

## **Annex I**

**List of the names, pharmaceutical form, strength of the veterinary medicinal products, animal species, route of administration, marketing authorisation holders in the Member States**

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Austria	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 450 mg/g Granulat zum Eingeben über das Trinkwasser	Tiamulin hydrogen fumarate	450 mg/g	Granules	Pigs, chickens, turkeys	Oral
Belgium	VMD nv Hoge Mauw 900 2370 Arendonk Belgium	Tiamutin 45% Pigs	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Pigs	Oral
Belgium	VMD nv Hoge Mauw 900 2370 Arendonk Belgium	Tiamutin 45% Chicken- Turkey	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Chickens, turkeys	Oral
Belgium	VMD nv Hoge Mauw 900 2370 Arendonk Belgium	Tiamutin 45% Pigs- Chicken-Turkey	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Pigs, chickens, turkeys	Oral
Czech Republic	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	DENAGARD 450 mg/g granule pro přípravu perorálního roztoku	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Pigs, chickens (broilers, pullets, layers and breeders), turkeys (fattening and breeding birds)	Oral
Finland	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard vet 450 mg/g rakeet	Tiamulin hydrogen fumarate	450 mg/g	Granules	Pigs	Oral to be administered in drinking water
Germany	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 45% Granulat	Tiamulin hydrogen fumarate	45% w/w (36.4% tiamulin w/w)	Granules	Pigs, chickens, turkeys	In drinking water

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
Germany	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 45% oral	Tiamulin hydrogen fumarate	45% w/w (36.4% tiamulin w/w)	Granules	Pigs	Use in drinking water or in feed
Greece	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	DENAGARD 45%, κοκκία για πόσιμο διάλυμα	Tiamulin hydrogen fumarate	450 mg/g	Granules for oral solution	Pigs, chickens, turkeys	Oral
Hungary	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 45% granulátum belsőleges oldathoz A.U.V.	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Pigs, chickens, turkeys	In drinking water use
Italy	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	DENAGARD 45%	Tiamulin hydrogen fumarate	450 mg/g	Powder for use in drinking water	Pigs, chickens	Oral
Latvia	Novartis Animal Health d.o.o. Verovškova 57 1000 Ljubljana Slovenia	Denagard 45% WSG	Tiamulin hydrogen fumarate	450 mg/g	Water soluble granules	Pigs, chickens, turkeys	In drinking water use
Lithuania	Novartis Animal Health d.o.o. Verovškova 57 1000 Ljubljana Slovenia	DENAGARD 45 %, vandenyje tirpios granulės	Tiamulin hydrogen fumarate	450 mg/g, corresponds to 365 mg tiamulin/g	Water soluble granules	Pigs, chickens (broiler, replacement pullet, layer / breeder), turkeys (grower and breeder)	Oral

Member State EU/EEA	Marketing authorisation holders	Name	INN	Strength	Pharmaceutical form	Animal species	Route of administration
The Netherlands	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	DENAGARD 45% W.S.G. voor varkens en kippen	Tiamulin hydrogen fumarate	450 mg/g	Granulate for administration through the drinking water	Pigs, chickens	Oral
Poland	Novartis Animal Health d.o.o. Verovškova 57 1000 Ljubljana Slovenia	Denagard 45% granulát dla šwiń, kur i indyków	Tiamulin hydrogen fumarate	450 mg/g	Granules	Pigs, chickens, turkeys	Oral use
Portugal	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 450 mg/g granulado oral para suínos, galinhas e perus	Tiamulin hydrogen fumarate	450 mg/g	Oral granules	Swine, chickens (broilers, rearing of broilers, layers / breeders), turkeys (for fattening and breeding)	Oral, administered in drinking water
Romania	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 45%	Tiamulin hydrogen fumarate	45mg tiamulin hydrogen fumarate /g product	Granules for use in drinking water	Pigs, chickens (broiler, replacement pullet, layer / breeder), turkeys (grower and breeder)	In drinking water
Slovak Republic	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 450 mg/g granulát na perorálny roztok	Tiamulin hydrogen fumarate	450 mg/g	Granules for oral solution	Pigs, chickens (broilers, laying and breeding hens), turkeys	Oral

<b>Member State EU/EEA</b>	<b>Marketing authorisation holders</b>	<b>Name</b>	<b>INN</b>	<b>Strength</b>	<b>Pharmaceutical form</b>	<b>Animal species</b>	<b>Route of administration</b>
Spain	Elanco Europe Ltd. Lilly House, Priestley Road Basingstoke, Hampshire RG24 9NL United Kingdom	Denagard 450 mg/g Granulado Oral	Tiamulin hydrogen fumarate	450 mg/g	Granules for use in drinking water	Pigs, chickens, turkeys	Oral

## **Annex II**

**Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet**

# Overall summary of the scientific evaluation of Denagard 45% and its associated names (see Annex I)

## 1. Introduction

Denagard 45% and its associated names are veterinary medicinal products presented as granules for use in drinking water for pigs, chicken and turkeys containing 450 mg tiamulin hydrogen fumarate as an active substance per gram product. Tiamulin hydrogen fumarate is a bacteriostatic semi-synthetic antibiotic belonging to the pleuromutilin group of antibiotics and acts at the ribosomal level to inhibit bacterial protein synthesis. Tiamulin has shown a high level of *in vitro* activity against porcine and avian *Mycoplasma* species as well as gram-positive aerobes (streptococci and staphylococci), anaerobes (clostridia), gram-negative anaerobes (*Brachyspira hyodysenteriae*, *Brachyspira pilosicoli*), and gram-negative aerobes (*Actinobacillus pleuropneumoniae* and *Pasteurella multocida*).

On 25 August 2015 Germany submitted a referral notification in accordance with Article 34(1) of Directive 2001/82/EC, to the CVMP/European Medicines Agency for Denagard 45% and its associated names (thereafter called Denagard 45%). Germany referred the issue due to divergent national decisions having been taken by the EU Member States resulting in discrepancies in the product information for Denagard 45%.

The main areas of disharmony in the existing product information relate to target species, indications, posology and withdrawal periods.

## 2. Discussion of data available

### Target species pigs, indications and posology

Treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

- *Dosage: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.*

The indication for treatment of Swine Dysentery caused by *B. hyodysenteriae* was re-evaluated through a review of literature and proprietary *in vitro* susceptibility data, and old clinical studies.

