard 10% Premix Plus	Premix	100mg/g	Pigs	Oral
Latvia	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% premix	Premix	100mg/g	Pigs	Oral
Lithuania	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% vaistinis premiksas kiaulėms	Premix	100mg/g	Pigs	Oral

Portugal	Novartis Farma Produtos Farmacêuticos S.A Rua do Centro Empresarial Edifício 8 Quinta da Beloura 2710-444 Sintra PORTUGAL	Denagard 20 g/Kg	Premix	20g/kg	Pigs Chickens Turkeys	Oral
Portugal	Novartis Farma Produtos Farmacêuticos S.A Rua do Centro Empresarial Edifício 8 Quinta da Beloura 2710-444 Sintra PORTUGAL	Denagard 100 g/Kg	Premix	100g/kg	Pigs Chickens Turkeys Rabbits	Oral
Portugal	Novartis Farma Produtos Farmacêuticos S.A Rua do Centro Empresarial Edifício 8 Quinta da Beloura 2710-444 Sintra PORTUGAL	Dynamutilin 100 g/Kg	Premix	100g/kg	Pigs Chickens Turkeys	Oral
Poland	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% premiks leczniczy dla świń	Premix	100mg/g	Pigs	Oral
Poland	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 2% 20 mg/g premiks do sporządzania paszy leczniczej dla świń	Premix	20mg/g	Pigs	Oral

Romania	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% Premix pentru furaje medicamentate pentru porci	Premix	100mg/g	Pigs Chickens Turkeys	Oral
Romania	Novartis Animal Health d.o.o. Verovškova 57, SI-1000 Ljubljana SLOVENIA	Tiamutin 80% coated	Premix	800 g/100 kg	Pigs Chickens Turkeys	Oral
Slovakia	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 10% prm. ad us. vet.	Premix	100mg/g	Pigs Chickens Turkeys	Oral
Slovakia	Novartis Animal Health d.o.o. Verovškova 57, 1000 Ljubljana SLOVENIA	Tiamutin 2% prm. ad us. vet.	Premix	20mg/g	Pigs Chickens Turkeys	Oral
Spain	Novartis Sanidad Animal, S.L. c/De la Marina, 206 08013 Barcelona SPAIN	Denagard 100 g/kg Premezcla medicamentosa	Premix	100g/kg	Pigs Chickens Turkeys Rabbits	Oral
Spain	Novartis Sanidad Animal, S.L. c/De la Marina, 206 08013 Barcelona SPAIN	Denagard 20 g/kg Premezcla medicamentosa	Premix	20g/kg	Pigs Rabbits	Oral

Spain	Novartis Sanidad Animal, S.L. c/De la Marina, 206 08013 Barcelona SPAIN	Dynamutilin 10 %	Premix	100g/kg	Pigs Chickens Turkeys	Oral
Sweden	Novartis Healthcare A/S Animal Health Lyngbyvej 172 DK-2100 Köpenhamn Ö DENMARK	Denagard vet.	Premix	20mg/g	Pigs	Oral
The Netherlands	Novartis Consumer health Claudius Prinsenlaan 142 4818 CP Breda The NETHERLANDS	Tiamutin 10%	Premix	100g/kg	Pigs	Oral
The Netherlands	Novartis Consumer health Claudius Prinsenlaan 142 4818 CP Breda The NETHERLANDS	Denagard 2%	Premix	20g/kg	Pigs	Oral
United Kingdom	Novartis Animal Health UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Denagard 2% w/w	Premix	2mg/g	Pigs	Oral

United Kingdom	Novartis Animal Health UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Denagard 80% w/w	Premix	80mg/g	Pigs	Oral
United Kingdom	Novartis Animal Health UK Ltd Frimley Business Park Frimley Camberley Surrey GU16 7SR United Kingdom	Denagard 10% w/w	Premix	100mg/g	Pigs	Oral

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND LABELLING

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF TIAMUTIN PREMIX AND ASSOCIATED NAMES *(see Annex I)*

1. Introduction

Premixes with tiamulin are marketed in 20 European Member States under a variety of invented names (see Annex I). The authorised premix-formulations are based on tiamulin hydrogen fumarate in a concentration of:

- 0.8%,
- 2%,
- 10% and
- 80%.

