SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Denagard 10% w/w Premix for medicated Feeding Stuff for Pigs, Chickens, Turkeys and Rabbits

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tiamulin hydrogen fumarate 100 mg/g

Excipients:
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff
Free flowing white to cream coloured, grey tinged powder

4. CLINICAL PARTICULARS

4.1 Target species

Pig
Chicken (broiler, replacement pullet, layer/breeder)
Turkey (poult (grower) and breeder)
Rabbit

4.2 Indications for use, specifying the target species

Pig
For the treatment and metaphylaxis, when the disease is present in the group, of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamulin. The presence of the disease in the group must be established before the product is used.
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*.

Chicken
For the treatment and prevention of chronic respiratory disease (CRD) and air sacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma synoviae*.

Turkey
For the treatment and prevention of infectious sinusitis and air sacculitis caused by *Mycoplasma gallisepticum*, *Mycoplasma meleagridis* and *Mycoplasma synoviae*.

Rabbit
For the treatment and prevention of epizootic rabbit enterocolitis (ERE) (see section 4.9 for further information regarding indications).

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 warnings 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 bwt) x bodyweight (kg) / daily feed intake (kg).

To ensure a correct dosage, bodyweight 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 and metaphylaxis 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 provided 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

Treatment of Porcine Proliferative Enteropathy (ileitis) caused by *L. intracellularis*
Dosage: 7.5 mg tiamulin hydrogen fumarate/kg bodyweight daily administered for 10 to 14 consecutive days. The dosage will normally be achieved by an inclusion level of 150 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	1.5 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 provided 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 air sacculitis and infectious synovitis caused by and *M. synoviae*.
Dosage – Treatment and prevention: 25 mg tiamulin hydrogen fumarate/kg bodyweight 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. 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 air sacculitis caused by *M. gallisepticum*, *M. synoviae* and *M. meleagridis*.
Dosage – Treatment and prevention: 40 mg tiamulin hydrogen fumarate/kg bodyweight 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 bodyweight 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 bodyweight 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 the pig.

Poultry: The LD_5 for chickens is 1290 mg/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
Meat and offal:
Treatment (at 5-10 mg/kg bwt): 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: QJ01XQ01

5.1 Pharmacodynamic properties

Tiamulin is a bacteriostatic semi-synthetic antibiotic belonging to the pleuromutilin group of antibiotics and acts at the ribosomal level to inhibit bacterial protein synthesis.
Tiamulin has shown a in-vitro activity against a wide range of bacteria such as *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

Pig
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.

Chicken
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 0.36 µg/ml (range 0.22-0.5 µg/ml).

Rabbit
There are no pharmacokinetic data available for rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Calcium carbonate
Soya-bean oil, refined

6.2 Major incompatibilities

None known

6.3 Shelf life

Shelf life of veterinary medicinal product as packaged for sale: 4 years.
Shelf life after first opening the container: 12 weeks
Shelf life after incorporation into meal or pelleted feed: 8 weeks.

6.4 Special precautions for storage

Do not store above 25ºC. Protect from direct sunlight.

6.5 Nature and composition of immediate packaging

Size: 1 kg, 5 kg, 25 kg
Container: 1 kg and 5 kg bags: laminated paper bags Paper/PE.
25 kg bag: multilayer bag PET/Alu/PET/ with inner layer of LDPE
Closure: All the bags are closed by heat sealing.
Not all pack sizes may be marketed.

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

Any unused product or waste materials should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Elanco Europe Ltd.
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA
United Kingdom

8. MARKETING AUTHORISATION NUMBER

Vm 00879/4051

9. DATE OF FIRST AUTHORISATION

10 October 2008

10. DATE OF REVISION OF THE TEXT

March 2021

PROHIBITION OF SALE, SUPPLY AND/OR USE

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

The product can be incorporated into pelleted feed at temperatures of 65ºC and maximums of 80ºC.

For incorporation into dry feed at the registered mill:

A manufacturer who is approved to incorporate directly at any concentration, veterinary medicinal products or premixtures containing such products must be responsible for mixing when incorporation is less than 2 kg per tonne for final feed.

Approved: 26/03/21