In European isolates collected between 1990 and 2012 the minimum inhibitory concentration (MICs) ranged from  $\leq 0.016$   $\mu\text{g/ml}$  to  $> 16$   $\mu\text{g/ml}$ , with MIC<sub>50</sub> of  $\leq 0.063$   $\mu\text{g/ml}$  to 4  $\mu\text{g/ml}$  and MIC<sub>90</sub> of  $\leq 0.016$   $\mu\text{g/ml}$  to  $> 16$   $\mu\text{g/ml}$ . The epidemiological cut-off value or wild-type MIC was approximately 0.5  $\mu\text{g/ml}$  while resistance MICs appeared to begin at  $> 2.0$   $\mu\text{g/ml}$ . Increased MICs against *B. hyodysenteriae* isolates in different European Member States give rise for concern as there are only limited antimicrobials left for the treatment of swine dysentery.

Clinical efficacy in the treatment of swine dysentery caused by *B. hyodysenteriae* was demonstrated in two artificial infection studies and in a series of six field trials. In these studies doses were expressed as concentrations in drinking water. The actual doses in mg/kg body weight could only be estimated. At 60 ppm tiamulin hydrogen fumarate equivalent to 8-9 mg tiamulin hydrogen fumarate/kg body weight administered for three to five days the infected pigs showed significant improvements in clinical endpoints, pathological signs and elimination of *B. hyodysenteriae*.

From these data the CVMP concluded that Denagard 45% at a dose of 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight for three to five consecutive days would be efficacious in the treatment of Swine Dysentery caused by *B. hyodysenteriae*.

Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

- *Dosage: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.*

The indication Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli* was supported by *in vitro* susceptibility data and field studies.

The susceptibility of *B. pilosicoli* towards tiamulin was investigated in three studies.

Ninety three isolates of *B. pilosicoli* collected in Sweden (Pringle *et al.* 2006<sup>1</sup>), 33 isolates collected in UK, Spain and Germany (MAH proprietary data 2008) as well as 324 isolates collected in Sweden between 2002 and 2010 (Pringle *et al.* 2012<sup>2</sup>) were tested. In these studies the MICs ranged from  $\leq 0.008$ -64  $\mu\text{g/ml}$ , with MIC<sub>50s</sub> of  $\leq 0.062$   $\mu\text{g/ml}$  up to 0.125  $\mu\text{g/ml}$  and MIC<sub>90s</sub> of 0.25  $\mu\text{g/ml}$  up to 8  $\mu\text{g/ml}$ . The epidemiological cut-off value or wild-type MIC was approximately  $\leq 0.25$   $\mu\text{g/ml}$  while resistance MICs appeared to begin at 0.5  $\mu\text{g/ml}$  (first-step mutant) and 4.0  $\mu\text{g/ml}$  (second-step mutant) (MAH proprietary data 2008).

Clinical efficacy in the treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli* was demonstrated in three field trials. Tiamulin at inclusion rates of 100 ppm (equivalent to 5 mg tiamulin hydrogen fumarate/kg body weight) and doses of 8 mg tiamulin hydrogen fumarate/kg body weight was administered for five to ten days. The animals treated showed significant improvements in clinical endpoints such as diarrhoea score, feed conversion efficiency, average daily gain, and bacterial shedding was completely stopped (not examined in all studies). No specific artificial challenge studies were available.

From these data the CVMP concluded that Denagard 45% at a dose of 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight for three to five consecutive days would be efficacious in the treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*.

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

- *Dosage: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 5 consecutive days.*

The indication treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis* was supported by *in vitro* susceptibility data, artificial infection studies and a field trial.

Susceptibility testing of *L. intracellularis* is challenging since this is an obligate intracellular organism. The *in vitro* susceptibility data available to support the indication are limited. McOrist *et al.* (1995)<sup>3</sup> examined three strains of *L. intracellularis* to find intracellular MIC (iMIC) and extracellular MIC (eMIC)

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<sup>1</sup> Pringle, M., Landen, A. and Franklin, A. (2006) Tiamulin resistance in porcine *Brachyspira pilosicoli*. Research in Veterinary Science, 80, 1-4.

<sup>2</sup> Pringle, M., Landen, A., Ericsson Unnerstad, H., Molander, B. & Bengtsson, B. (2012) Antimicrobial susceptibility of porcine *Brachyspira hyodysenteriae* and *Brachyspira pilosicoli* isolated in Sweden between 1990 and 2010. Acta veterinaria Scandinavica, 54, 54.

<sup>3</sup> McOrist, S., Mackie, R.A. and Lawson, G.H.K. (1995) Antimicrobial susceptibility of Ileal Symbiont intracellularis isolated from pigs with Proliferative Enteropathy. Journal of Clinical Microbiology, 33, 5, 1314 -1317.



of tiamulin to be 4 µg/ml. McOrist and Gebhart (1995)<sup>4</sup> found an intracellular minimum bactericidal concentration (iMBC) of <2 µg/ml in another strain. Wattanaphansak *et al.* (2009)<sup>5</sup>, tested 10 isolates of *L. intracellularis* (six from USA, four from Europe). iMIC<sub>50</sub> was 0.125 µg/ml, iMIC<sub>90</sub> 0.125 µg/ml with an iMIC range of 0.125-0.5 µg/ml. eMIC<sub>50</sub> was 4.0 µg/ml, eMIC<sub>90</sub> 8.0 µg/ml with an eMIC range of 1.0-32 µg/ml. Considering all data available, the epidemiological cut-off value appeared to be at 0.5 µg/ml while less susceptible strains grouped at ≥2.0 µg/ml. Currently further isolates have been tested from Korea (Yeh *et al.*, 2011)<sup>6</sup>, Brazil and from Thailand (MAH proprietary data, 2016). A number of isolates in Korea and Thailand may have higher iMIC figures than previously reported in the EU and USA by Wattanaphansak *et al.* (2009). This suggests that reduced sensitivity of individual *Lawsonia* strains can occur but as there have been no reported adverse events in the EU regarding treatment of ileitis failures it suggests that such reduced sensitivity has not developed extensively in the EU. The tiamulin MIC data determined for the available EU *Lawsonia* strains are all below the estimated ileal tiamulin contents of 0.63 µg/ml.

Clinical efficacy in the treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis* was demonstrated in three artificial infection studies and one field trial. In these studies doses were expressed as concentrations in drinking water. The actual doses in mg/kg body weight were estimated at 8.8 mg mg tiamulin hydrogen fumarate/kg body weight. Administered for five days these doses caused significant improvements in clinical endpoints (e.g. feed conversion efficiency, average daily gain, diarrhoea score) and pathological signs though complete elimination of *L. intracellularis* could not be achieved.

From these data the CVMP concluded that Denagard 45% at a dose of 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight for five consecutive days would be efficacious in the treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*.

Treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

- Dosage: 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.