In France the registered 0.65% premix refers to tiamulin base equivalent to a premix containing 0.8% tiamulin hydrogen fumarate, and the registered 1.62% premix refers to tiamulin base which is equivalent to a premix containing 2.0 % tiamulin hydrogen fumarate.

The target animals are:

- Pigs
- Chickens
- Turkeys
- Rabbits

Certain concentrations of these premix formulations are not currently authorised in these Member States in certain species e.g. 0.8% concentration not authorised in chickens and turkeys, 80% concentration not authorised in rabbits.

Due to the divergent national decisions taken by Member States concerning the authorisation of these products, the issue was referred to CVMP under Article 34(1) of Directive 2001/82/EC, in order to resolve divergences amongst the nationally authorised Summary of Product Characteristics (SPC) across the European Union.

The main sections of disharmony of the existing SPCs were:

1. Indications for use;
2. Amount to be administered and administration route;
3. Withdrawal period(s).

2. Discussion

The Marketing Authorisation Holders were requested:

1. to provide an exhaustive list of differences between the SPCs of the product authorised in the Member States;
2. to review all sections of the SPCs and to suggest appropriate changes in the text where divergences exist and to propose a harmonised Product Information (SPC and labelling), taking into account the latest guidance;
3. to provide available relevant data, in particular substantiating such proposed harmonised Product Information in relation to the discrepancies identified above.

As regards harmonisation of indications and based on the efficacy data provided it is agreed to harmonise the indications as follows:

<u>Pigs:</u>

The use of tiamutin premix and associated names in the treatment and prevention of swine dysentery, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli*, treatment of Porcine Proliferative Entheropaty (ileitis) caused by *L. intracellularis* and treatment of enzootic pneumonia caused by *M. hyopneumoniae* is agreed.

The indication in pigs concerning the use of tiamutin premix and associated names for the prevention of enzootic pneumonia caused by *M. hyopneumoniae* is not agreed. It is not justified that tiamulin can be used in the prevention of enzootic pneumonia based on the data presented. It would not be compliant with responsible use recommendations (see e.g. The Codex Code of practice to minimize and contain antimicrobial resistance (CAC/RCP 61-2005), OIE Guidelines for the responsible and prudent use of antimicrobial agents in veterinary medicine, and Federation of Veterinarians of Europe: Antibiotic Resistance & Prudent use of Antibiotics in Veterinary Medicine)

to use an antimicrobial preventively unless there is a direct benefit in terms of a reduced level of clinical infection and/or reduction of the spread of the infection in the herd. Notably although emergence of antimicrobial resistance against *M. hyopneumoniae* does not seem to be of immediate concern there is a need to consider resistance also against other microbes present in swine herds such as *B. hyodysenteriae*.

Chickens (broiler, replacement pullet, laying and breeding hens):

The use of tiamutin premix and associated names in the treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae* is agreed.

Turkeys (young poults, breeding turkeys):

The use of tiamutin premix and associated names in the treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis* is agreed.

Rabbits:

The use of tiamutin premix and associated names in the treatment of epizootic rabbit enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm is agreed.

The variation in posology amongst the nationally authorised Summary of Product Characteristics (SPC) meant that this issue also needed to be addressed in this referral procedure. For each approved indication and based on the data provided it is agreed to harmonise the amount to be administered for each indication as shown in the tables below.

Concerning withdrawal periods the very wide variation in currently approved withdrawal periods was noted (e.g. ranging from 1 day to 20 days in pigs, 3 to 8 days in chickens and turkeys, 0 days in rabbits).
Exceptionally, in this case CVMP agreed with the different withdrawal periods proposed in pigs for the prevention and treatment indications, due to the separate posologies proposed and based on the data provided by the Marketing Authorisation Holders.

Conclusion: Having considered the grounds for referral and the responses provided by the Marketing Authorisation Holders, the CVMP concluded as follows:

Indications for use and amount to be administered and administration route

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg
20.0	5.0 – 10.0 kg
100.0	1.0 – 2.0 kg
800.0	0.125 – 0.25 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysent*eriae and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	5.0 kg
20.0	2.0 kg
100.0	0.4 kg
800.0	0.05 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	18.75 kg
20.0	7.5 kg
100.0	1.5 kg
800.0	0.188 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg
20.0	5.0 – 10.0 kg
100.0	1.0 – 2.0 kg
800.0	0.125 – 0.25 kg

Chickens (broiler, replacement pullet, laying and breeding hens)
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 – 25.0 kg
100.0	2.5 – 5.0 kg
800.0	0.313 – 0.625 kg

Turkeys (young poults, breeding turkeys)
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 – 25.0 kg
100.0	2.5 – 5.0 kg
800.0	0.313 – 0.625 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

Rabbits

Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.

Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of tiamulin hydrogen fumarate (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg
20.0	5.0 – 10.0 kg
100.0	1.0 – 2.0 kg

Withdrawal period(s)

Pigs
Prevention (at 2.0mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days

Exceptionally, in this case CVMP agreed with the different withdrawal periods proposed in pigs for the prevention and treatment indications, due to the separate posologies proposed and based on the data provided by the Marketing Authorisation Holders.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND LABELLING

Whereas

- the CVMP considered that the indications for use should be harmonised for each species but that the indication for tiamulin to be used in the prevention of enzootic pneumonia could not be accepted based on the data presented;

- the CVMP considered that the amount to be administered and administration route should be harmonised for each species;

- the CVMP considered that the withdrawal periods should be harmonised for each species as follows:
Pigs
Prevention (at 2.0mg/kg bodyweight); Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight); Meat and offal: 6 days

Chickens
Meat and offal: 1 day Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days.

Exceptionally, in this case CVMP agreed with the different withdrawal periods proposed in pigs for the prevention and treatment indications, due to the separate posologies proposed and based on the data provided by the Marketing Authorisation Holders;

- the CVMP considered that the SPC should be harmonised in the framework of this referral procedure, while also noting that certain concentrations of the premix formulations are not currently authorised in Member States in certain species e.g. 0.8% concentration not authorised in chickens and turkeys, 80% concentration not authorised in rabbits;

the CVMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics and labelling are set out in Annex III for Tiamutin premix and associated names (see Annex I).

It should be noted that the 0.65% strength currently authorised in France is covered by the 0.8% Premix SPC/label (0.65% tiamulin base is eqivalent to 0.8% tiamulin hydrogen fumarate) and the 1.62% strength currently authorized in France is covered by the 2% Premix SPC/label (1.62% tiamulin base is eqivalent to 2 % tiamulin hydrogen fumarate).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

Premix for medicated feed for pigs and rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tiamulin hydrogen fumarate - 8 mg/g
In the case of the 0.65% premix authorised in France this refers to tiamulin base equivalent to a premix containing 0.8% tiamulin hydrogen fumarate and so is covered by the 0.8% Premix SPC.

Excipients: For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. CLINICAL PARTICULARS

4.1 Target species

Pigs
Rabbits

4.2 Indications for use, specifying the target species

Pigs
For the treatment and prevention of swine dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

4.3 Contraindications

Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven 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

4.4 Special warning for each target species

In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.

4.5 Special precautions for use

Special precautions for use in animals

It is sound clinical practice to base treatment 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.

Refer to section 4.8 for information regarding interaction between tiamulin and ionophores.

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

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.
People with known hypersensitivity to tiamulin should administer the product with caution.

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.

4.7 Use during pregnancy, lactation or lay

Can be used in pigs during pregnancy and lactation.
Can be used in rabbits during pregnancy and lactation.

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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

4.9 Amounts to be administered and administration route

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	5.0 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	18.75 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	5.0 kg

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

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

4.11 Withdrawal period(s)

Pigs
Prevention (at 2.0mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight): Meat and offal: 6 days

Rabbits
Meat and offal: 0 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for systemic use
ATCvet code: QJ 01 XQ 01

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 *in-vitro* activity against a wide range of bacteria including *Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*, *Lawsonia intracellularis* and Mycoplasma spp.
Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S ribosome level and the primary binding site is on the 50S subunit and possibly a secondary site where the 50S and 30S subunits join. It appears to inhibit microbial protein production by producing biochemical inactive initiation complexes, which prevent elongation of the polypeptide chain.
Mechanisms responsible for resistance development in Brachyspira spp to the pleuromutilin class of antibiotics are considered to be based on mutations at the ribosomal target site. Clinically relevant resistance to tiamulin requires combinations of mutations around the tiamulin binding site. Resistance to tiamulin may be associated with decreased susceptibility to other pleuromutilins.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin 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/kg bodyweight the Cmax was 1.03 µg/ml and 1.82 µg/ml respectively by microbiological assay and the Tmax was 2 hours for both. Tiamulin has been shown to concentrate in the lung, a target tissue and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon and concentrates there.