The indication for treatment and metaphylaxis of Enzootic Pneumonia caused by *M. hyopneumoniae*, including infections complicated by *P. multocida* was supported by *in vitro* susceptibility data from the European MycoPath I project, proprietary clinical studies and literature.

In European isolates tiamulin was highly active against *M. hyopneumoniae*, with MIC<sub>50</sub> of 0.016 µg/ml, MIC<sub>90</sub> of 0.062 µg/ml, and a MIC range of 0.002-0.125 µg/ml (MycoPath I project, 2014). Similar findings were reported from other studies dating from 1997 - 2014 with MIC<sub>50</sub> ranging from ≤0.015 µg/ml - 0.06 µg/ml, MIC<sub>90</sub> ranging from 0.031 µg/ml – 0.125 µg/ml, and MIC ranges of 0.002-0.125 µg/ml. The susceptibility patterns determined in these studies were of a wild-type pattern indicating that no resistance had developed in the period investigated.

The treatment of enzootic pneumonia caused by *M. hyopneumoniae* was investigated in two artificial infection studies and a series of eight field trials. Doses administered ranged from 8.8–20 mg tiamulin hydrogen fumarate/kg body weight for 5 days. Lower doses of 8.8 mg tiamulin hydrogen fumarate/kg body weight were considered to give an inhibitory/bacteriostatic effect at the MIC<sub>90</sub> level. Higher doses

<sup>4</sup> McOrist, S. and Gebhart, C.J. (1995) In vitro testing of antimicrobial agents for Proliferative Enteropathy (ileitis). Swine Health and Production, 3, 4, 146-149.

<sup>5</sup> Wattanaphansak, S., Singer, R.S. and Gebhart, C.J. (2009) In vitro antimicrobial activity against 10 North American and European *Lawsonia intracellularis* isolates. Veterinary Microbiology, 134, 305-310.

<sup>6</sup> Yeh, J.Y., J.H. Lee, H.R. Yeh, A. Kim, J.Y. Lee, J.M. Hwang, B.K. Kang, J.M. 783 Kim, I.S. Choi, and J.B. Lee. 2011. Antimicrobial susceptibility testing of two *Lawsonia intracellularis* isolates associated with proliferative hemorrhagic enteropathy and porcine intestinal adenomatosis in South Korea. Antimicrobial agents and chemotherapy 55: 4451-4453.

administered in the drinking water gave a mycoplasmacidal effect at MIC<sub>90</sub>, reduced lung lesions and eliminated the organism in some cases.

From these data the CVMP concluded that Denagard 45% at a dose of 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight for five consecutive days would be efficacious in the treatment and metaphylaxis of Enzootic Pneumonia caused by *M. hyopneumoniae*, including infections complicated by *P. multocida*.

Treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

- *Dosage: 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.*

The indication Pleuropneumonia caused by *A. pleuropneumoniae* was supported by *in vitro* susceptibility data and by artificial infection studies.

In European isolates collected between 2009 and 2012 as part of the VetPath III project the following MICs of tiamulin were obtained: MIC<sub>50</sub> of 8.0 µg/ml, MIC<sub>90</sub> of 16 µg/ml, MIC range of 2.0-16 µg/ml. The MIC<sub>50</sub> was considered high, but the isolates presented a wild-type susceptibility pattern suggesting lack of resistance. Data reported from further studies (Felmingham, 2009<sup>7</sup>; Kucerova *et al.*, 2011<sup>8</sup>) confirm these findings with MIC<sub>50</sub> and MIC<sub>90</sub> of 8 µg/ml and 16 µg/ml resp. and MIC ranges of 0.25-16 µg/ml and 0.5-64 µg/ml. Tiamulin MICs are high against *A. pleuropneumoniae*. The single mode susceptibility pattern suggested that there has been little resistance development to date. The epidemiological cut-off value was considered at 16 µg/ml which corresponds to the current Clinical and Laboratory Standards Institute (CLSI) standard (S ≤16 µg/ml, R ≥32 µg/ml).

Artificial challenge studies were carried out using tiamulin inclusion rates in drinking water ranging from 120 to 180 ppm equivalent to doses of 20 to 40 mg tiamulin hydrogen fumarate/kg body weight. Dose-related reductions in mortality, average lung lesion area and *A. pleuropneumoniae* re-isolation but no complete clinical cure were observed at lower doses (20 mg). At higher doses (40 mg) no deaths, significantly reduced lung lesion scores, as well as no *A. pleuropneumoniae* re-isolation, indicating a strong bactericidal effect, were observed.

From these data the CVMP concluded that Denagard 45% at a dose of 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight for five consecutive days would be efficacious in the treatment Pleuropneumonia caused by *A. pleuropneumoniae*.

### **Target species chickens, indications and posology**

Treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae* susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used.

- *Dosage: 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight administered daily for 3 to 5 consecutive days.*

The indications in chickens were supported by *in vitro* susceptibility data from three studies, and various artificial infection and field studies.

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<sup>7</sup> Felmingham, D. (May 2009) Report 'Determination of the antimicrobial susceptibility of the VetPath II (2004-2006) collection of bacterial pathogens'.

<sup>8</sup> Kucerova, Z., Hradecka, H., Nechvatalova, K. & Nedbalcova, K. (2011) Antimicrobial susceptibility of *Actinobacillus pleuropneumoniae* isolates from clinical outbreaks of porcine respiratory diseases. *Veterinary Microbiology*, 150, 1/2, 203-206.

The *in vitro* susceptibility of *M. gallisepticum* and *M. synoviae* from chickens and turkeys was tested in two studies with isolates from European Member States collected from 2005-2007, and 2010-2013, and in one study with global isolates collected before 1997. In the older European data there was a wider range of MICs for *M. gallisepticum* ( $\leq 0.004$  and  $> 256$   $\mu\text{g/ml}$ ) with a MIC<sub>50</sub> of 0,008  $\mu\text{g/ml}$  and a MIC<sub>90</sub> of 1  $\mu\text{g/ml}$ . Three distinct multi-resistant strains were isolated. For *M. synoviae* MICs ranged from 0.004 to 0.5  $\mu\text{g/ml}$  with a MIC<sub>50</sub> of 0,125  $\mu\text{g/ml}$  and a MIC<sub>90</sub> of 0.25  $\mu\text{g/ml}$ .

In the newer European strains and the older global isolates MIC ranges were similar for *M. gallisepticum* ranging from 0.001 – 0.037  $\mu\text{g/ml}$  with MIC<sub>50s</sub> of 0,001 and 0.008  $\mu\text{g/ml}$  and MIC<sub>90s</sub> of 0.025 and 0.031  $\mu\text{g/ml}$ . No resistant strains were found. For *M. synoviae* MICs ranged from 0.05 to 0.5  $\mu\text{g/ml}$  with MIC<sub>50s</sub> of 0.1  $\mu\text{g/ml}$  and a MIC<sub>90</sub> of 0.25  $\mu\text{g/ml}$ .