Rabbits
There are no pharmacokinetic data available for rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed nationally

6.2 Incompatibilities

None known

6.3 Shelf-life

To be completed nationally

6.4 Special precautions for storage

To be completed nationally

6.5 Nature and composition of immediate packaging

To be completed nationally

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

Any unused product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

Prohibition of sale, supply and/or use

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

Premix for medicated feed for pigs, chickens, turkeys and rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tiamulin hydrogen fumarate - 20 mg/g
In the case of the 1.62% premix authorised in France this refers to tiamulin base equivalent to a premix containing 2% tiamulin hydrogen fumarate and so is covered by the 2% Premix SPC.
Excipients: For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

Pigs
For the treatment and prevention of swine dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

4.3 Contraindications

Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven 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

4.4 Special warning for each target species

In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.

4.5 Special precautions for use

Special precautions for use in animals

It is sound clinical practice to base treatment 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.

Refer to section 4.8 for information regarding interaction between tiamulin and ionophores.

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

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.
People with known hypersensitivity to tiamulin should administer the product with caution.

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.

4.7 Use during pregnancy, lactation or lay

Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.
Can be used in rabbits during pregnancy and lactation.

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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

4.9 Amounts to be administered and administration route

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

<u>Pigs</u>
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	5.0 – 10.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	2.0 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	7.5 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	5.0 – 10.0 kg

<u>Chickens (broiler, replacement pullet, laying and breeding hens)</u>
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 – 25.0 kg

<u>Turkeys (young poults, breeding turkeys)</u>
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is

unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 - 25.0 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	2.0 kg

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD_5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

4.11 Withdrawal period(s)

Pigs
Prevention (at 2.0mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for systemic use
ATCvet code: QJ 01 XQ 01

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 *in-vitro* activity against a wide range of bacteria including *Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*, *Lawsonia intracellularis* and Mycoplasma spp.
Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S ribosome level and the primary binding site is on the 50S subunit and possibly a secondary site where the 50S and 30S subunits join. It appears to inhibit microbial protein production by producing biochemical inactive initiation complexes, which prevent elongation of the polypeptide chain.
Mechanisms responsible for resistance development in Brachyspira spp to the pleuromutilin class of antibiotics are considered to be based on mutations at the ribosomal target site. Clinically relevant resistance to tiamulin requires combinations of mutations around the tiamulin binding site.
Resistance to tiamulin may be associated with decreased susceptibility to other pleuromutilins.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin 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/kg bodyweight the Cmax was 1.03 µg/ml and 1.82 µg/ml respectively by microbiological assay and the Tmax was 2 hours for both.Tiamulin has been shown to concentrate in the lung, a target tissue and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon and concentrates there.

Chickens
Tiamulin is well absorbed in chickens (70-95%) after oral administration.
Tiamulin 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.

Turkeys
In turkeys serum levels of tiamulin are similar to chickens. In breeders on 0.025% tiamulin the average serum level was 0.36µg/ml (range 0.22-0.5µg/ml).

Rabbits
There are no pharmacokinetic data available for rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed nationally

6.2 Incompatibilities

None known

6.3 Shelf-life

To be completed nationally

6.4 Special precautions for storage

To be completed nationally

6.5 Nature and composition of immediate packaging

To be completed nationally

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

Any unused product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

Prohibition of sale, supply and/or use

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

Premix for medicated feed for pigs, chickens, turkeys and rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tiamulin hydrogen fumarate - 100 mg/g
Excipients: For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

Pigs
For the treatment and prevention of swine dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

4.3 Contraindications

Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven 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

4.4 Special warning for each target species

In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.

4.5 Special precautions for use

Special precautions for use in animals

It is sound clinical practice to base treatment 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.

Refer to section 4.8 for information regarding interaction between tiamulin and ionophores.

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

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.
People with known hypersensitivity to tiamulin should administer the product with caution.

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.