Nine older artificial infection studies and three old field studies were presented to support the indication 'treatment and metaphylaxis of Chronic Respiratory Disease caused by *M. gallisepticum*'.

Artificial challenge studies were carried out using tiamulin inclusion rates in drinking water ranging from 60 to 250 ppm or estimated doses from 10 to 64.2 mg tiamulin hydrogen fumarate/kg body weight. In the field trials tiamulin was administered at inclusion rates of 125 – 250 ppm and estimated doses from 13.3 – 32.5 mg tiamulin hydrogen fumarate/kg body weight for three days. Doses as low as 10 mg tiamulin hydrogen fumarate/kg body weight by gavage gave excellent microbiological results when used for prevention/metaphylaxis but much higher doses were required for treatment. At 250 ppm tiamulin hydrogen fumarate administered for three days significant improvements in clinical endpoints, pathological signs and elimination of *M. gallisepticum* were shown.

From these data the CVMP concluded that Denagard 45% at a dose of 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight for three to five consecutive days would be efficacious in the treatment and metaphylaxis of Chronic Respiratory Disease caused by *M. gallisepticum*.

Concerning the indication 'treatment and metaphylaxis of Airsacculitis and Infectious Synovitis caused by *M. synoviae*' two artificial infection studies and two old and one new field studies were presented to support the claim. The artificial infection studies were carried out using tiamulin inclusion rates in drinking water ranging from 60 to 250 ppm or estimated daily doses from 15.4 to 64.2 mg tiamulin hydrogen fumarate/kg body weight. In the field trials tiamulin was administered at inclusion rates of 125 – 250 ppm or daily doses from 12.7 to 59.7 mg tiamulin hydrogen fumarate/kg body weight for three days. Doses as low as 10 mg tiamulin hydrogen fumarate/kg body weight by gavage gave excellent microbiological results when used for prevention/metaphylaxis but much higher doses were required for treatment. Field exposure to tiamulin at around the proposed dose rate of 25 mg/kg body weight yielded a 100% microbiological response.

The CVMP agreed that although there is limited data for *M. synoviae* in comparison with *M. gallisepticum*, the available information from the studies provided is sufficient to support the conclusion that Denagard 45% at a dose of 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight for three to five consecutive days would be efficacious in the treatment and metaphylaxis of Airsacculitis and Infectious Synovitis caused by *M. synoviae*.

### **Target species turkeys, indications and posology**

Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis* susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used.

- Dosage: 40 mg tiamulin hydrogen fumarate (equivalent to 88.9 mg of product)/kg body weight administered daily for 3 to 5 consecutive days.

The indications in turkeys were supported by *in vitro* susceptibility data from the same three studies as in chickens and limited susceptibility data on *M. meleagridis*, a limited number of artificial infection and field studies, and a number of case reports published in the late 1970s and early 1980s.

The susceptibility (MIC data) of *M. gallisepticum* and *M. synoviae* from turkey to tiamulin is summarised above with the *in vitro* susceptibility data in chickens. For five French isolates of *M. meleagridis* the MIC ranged from 0.03 – 0.06 µg/ml. Recent *M. meleagridis*-isolates are difficult to obtain as it was eradicated from most breeding flocks and only rarely occurs in the field.

Three artificial infection studies already discussed for chickens and two field trials supported the claims treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis. Tiamulin was administered for three days by gavage at 20-30 mg tiamulin hydrogen fumarate/kg body weight or in the drinking water. When administered in the drinking water at 125, 250, or 500 ppm the estimated dose rates ranged from as low as 22 mg tiamulin hydrogen fumarate/kg body weight to a maximum of 102 mg tiamulin hydrogen fumarate/kg body weight. There was some variation in the clinical results and there was a reported reduction in water intake with tiamulin in the drinking water. Lesion score reduction and reduction in microbiological re-isolation varied from 55% to 100% for prevention/metaphylaxis but were as low as 33% to 67% for treatment of *M. gallisepticum*. Further studies showed a 95% lesion reduction for prevention and 74% during treatment at around the proposed dose of 40 mg tiamulin hydrogen fumarate/kg body weight given in the drinking water. Clinical case reports did suggest that *M. synoviae* was treated effectively in a French study, and Hungarian and UK studies showed that *M. meleagridis* was also effectively treated causing reductions in clinical signs, airsacculitis and sinusitis.

From these data the CVMP concluded that Denagard 45% at a dose of 40 mg tiamulin hydrogen fumarate (equivalent to 88.9 mg of product)/kg body weight for three to five consecutive days would be efficacious in the treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis* susceptible to tiamulin.

### **Withdrawal periods**

In pigs appropriate GLP-compliant study data were provided to derive withdrawal periods for edible tissues for two different dosage regimens. For the lower dose (8.8 mg tiamulin hydrogen fumarate per kg body weight for up to five days) a study was conducted in 20 pigs treated via drinking water under field conditions. At 0, 24, 36 and 48 hours after the last treatment, animals were necropsied and the entire liver was analysed for 8- $\alpha$ -hydroxymutilin based on a GC analytical method. The liver residue data were subjected to log-linear regression using the WT1.4 calculation program and the resulting withdrawal period was 42 hours, rounded up to two days.

For the higher dosage (20 mg tiamulin hydrogen fumarate per kg body weight for up to five days) a GLP-compliant residue depletion study using a bioequivalent product containing 125 mg tiamulin hydrogen fumarate per ml (Tiamutin 12.5 % Solution) was provided. Pigs were treated at the intended dose and sacrificed 24 hours, 3, 4, 5 and 6 days after last administration. From each individual pig, specimens from liver and muscle were collected and analysed for 8- $\alpha$ -hydroxymutilin using a validated LCMS-MS analytical method. A withdrawal period of 4 days was calculated based on residue concentrations in liver tissues using the WT1.4 calculation program and setting values below limit of quantification (LOQ) at ½ LOQ according to the CVMP note for guidance "Approach towards harmonisation of withdrawal periods" (EMEA/CVMP/036/95)<sup>9</sup>.