4.7 Use during pregnancy, lactation or lay

Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.
Can be used in rabbits during pregnancy and lactation.

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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

4.9 Amounts to be administered and administration route

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

<u>Pigs</u>
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.0 – 2.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	0.4 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.5 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.0 – 2.0 kg

<u>Chickens (broiler, replacement pullet, laying and breeding hens)</u>
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	2.5 – 5.0 kg

<u>Turkeys (young poults, breeding turkeys)</u>
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	2.5 - 5.0 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	0.4 kg

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

Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD_5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

4.11 Withdrawal period(s)

Pigs
Prevention (at 2.0mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for systemic use
ATCvet code: QJ 01 XQ 01

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 *in-vitro* activity against a wide range of bacteria including *Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*, *Lawsonia intracellularis* and Mycoplasma spp.
Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S ribosome level and the primary binding site is on the 50S subunit and possibly a secondary site where the 50S and 30S subunits join. It appears to inhibit microbial protein production by producing biochemical inactive initiation complexes, which prevent elongation of the polypeptide chain.
Mechanisms responsible for resistance development in Brachyspira spp to the pleuromutilin class of antibiotics are considered to be based on mutations at the ribosomal target site. Clinically relevant resistance to tiamulin requires combinations of mutations around the tiamulin binding site. Resistance to tiamulin may be associated with decreased susceptibility to other pleuromutilins.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin 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/kg bodyweight the Cmax was 1.03 µg/ml and 1.82 µg/ml respectively by microbiological assay and the Tmax was 2 hours for both.Tiamulin has been shown to concentrate in the lung, a target tissue and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon and concentrates there.

Chickens
Tiamulin is well absorbed in chickens (70-95%) after oral administration.
Tiamulin 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.

Turkeys
In turkeys serum levels of tiamulin are similar to chickens. In breeders on 0.025% tiamulin the average serum level was 0.36µg/ml (range 0.22-0.5µg/ml).

Rabbits
There are no pharmacokinetic data available for rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed nationally

6.2 Incompatibilities

None known

6.3 Shelf-life

To be completed nationally

6.4 Special precautions for storage

To be completed nationally

6.5 Nature and composition of immediate packaging

To be completed nationally

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

Any unused product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

Prohibition of sale, supply and/or use

Not applicable.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

Premix for medicated feed for pigs, chickens and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tiamulin hydrogen fumarate - 800 mg/g
Excipients: For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. CLINICAL PARTICULARS

4.1 Target species

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

4.2 Indications for use, specifying the target species

Pigs
For the treatment and prevention of swine dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

4.3 Contraindications

Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven 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

4.4 Special warning for each target species

In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.

4.5 Special precautions for use

Special precautions for use in animals

It is sound clinical practice to base treatment 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.

Refer to section 4.8 for information regarding interaction between tiamulin and ionophores.

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

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.
People with known hypersensitivity to tiamulin should administer the product with caution.

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.

4.7 Use during pregnancy, lactation or lay

Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.

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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

4.9 Amounts to be administered and administration route

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.125 – 0.25 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.05 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.188 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.125 – 0.25 kg

<u>Chickens (broiler, replacement pullet, laying and breeding hens)</u>
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.313 – 0.625 kg

<u>Turkeys (young poults, breeding turkeys)</u>
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.313 - 0.625 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

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

Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD_5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

4.11 Withdrawal period(s)

Pigs
Prevention (at 2.0mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5-10mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterial for systemic use
ATCvet code: QJ 01 XQ 01

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 *in-vitro* activity against a wide range of bacteria including *Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*, *Lawsonia intracellularis* and Mycoplasma spp.
Tiamulin is bacteriostatic at therapeutic concentrations and has been shown to act at the 70S ribosome level and the primary binding site is on the 50S subunit and possibly a secondary site where the 50S and 30S subunits join. It appears to inhibit microbial protein production by producing biochemical inactive initiation complexes, which prevent elongation of the polypeptide chain.
Mechanisms responsible for resistance development in Brachyspira spp to the pleuromutilin class of antibiotics are considered to be based on mutations at the ribosomal target site. Clinically relevant resistance to tiamulin requires combinations of mutations around the tiamulin binding site. Resistance to tiamulin may be associated with decreased susceptibility to other pleuromutilins.

5.2 Pharmacokinetic particulars

Pigs
Tiamulin 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/kg bodyweight the Cmax was 1.03 µg/ml and 1.82 µg/ml respectively by microbiological assay and the Tmax was 2 hours for both.Tiamulin has been shown to concentrate in the lung, a target tissue and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon and concentrates there.

Chickens
Tiamulin is well absorbed in chickens (70-95%) after oral administration.
Tiamulin 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.

Turkeys
In turkeys serum levels of tiamulin are similar to chickens. In breeders on 0.025% tiamulin the average serum level was 0.36µg/ml (range 0.22-0.5µg/ml).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

To be completed nationally

6.2 Incompatibilities

None known

6.3 Shelf-life

To be completed nationally

6.4 Special precautions for storage

To be completed nationally

6.5 Nature and composition of immediate packaging

To be completed nationally

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

Any unused product or waste material should be disposed of in accordance with national requirements.

7. MARKETING AUTHORISATION HOLDER

To be completed nationally

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally

10. DATE OF REVISION OF THE TEXT

To be completed nationally

Prohibition of sale, supply and/or use

Not applicable.

LABELLING

<PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

8 mg/g Premix for medicated feed for pigs and rabbits

Tiamulin hydrogen fumarate

In the case of the 0.65% premix authorised in France this refers to tiamulin base equivalent to a premix containing 0.8% tiamulin hydrogen fumarate and so is covered by the 0.8% Premix label.

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

To be completed nationally

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PACKAGE SIZE

To be completed nationally

5. TARGET SPECIES

Pigs
Rabbits

6. INDICATION(S)

Pigs
For the treatment and prevention of Swine Dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	5.0 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	18.75 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	12.5 – 25.0 kg

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
8.0	5.0 kg

8. WITHDRAWAL PERIOD

Pigs
Prevention (at 2.0 mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5 -10 mg/kg bodyweight): Meat and offal: 6 days

Rabbits
Meat and offal: 0 days

9. SPECIAL WARNING(S), IF NECESSARY

Contraindication
Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Warnings
In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.
It is sound clinical practice to base treatment 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.

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

Use during pregnancy, lactation or lay
Can be used in pigs during pregnancy and lactation.
Can be used in rabbits during pregnancy and lactation.

Interactions
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 recieve 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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Overdose
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Operator warnings
When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.

People with known hypersensitivity to tiamulin should administer the product with caution.

10. EXPIRY DATE

To be completed nationally

11. SPECIAL STORAGE CONDITIONS

To be completed nationally

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

Dispose of waste material 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

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

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

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{For national implementation}

16. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

17. MANUFACTURER'S BATCH NUMBER

{For national implementation}

18. CONTRAINDICATIONS

19. ADVERSE REACTIONS

<PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

20 mg/g Premix for medicated feed for pigs, chickens, turkeys and rabbits

Tiamulin hydrogen fumarate

In the case of the 1.62% premix authorised in France this refers to tiamulin base equivalent to a premix containing 2% tiamulin hydrogen fumarate and so is covered by the 2% Premix label.

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

To be completed nationally

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PACKAGE SIZE

To be completed nationally

5. TARGET SPECIES

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

6. INDICATION(S)

Pigs
For the treatment and prevention of Swine Dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	5.0 – 10.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	2.0 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	7.5 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	5.0 – 10.0 kg

Chickens (broiler, replacement pullet, laying and breeding hens)
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.

Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 – 25.0 kg

Turkeys (young poults, breeding turkeys)
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
20.0	12.5 - 25.0 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	2.0 kg

8. WITHDRAWAL PERIOD

Pigs
Prevention (at 2.0 mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5 -10 mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days

9. SPECIAL WARNING(S), IF NECESSARY

Contraindication
Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Warnings
In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.
It is sound clinical practice to base treatment 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.

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

Use during pregnancy, lactation or lay
Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.
Can be used in rabbits during pregnancy and lactation.

Interactions
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 recieve 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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Overdose
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

Operator warnings
When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.

People with known hypersensitivity to tiamulin should administer the product with caution.