In chicken a GLP-compliant residue depletion study in laying hens was conducted. Animals received a mean dose of 29 mg tiamulin hydrogen fumarate /kg body weight for five days via drinking water; this

<sup>9</sup> CVMP note for guidance "Approach towards harmonisation of withdrawal periods" (EMEA/CVMP/036/95) [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/10/WC500004428.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004428.pdf)

dose was in excess of the indicated dose (25 mg tiamulin hydrogen fumarate). Eggs were sampled twice daily. Groups of birds were sacrificed at 0 hours, 8 hours, 1 day, 2 days, 3 days and 5 days after withdrawal of treatment and samples from muscle (mixed samples from breast and leg), liver, skin and underlying subcutaneous fat were taken for residue analysis. For edible tissues and based on residue concentrations in liver, a withdrawal period of 26.2 hours was calculated using the WT1.4 calculation program, rounded up to 2 days.). Residues in eggs were well below the MRL at all time points. Although VICH guideline GL48 on Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods (EMA/CVMP/VICH/463199/2009) recommends sampling eggs until at least 12 days after the end of treatment, data from two other studies (one of which measured tiamulin-like activity using a microbiological method and the other of which measured total radioactive residues) indicate that tiamulin levels in eggs peak immediately after the end of treatment and consequently there is no concern that increased tiamulin levels in eggs will occur at time points beyond those measured in the pivotal residue depletion study. Consequently, a withdrawal period in eggs of zero days is accepted.

For meat and offal from turkey, a GLP-compliant residue depletion study was provided. Animals were treated at the intended dose (40 mg tiamulin hydrogen fumarate/kg body weight administered daily for 5 days) and sacrificed at 0 hours, 8 hours, 1 day, 2 days and 3 days post treatment and samples from skeletal muscle, skin and underlying fat as well as liver were taken. Withdrawal periods were calculated based on residue concentrations in liver and using the 99/95 tolerance interval to account for one residue concentration above the MRL at day 3 after treatment, resulting in a withdrawal period of 6 days calculated using the WT1.4 calculation program.

### 3. Benefit-risk assessment

#### Introduction

Denagard 45% is a veterinary medicinal product presented as granules for use in drinking water for pigs, chicken and turkeys containing 450 mg tiamulin hydrogen fumarate per gram product. It has been authorised in 16 EU Member States.

It has been noted that Denagard 45% and its associated names do not have the same product information across the Member States with respect to e.g. target species, indications, posology and withdrawal periods

#### Benefit assessment

During this referral, adequate data have been submitted to support the following indications:

##### Pigs

- Treatment of Swine Dysentery caused by *B. hyodysenteriae* susceptible to tiamulin.
- Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli* susceptible to tiamulin.
- Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis* susceptible to tiamulin.
- Treatment and metaphylaxis of Enzootic Pneumonia caused by *M. hyopneumoniae*, including infections complicated by *P. multocida* susceptible to tiamulin.
- Treatment of Pleuropneumonia caused by *A. pleuropneumoniae* susceptible to tiamulin.

### Chickens

- Treatment and metaphylaxis of Chronic Respiratory Disease caused by *M. gallisepticum* and Airsacculitis and Infectious Synovitis caused by *M. synoviae* susceptible to tiamulin.

### Turkeys

- Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis* susceptible to tiamulin.

### **Risk assessment**

During this referral and considering the scope of the procedure, adequate data have been submitted to support the following posology:

### Pigs

- Swine Dysentery caused by *B. hyodysenteriae* or Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli*: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.
- Increased MICs against *B. hyodysenteriae* isolates in different European Member States give rise for concern as there are only limited antimicrobials left for the treatment of swine dysentery. Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*: 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 5 consecutive days.
- Enzootic Pneumonia caused by *M. hyopneumoniae*, including infections complicated by *Pasteurella multocida*, or Pleuropneumonia caused by *A. pleuropneumoniae*: 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.

### Chickens

- Chronic Respiratory Disease caused by *M. gallisepticum* and Airsacculitis and Infectious Synovitis caused by *M. synoviae*: 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight administered daily for the period of 3 to 5 consecutive days.

### Turkeys

- Infectious Sinusitis and Airsacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*: 40 mg tiamulin hydrogen fumarate (equivalent to 88.9 mg of product)/kg body weight administered daily for the period of 3 to 5 consecutive days

The recommended harmonised indications and dosing regimens have not been extended and consequently the use of the product as recommended in the product information should not lead to increased exposure of the environment.

Denagard 45% is generally well tolerated in the target species and appropriate information is included in the product information. Target animal safety can be compromised in case of inadvertent co-administration of ionophores such as monensin, salinomycin, and narasin. Corresponding wordings is added in the product information.

The risk for users is related to the potential for contamination of the user's eyes and topical exposure of skin when preparing the product for administration. Appropriate guidance has been included in the product information to mitigate the risk.

Based on the residue depletion data available the following withdrawal periods are recommended:

### Pigs

- Meat and offal: 2 days (when the administered dose is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight)
- Meat and offal: 4 days (when the administered dose is 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight)

### Chickens

- Meat and offal: 2 days
- Eggs: Zero days

### Turkeys

- Meat and offal: 6 days

### **Risk management or mitigation measures**

The harmonised product information of Denagard 45% contains the necessary information to ensure the safe and effective use of the product. This includes the specification of target pathogens, replacement of the prevention claim by metaphylaxis and clear dose recommendations based on mg tiamulin hydrogen fumarate/kg body weight for each target species and indication as well as prudent use recommendations for antimicrobial veterinary medicinal products authorised in the EU. Users are advised to take appropriate precautions when handling the product in order to avoid exposure. A contraindication for specific ionophores is included in the product information. The withdrawal periods have been revised following assessment of the available residue depletion data to ensure consumer safety.

### **Evaluation and conclusions on the benefit-risk balance**

The product has been shown to be efficacious in the treatment of Swine Dysentery caused by *B. hyodysenteriae*, Porcine Colonic Spirochaetosis (colitis) caused by *B. pilosicoli* and Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*. Increased MICs against *B. hyodysenteriae* isolates in different European Member States give rise for concern as there are only limited antimicrobials left for the treatment of swine dysentery.

Denagard 45% has also been shown to be efficacious for the treatment of Enzootic Pneumonia caused by *M. hyopneumoniae* including infections complicated by *Pasteurella multocida*. The resistance situation for these pathogens is considered favourable. Denagard 45% is also effective in the treatment of Pleuropneumonia caused by *A. pleuropneumoniae* in pigs.

There is little evidence for serious adverse reactions, except when it is used with the incompatible coccidiostatic ionophores monensin, salinomycin, and narasin. As long as combined use with these ionophores is avoided, especially in broilers, Denagard 45% has proven to be safe and effective in the treatment of airsacculitis, synovitis and sinusitis caused by *M. gallisepticum*, *M. synoviae* and/or *M. meleagridis* in chickens and turkeys. Water intake may be depressed in chickens and turkeys during the administration of tiamulin in drinking water and an inclusion rate of 250 ppm must not be exceeded.

Risks for users were considered low and adequate information is included in the product information to ensure the safety for the user.