10. EXPIRY DATE

To be completed nationally

11. SPECIAL STORAGE CONDITIONS

To be completed nationally

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

Dispose of waste material 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

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

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

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{For national implementation}

16. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

17. MANUFACTURER'S BATCH NUMBER

{For national implementation}

18. CONTRAINDICATIONS

19. ADVERSE REACTIONS

<PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

100 mg/g Premix for medicated feed for pigs, chickens, turkeys and rabbits

Tiamulin hydrogen fumarate

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

To be completed nationally

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PACKAGE SIZE

To be completed nationally

5. TARGET SPECIES

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

6. INDICATION(S)

Pigs
For the treatment and prevention of Swine Dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

Rabbits
For the treatment and prevention of epizootic rabbit enterocolitis (ERE)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.0 – 2.0 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	0.4 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.5 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	1.0 – 2.0 kg

Chickens (broiler, replacement pullet, laying and breeding hens)
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	2.5 – 5.0 kg

Turkeys (young poults, breeding turkeys)
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	2.5 - 5.0 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

Rabbits
Treatment of Epizootic Rabbit Enterocolitis (ERE) and prevention of ERE in farms with clinical signs of ERE in the previous fattening cycle as part of a programme including measures aiming to eradicate or control the infection in the farm.
Dosage: 3 mg tiamulin hydrogen fumarate /kg body weight daily. The dosage will normally be achieved by an inclusion level of 40 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Treatment should be administered until 2 – 3 days after clinical signs has resolved. Prevention should be administered during 3 – 4 weeks from the first week after weaning.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
100.0	0.4 kg

8. WITHDRAWAL PERIOD

Pigs
Prevention (at 2.0 mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5 -10 mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

Rabbits
Meat and offal: 0 days

9. SPECIAL WARNING(S), IF NECESSARY

Contraindication
Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Warnings
In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.
It is sound clinical practice to base treatment 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.

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

Use during pregnancy, lactation or lay
Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.
Can be used in rabbits during pregnancy and lactation.

Interactions
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 recieve 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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Overdose
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

Operator warnings
When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn when mixing the veterinary medicinal product or handling the medicated feed: overalls, impervious gloves and either a disposable half-mask respirator conforming to European Standard EN 149 or a non-disposable respirator conforming to European Standard EN 140, with a filter to European Standard EN 143. Wash contaminated skin.

In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.

People with known hypersensitivity to tiamulin should administer the product with caution.

10. EXPIRY DATE

To be completed nationally

11. SPECIAL STORAGE CONDITIONS

To be completed nationally

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

Dispose of waste material 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

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

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

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{For national implementation}

16. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

17. MANUFACTURER'S BATCH NUMBER

{For national implementation}

18. CONTRAINDICATIONS

19. ADVERSE REACTIONS

<PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE>

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

800 mg/g Premix for medicated feed for pigs, chickens and turkeys

Tiamulin hydrogen fumarate

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

To be completed nationally

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PACKAGE SIZE

To be completed nationally

5. TARGET SPECIES

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

6. INDICATION(S)

Pigs
For the treatment and prevention of Swine Dysentery caused by *Brachyspira hyodysenteriae*
For the treatment of colitis caused by *Brachyspira pilosicoli*
For the treatment of ileitis caused by *Lawsonia intracellularis*
For the treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*

Chickens
For the treatment and prevention of chronic respiratory disease (CRD) and airsacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

Turkeys
For the treatment and prevention of infectious sinusitis and airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Calculations to achieve the correct dose rate and achieve the correct inclusion rate should be based on: - Inclusion rate (ppm) = dose rate (mg/kg bodyweight) x bodyweight (kg) / daily feed intake (kg)

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

The intake of medicated feed depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin hydrogen fumarate has to be adjusted accordingly

Pigs
Treatment of Swine Dysentery caused by *B. hyodysenteriae*, treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*

Dosage: 5 - 10 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 - 200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.125 – 0.25 kg

Prevention of Swine Dysentery caused by *B. hyodysenteriae*
Dosage: 2.0 mg tiamulin hydrogen fumarate/kg bodyweight daily. The dosage will normally be achieved by an inclusion level of 40ppm tiamulin hydrogen fumarate in the finished feed, providing feed intake is unaffected. Preventive medication with tiamulin should be given for 2-4 weeks.