Satisfactory withdrawal periods have been set to provide assurance of consumer safety.

Overall, the benefit-risk balance of Denagard 45% is considered positive subject to the recommended changes in the product information (see Annex III).

## **Grounds for amendment of the summary of product characteristics, labelling and package leaflet**

Whereas

- the CVMP considered the scope of the referral was the harmonisation of the summary of product characteristics, labelling and package leaflet;
- the CVMP reviewed the summary of product characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP has recommended the amendment of the marketing authorisations for Denagard 45% and its associated names as referred in Annex I for which the summary of product characteristics, labelling and package leaflet are set out in Annex III.



## **Annex III**

### **Summary of product characteristics, labelling and package leaflet**

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Denagard 450 mg/g granules for use in drinking water for pigs, chickens and turkeys

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active substance:** Tiamulin hydrogen fumarate 450 mg/g  
(equivalent to tiamulin 365 mg/g)

### Excipients:

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Granules for use in drinking water  
White to pale yellow granules

## 4. CLINICAL PARTICULARS

### 4.1 Target species

Pigs  
Chickens  
Turkeys

### 4.2 Indications for use, specifying the target species

#### Pigs

i) Treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

ii) Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

iii) Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

iv) Treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

v) Treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin. The presence of the disease in the herd must be established before the product is used.

#### Chickens

Treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae* susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used.

## Turkeys

Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis* susceptible to tiamulin. The presence of the disease in the flock must be established before the product is used.

### **4.3 Contraindications**

Do not use in pigs and birds that could receive products containing monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Do not use in cases of hypersensitivity to the active substance or to the excipient.

See section 4.8 for information regarding interaction between tiamulin and ionophores.

### **4.4 Special warnings for each target species**

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

Water intake may be depressed during the administration of tiamulin in birds. It appears to be concentration-dependent with 500 mg tiamulin hydrogen fumarate (equivalent to 1.11 g of product) in 4 litres of water reducing intake by approximately 10% and 500 mg tiamulin hydrogen fumarate (equivalent to 1.11 g of product) in 2 litres of water by 15% in chickens. It does not appear to have any adverse effect on overall performance of the birds or efficacy of the veterinary medicinal product but water intake should be monitored at frequent intervals, especially in hot weather. In turkeys, it is more marked, with approximately 20% reduction and therefore it is recommended not to exceed a concentration of 500 mg tiamulin hydrogen fumarate in 2 litres of the drinking water.

### **4.5 Special precautions for use**

#### Special precautions for use in animals

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria.

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tiamulin.

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

Personal protective equipment consisting of safety glasses or goggles and gloves should be worn when handling the veterinary medicinal product in order to avoid contamination of the user's eyes and topical exposure of skin. Due to the irritant properties, it is also recommended to wear a dust mask to minimise inhalation exposure.

In case of exposure or accidental spillage onto skin the affected area should be washed with soap and water. In case of accidental spillage into the eyes, the open eyes should be flushed with water.

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

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

#### **4.6 Adverse reactions (frequency and seriousness)**

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

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

#### **4.7 Use during pregnancy, lactation or lay**

##### Pregnancy and lactation:

Can be used in pigs during pregnancy and lactation.

##### Laying birds:

Can be used in laying chickens and in 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, stop both the administration of tiamulin-medicated drinking water and also the administration of ionophore-contaminated feed immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Concomitant use of tiamulin and the divalent ionophore anticoccidials lasalocid and semduramicin do not appear to cause any interaction, however the concomitant use of maduramicin may lead to a mild to moderate growth depression in chickens. The situation is transient and recovery normally occurs within 3-5 days following withdrawal of tiamulin treatment.

#### **4.9 Amounts to be administered and administration route**

##### Guidance for preparing product solutions:

When medicating large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration.

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

To ensure the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage the concentration of tiamulin has to be adjusted accordingly.

In order to avoid interactions between the ionophores and tiamulin, the veterinarian and farmer should check that the feed label does not state that it contains salinomycin, monensin and narasin. For chickens and turkeys, in order to avoid interactions between the incompatible ionophores monensin, narasin and salinomycin and tiamulin, the feed mill supplying the birds feed should be notified that tiamulin will be used and that these anticoccidials should not be included in the feed or contaminate the feed.

The feed should be tested for the ionophores prior to use if there is any suspicion that contamination of the feed might occur.

If an interaction does occur, stop tiamulin medication immediately and replace with fresh drinking water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

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

$$\frac{\text{Dose (mg product per kg body weight per day)} \times \text{Mean body weight (kg) of animals to be treated}}{\text{Mean daily water consumption (litre) per animal per day}} = \text{mg product per litre of drinking water}$$

### Pigs

i) For the treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

ii) For the treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

iii) For the treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight administered daily in the drinking water of pigs for 5 consecutive days.

iv) For the treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.

v) For the treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight administered daily for 5 consecutive days.

### Chickens

For the treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*.

The dosage is 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight administered daily for the period of 3 to 5 consecutive days.

### Turkeys

For the treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis*.

The dosage is 40 mg tiamulin hydrogen fumarate (equivalent to 88.9 mg of product)/kg body weight administered daily for the period of 3 to 5 consecutive days.

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

Single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg tiamulin hydrogen fumarate/kg body weight no central nervous system effects were noted except for tranquillisation. At 55 mg tiamulin hydrogen fumarate/kg body weight given

daily for 14 days, a transient salivation and slight gastric irritation occurred. Tiamulin hydrogen fumarate is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.

Regarding poultry, there is a relatively high therapeutic index with tiamulin hydrogen fumarate and the likelihood of an overdose is considered remote especially as water intake and hence tiamulin hydrogen fumarate intake is reduced if abnormally high concentrations are given. The LD<sub>5</sub> is 1090 mg/kg body weight for chickens and 840 mg/kg body weight for turkeys.

The clinical signs of acute toxicity in chickens are – vocalisation, clonic cramps and lying in a lateral position, and in turkeys – clonic cramps, lateral or dorsal position, salivation and ptosis.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

#### **4.11 Withdrawal period(s)**

##### Pigs

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight)

Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight)

##### Chickens

Meat and offal: 2 days

Eggs: Zero days

##### Turkeys

Meat and offal: 6 days

## **5. PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: antibacterial for systemic use / Pleuromutilins / tiamulin

ATC vet code: QJ 01 XQ 01

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.

### **5.1 Pharmacodynamic properties**

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

Tiamulin has been shown to act at the 70S ribosome level and the primary binding sites are on the 50S subunit. It appears to inhibit microbial protein production by producing biochemically inactive initiation complexes, which prevent elongation of the polypeptide chain.

Bactericidal concentrations can be reached but vary according to the bacterium. It can be as little as two times the MIC for *Brachyspira hyodysenteriae* and *Actinobacillus pleuropneumoniae* but as high as 50 - 100 times the bacteriostatic level for *Staphylococcus aureus*. The MIC distribution for tiamulin against *Brachyspira hyodysenteriae* is bimodal, suggesting reduced susceptibility of some strains to tiamulin. Due to technical constraints the susceptibility of *Lawsonia intracellularis* is difficult to test *in vitro*.

## 5.2 Pharmacokinetic particulars

### Pigs

Tiamulin hydrogen fumarate is well absorbed in the pig (over 90%) following oral administration and widely distributed through the body. Following a single oral dose of 10 mg and 25 mg tiamulin hydrogen fumarate/kg body weight the  $C_{max}$  was 1.03  $\mu\text{g/ml}$  and 1.82  $\mu\text{g/ml}$  in serum respectively by microbiological assay and the  $T_{max}$  was 2 hours for both. It has been shown to concentrate in the lung, polymorphonuclear leucocytes and also in liver, where it is metabolised and excreted (70-85%) in the bile, the remainder is excreted via the kidney (15-30%). Serum protein binding is approximately 30%. Tiamulin, which has not been absorbed or metabolised, passes down the intestines to the colon. Colon contents concentrations of tiamulin have been estimated at 3.41  $\mu\text{g/ml}$  following administration of tiamulin hydrogen fumarate at 8.8 mg/kg body weight.

### Chickens

Tiamulin hydrogen fumarate is well absorbed in chickens (70-95%) after oral administration and reaches peak concentrations in 2-4 hours ( $T_{max}$  2.85 hours). Following a 50 mg tiamulin hydrogen fumarate/kg body weight single dose the  $C_{max}$  was 4.02  $\mu\text{g/ml}$  in serum by microbiological assay and after a 25 mg/kg dose it was 1.86  $\mu\text{g/ml}$ . In drinking water the 250 ppm (0.025%) tiamulin hydrogen fumarate concentration provided a rolling serum level over a 48 hour medication period of 0.78  $\mu\text{g/ml}$  (range 1.4-0.45  $\mu\text{g/ml}$ ) and at 125 ppm (0.0125%), 0.38  $\mu\text{g/ml}$  (range 0.65-0.2  $\mu\text{g/ml}$ ) in eight-week old chickens. Serum protein-binding was approximately 45%. It distributes widely through the body and has been shown to concentrate in the liver and kidney (sites of excretion) and in the lung (30 times serum level). Excretion is mainly via the bile (55-65%) and kidney (15-30%) as mainly microbiologically inactive metabolites and is quite rapid, 99% of the dose within 48 hours.

### Turkeys

In turkeys serum levels of tiamulin hydrogen fumarate are lower with a 50 mg tiamulin hydrogen fumarate/kg body weight single dose giving a  $C_{max}$  of 3.02  $\mu\text{g/ml}$  in serum, and 25 mg/kg giving 1.46  $\mu\text{g/ml}$ . These were achieved at about 2-4 hours after dosing. In breeders on 0.025% tiamulin hydrogen fumarate the average serum level was 0.36  $\mu\text{g/ml}$  (range 0.22-0.5  $\mu\text{g/ml}$ ). Serum protein-binding was approximately 50%.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Lactose

### 6.2 Major incompatibilities

None known.

### 6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 3 months.

Shelf life after dilution or reconstitution according to directions: The solution remains stable for 24 hours.

### 6.4 Special precautions for storage

Do not store above 25°C.



## **6.5 Nature and composition of immediate packaging**

Aluminium foil sachets of 55.6 g and 111.2 g

Pre-formed foil bag of 1112 g and 5000 g

Not all pack sizes may be marketed.

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

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

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

**A. COMBINED LABEL-LEAFLET**

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE - COMBINED LABEL AND PACKAGE LEAFLET**

**ALUMINIUM LAMINATE BAG**

**1. Name and address of the marketing authorisation holder and of the manufacturing authorisation holder responsible for batch release, if different**

Marketing authorisation holder:

*To be completed nationally.*

Manufacturer responsible for batch release:

Elanco France S.A.S.  
26 Rue de la Chapelle  
68330 Huningue  
France

**2. Name of the veterinary medicinal product**

Denagard 450 mg/g granules for use in drinking water for pigs, chickens and turkeys  
Tiamulin hydrogen fumarate

**3. Statement of the active substance (s) and other ingredients**

Each g contains:  
Tiamulin hydrogen fumarate 450 mg

**4. Pharmaceutical form**

Granules for use in drinking water  
White to pale yellow granules

**5. Package size**

55.6 g  
111.2 g  
1112 g  
5000 g

## 6. Indication(s)

### Pigs

- Treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin.
- Treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli* susceptible to tiamulin.
- Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis* susceptible to tiamulin.
- Treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin.
- Treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

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

### Chickens

- Treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae* susceptible to tiamulin.

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

### Turkeys

- Treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis* susceptible to tiamulin.

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

## 7. Contraindications

Do not use in pigs and birds that could receive products containing monensin, narasin or salinomycin during or for at least seven days before or after treatment with tiamulin. Severe growth depression or death may result.

Do not use in cases of hypersensitivity to the active substance or to the excipient.

## 8. Adverse reactions

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

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

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

## 9. Target species

Pigs  
Chickens  
Turkeys

## 10. Dosage for each species, route(s) and method of administration

In drinking water use.

### Guidance for preparing product solutions:

When medicating large volumes of water, prepare a concentrated solution first and then dilute to the required final concentration.

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

To ensure the correct dosage, body weight should be determined as accurately as possible to avoid underdosing. The intake of medicated water depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of tiamulin has to be adjusted accordingly.

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

$$\frac{\text{Dose (mg product per kg body weight per day)}}{\text{Mean daily water consumption (litre) per animal per day}} \times \text{Mean body weight (kg) of animals to be treated} = \text{mg product per litre of drinking water}$$

### Pigs

i) For the treatment of Swine Dysentery caused by *Brachyspira hyodysenteriae*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight daily administered in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

ii) For the treatment of Porcine Colonic Spirochaetosis (colitis) caused by *Brachyspira pilosicoli*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight daily administered in the drinking water of pigs for 3 to 5 consecutive days depending on the severity of the infection and/or the duration of the disease.

iii) For the treatment of Porcine Proliferative Enteropathy (ileitis) caused by *Lawsonia intracellularis*.