Preventive treatment with tiamulin should only be initiated after confirmed infection with *B. hyodysenteriae* and then as part of a program including measures aiming to eradicate or control the infection in the herd.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.05 kg

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10-14 consecutive days. The dosage will normally be achieved by an inclusion level of 150ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.188 kg

Treatment of Enzootic Pneumonia caused by *M. hyopneumoniae*
Dosage: 5.0 – 10.0 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 7 to 10 consecutive days. The dosage will normally be achieved by an inclusion level of 100 -200 ppm tiamulin hydrogen fumarate in the finished feed providing that feed intake is unaffected.

Secondary infection by organisms such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* may complicate enzootic pneumonia and require specific medication.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.125 – 0.25 kg

Chickens (broiler, replacement pullet, laying and breeding hens)
Treatment and prevention of chronic respiratory disease (CRD) caused by *M. gallisepticum* and airsacculitis and infectious synovitis caused by *M. synoviae*.
Dosage – Treatment and prevention: 25mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in the finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. broiler chickens during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.313 – 0.625 kg

Turkeys (young poults, breeding turkeys)
Treatment and prevention of infectious sinusitis and airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40mg tiamulin hydrogen fumarate/kg body weight daily administered for the period of 3 to 5 consecutive days. This is normally achieved by an inclusion level of 250 - 500 ppm tiamulin hydrogen fumarate in finished feed provided that feed intake is unaffected. Inclusion levels in the higher range will in most cases be needed to avoid underdosing. In fast growing birds, e.g. poults during the first 2-4 weeks of life, inclusion levels in the lower range may be sufficient.

Amount of THF (mg/g) per premix formulation	Amount of premix formulation per one tonne of feed
800.0	0.313 - 0.625 kg

Preventive treatment with tiamulin should only be initiated after confirmed infection with *M. gallisepticum*, *M. synoviae* or *M. meleagridis* and then as an aid in the prevention strategy to reduce the clinical signs and mortality from respiratory disease in flocks, where infection in ovum is likely because the disease is known to exist in the parent generation. The prevention strategy should include efforts to eliminate the infection from the parent generation.

8. WITHDRAWAL PERIOD

Pigs
Prevention (at 2.0 mg/kg bodyweight): Meat and offal: 1 day
Treatment (at 5 -10 mg/kg bodyweight): Meat and offal: 6 days

Chickens
Meat and offal: 1 day
Eggs: 0 days

Turkeys
Meat and offal: 4 days

9. SPECIAL WARNING(S), IF NECESSARY

Contraindication
Animals should not receive products containing ionophores (monensin, narasin or salinomycin) during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Warnings
In case of reduced feed intake, the inclusion levels in feed may need to be increased to achieve target dosage. Acute cases and severely diseased animals with reduced feed intake should be treated with a product of suitable formulation such as an injectable or water solution.
It is sound clinical practice to base treatment 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.

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

Use during pregnancy, lactation or lay
Can be used in pigs during pregnancy and lactation.
Can be used in laying and breeding chickens and turkeys.

Interactions
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 recieve 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, administration of contaminated feed should be stopped immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Overdose
Pigs: Single oral doses of 100 mg/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg/kg no CNS effects were noted except for sedation. At 55 mg/kg given for 14 days a transient salivation and slight gastric irritation occurred. A minimum lethal dose has not been established in pigs.

Chickens and turkeys: The LD5 for chickens is 1290mg/kg and turkeys 840 mg/kg bodyweight. The clinical signs of acute toxicity in chickens are - vocalization, clonic cramps and lateral recumbency. In turkeys signs of acute toxicity include clonic cramps, lateral or dorsal recumbency, salivation and ptosis.
If signs of intoxication do occur promptly remove the medicated feed, replace with fresh unmedicated feed and apply supportive, symptomatic therapy.

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In case of accidental ingestion, seek medical advice immediately and show the package insert or label to the physician.

People with known hypersensitivity to tiamulin should administer the product with caution.

10. EXPIRY DATE

To be completed nationally

11. SPECIAL STORAGE CONDITIONS

To be completed nationally

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

Dispose of waste material 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

Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.

14. THE WORDS “KEEP OUT OF THE REACH AND SIGHT OF CHILDREN”

Keep out of the reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{For national implementation}

16. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

17. MANUFACTURER'S BATCH NUMBER

{For national implementation}

18. CONTRAINDICATIONS

19. ADVERSE REACTIONS