The dosage is 8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight daily administered in the drinking water of pigs for 5 consecutive days.

iv) For the treatment and metaphylaxis of Enzootic Pneumonia caused by *Mycoplasma hyopneumoniae*, including infections complicated by *Pasteurella multocida* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight daily administered for 5 consecutive days.

v) For the treatment of Pleuropneumonia caused by *Actinobacillus pleuropneumoniae* susceptible to tiamulin.

The dosage is 20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight daily administered for 5 consecutive days.

### Chickens

For the treatment and metaphylaxis of Chronic Respiratory Disease caused by *Mycoplasma gallisepticum* and Airsacculitis and Infectious Synovitis caused by *Mycoplasma synoviae*.

The dosage is 25 mg tiamulin hydrogen fumarate (equivalent to 55.6 mg of product)/kg body weight daily administered for the period of 3 to 5 consecutive days.

### Turkeys

For the treatment and metaphylaxis of Infectious Sinusitis and Airsacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma synoviae* and *Mycoplasma meleagridis*.

The dosage is 40 mg tiamulin hydrogen fumarate (equivalent to 88.9 mg of product)/kg body weight daily administered for the period of 3 to 5 consecutive days.

## **11. Advice on correct administration**

In order to avoid interactions between the ionophores and tiamulin, the veterinarian and farmer should check that the feed label does not state that it contains salinomycin, monensin and narasin.

For chickens and turkeys, in order to avoid interactions between the incompatible ionophores monensin, narasin and salinomycin and tiamulin, the feed mill supplying the birds feed should be notified that tiamulin will be used and that these anticoccidials should not be included in the feed or contaminate the feed.

The feed should be tested for the ionophores prior to use if there is any suspicion that contamination of the feed might occur.

If an interaction does occur, stop tiamulin medication immediately and replace with fresh drinking water. Remove contaminated feed as soon as possible and replace with feed not containing the tiamulin-incompatible ionophores.

## **12. Withdrawal period(s)**

### Pigs

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate (equivalent to 19.6 mg of product)/kg body weight)

Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate (equivalent to 44.4 mg of product)/kg body weight)

### Chickens

Meat and offal: 2 days

Eggs: Zero days

### Turkeys

Meat and offal: 6 days

## **13. Special storage precautions**

Do not store above 25°C.

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

#### **14. Special warning(s)**

##### Special warnings for each target species:

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

Water intake may be depressed during the administration of tiamulin in birds. It appears to be concentration-dependent with 500 mg tiamulin hydrogen fumarate (equivalent to 1.11 g of product) in 4 litres of water reducing intake by approximately 10% and 500 mg tiamulin hydrogen fumarate (equivalent to 1.11 g of product) in 2 litres of water by 15% in chickens. It does not appear to have any adverse effect on overall performance of the birds or efficacy of the veterinary medicinal product but water intake should be monitored at frequent intervals, especially in hot weather. In turkeys, it is more marked, with approximately 20% reduction and therefore it is recommended not to exceed a concentration of 500 mg tiamulin hydrogen fumarate in 2 litres of the drinking water.

##### Special precautions for use in animals:

Use of the product should be based on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria.

Inappropriate use of the veterinary medicinal product may increase the prevalence of bacteria resistant to tiamulin.

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

Personal protective equipment consisting of safety glasses or goggles and gloves should be worn when handling the veterinary medicinal product in order to avoid contamination of the user's eyes and topical exposure of skin. Due to the irritant properties, it is also recommended to wear a dust mask to minimise inhalation exposure.

In case of exposure or accidental spillage onto skin the affected area should be washed with soap and water. In case of accidental spillage into the eye, the open eye should be flushed with water.

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

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

##### Pregnancy and lactation:

Can be used in pigs during pregnancy and lactation.

##### Lay:

Can be used in laying chickens and in breeding chickens and turkeys.

##### Interaction with other medicinal products and other forms of interaction:

Tiamulin has been shown to interact with ionophores such as monensin, salinomycin and narasin and may result in signs indistinguishable from an ionophore toxicosis. Animals should not receive products containing monensin, salinomycin or narasin during or at least 7 days before or after treatment with tiamulin. Severe growth depression, ataxia, paralysis or death may result.

If signs of an interaction do occur, stop both the administration of tiamulin-medicated drinking water and also the administration of ionophore-contaminated feed immediately. The feed should be removed and replaced with fresh feed not containing the anticoccidials monensin, salinomycin or narasin.

Concomitant use of tiamulin and the divalent ionophore anticoccidials lasalocid and semduramicin do not appear to cause any interaction, however the concomitant use of maduramicin may lead to a mild to



moderate growth depression in chickens. The situation is transient and recovery normally occurs within 3-5 days following withdrawal of tiamulin treatment.

Overdose (symptoms, emergency procedures, antidotes):

Single oral doses of 100 mg tiamulin hydrogen fumarate/kg body weight in pigs caused hyperpnoea and abdominal discomfort. At 150 mg tiamulin hydrogen fumarate/kg body weight no central nervous system effects were noted except for tranquillisation. At 55 mg tiamulin hydrogen fumarate/kg body weight daily given for 14 days, a transient salivation and slight gastric irritation occurred. Tiamulin hydrogen fumarate is considered to have an adequate therapeutic index in the pig and a minimum lethal dose has not been established.

Regarding poultry, there is a relatively high therapeutic index with tiamulin hydrogen fumarate and the likelihood of an overdose is considered remote especially as water intake and hence tiamulin hydrogen fumarate intake is reduced if abnormally high concentrations are given. The LD<sub>5</sub> is 1090 mg/kg body weight for chickens and 840 mg/kg body weight for turkeys.

The clinical signs of acute toxicity in chickens are – vocalisation, clonic cramps and lying in a lateral position, and in turkeys – clonic cramps, lateral or dorsal position, salivation and ptosis.

If signs of intoxication do occur promptly remove the medicated water and replace with fresh water.

Incompatibilities:

None known.

**15. Special precautions for the disposal of unused product or waste materials, if any**

Dispose of waste material in accordance with local requirements.

**16. Date on which the label was last approved**

*To be completed nationally.*

**17. Other information**

Not all pack sizes may be marketed.

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

<b>18. The words “For animal treatment only” and conditions or restrictions regarding supply and use, if applicable</b>
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For animal treatment only. To be supplied only on veterinary prescription.

<b>19. The words “Keep out of the sight and reach of children”</b>
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Keep out of the sight and reach of children.

**20. Expiry date**

EXP {month/year}

Shelf life after first opening the immediate packaging: 3 months

Shelf life after dilution or reconstitution according to directions: The solution remains stable for 24 hours.

**21. Marketing authorisation number(s)**

*To be completed nationally.*

**22. Manufacturer's batch number**

<Batch> <Lot> {number}