

Product Name: Denagard 10% Premix for Medicated Feed for Pigs, Chickens, Turkeys and Rabbits

MA Holder: Elanco Europe Ltd

I. INTRODUCTION

Denagard 10% Premix, for Medicated Feed for Pigs, Chickens, Turkeys and Rabbits¹ is a premix for medicated feed. The product is available as meal or pellets, containing 100 g tiamulin hydrogen fumarate per kg in a maize starch carrier. This product was originally authorised as a Line Extension application to add a new strength to the existing Tiamutin 2% Premix. Subsequently, a variation was submitted to implement a Commission decision following a referral for Tiamutin premix and associated names to harmonise the indications for use, amount to be administered and administration route and withdrawal periods. The outcome of the referral recommended the amendment of the marketing authorisations in terms of the SPCs (Summary of Product Characteristics). The referral procedure was conducted under Article 34 of Directive 2001/82/EC, further details of which can be found on the European Medicines Agency's (EMA) website.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

Refer to the SPC for contraindications.

Indications

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*.

Dosage

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

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 40 ppm tiamulin hydrogen fumarate in the finished feed,

¹ Additional species chickens, (broiler, replacement pullet, layerbreeder), turkeys, (poult grower and breeder) and rabbits, and to add an additional indication for pigs. Variation procedure to implement Commission decision June 2011.

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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: 7.5 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

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

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

Dosage

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.

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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)

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

Dosage

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	2.0 – 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

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

Dosage

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

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II. QUALITY ASPECTS

(Quality data submitted for original product)

Product Development and Composition

The product contains the active substance tiamulin hydrogen fumarate and excipients gelatine and maize starch. The main component of the vehicle is maize starch, widely used within the pharmaceutical industry as a carrier, which also has nutrient value. The tiamulin hydrogen fumarate is sprayed with a solution of gelatin in potable water which is intended to reduce the dustiness of the active ingredient and hence its potential for producing skin, eye or mucous membrane irritation. It is also claimed to reduce the potential for enzymatic degradation of tiamulin when the product is incorporated into feedstuffs. The choice of the formulation is justified.

The container/closure system comprises of a laminated paper sack with an inner layer of LDPE. The sacks are 1 kg, 5 kg or 25 kg in size. The 1 kg and 5 kg sacks are heat-sealed. The 25 kg sacks polyethylene layer is tied and paper layers are sewn in. The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Active Substance

The active substance is tiamulin hydrogen fumarate, an established active substance described in the European Pharmacopoeia. An up to date certificate of suitability was provided. The active substance is manufactured in accordance with the principles of good manufacturing practice. The active substance specification is considered adequate to control the quality of the material.

Other Substances

The excipients gelatin and maize starch comply with the requirements of the relevant monographs of the current European Pharmacopoeia.

Packaging Materials

Satisfactory specifications have been supplied for containers for the active ingredient and for the intermediate and finished products:

Manufacture of the Finished Product

The manufacturing formula, method of manufacture, and in-process controls are appropriately described. The process involves coating the active substance by spraying with gelatin dissolved in potable water. Appropriate temperature controls are put in place and the granules are then sieved. This intermediate product is filled into pre-formed pouches of polyester/aluminium/polyester/polyethylene laminate, which are heat-sealed. Mixing with maize starch occurs at a later stage to form the final product. Details of in-process controls were provided.

Certificates of analysis showing ready compliance with specifications have been presented for three representative samples of the concentrate and for all batches of premix prepared in the process validation studies. All evidence confirmed that a reproducibly high quality of intermediate and finished product could be achieved.

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Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Finished and Intermediate Product Quality Control

Formal certificates of analysis for the intermediate product were presented on several batches which showed consistent compliance with the requirements.

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

Stability of the Product

Active Ingredient

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Intermediate Product

Results after 24 months storage in on-going tests support a 36 month shelf life for the intermediate product. The applicant undertook to report any adverse findings as testing continued.

Finished Product

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its 4 year shelf life when stored under the approved conditions. Special precautions for storage include “protect from direct sunlight.”

Transport Stability

Three 25 kg packs of the product were each sampled at 12 points following transport by road haulage for 100 km. Statistical analysis of the results in comparison with a control pack showed the product remained homogeneous.

In-use Stability

The results of a test in which a partly-emptied 1 kg pack of the product was tightly closed and stored at 25°C/60%RH were presented. Negligible change occurred in any parameter examined over a 12-week period thus a shelf life of 12 week after opening was justified.

In-feed Stability

Stability following incorporation of the premixes was investigated using wheat-based feed and corn-based feed in the forms of mash and pelleted feed at the recommended levels of incorporation, 100 ppm and 200 ppm. An in-feed stability of 8 weeks was justified.

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CONCLUSIONS ON QUALITY

The application was supported with respect to quality. The composition of the product and the methods of manufacture were soundly justified. Data provided justify a shelf-life of 4 years for product stored without restriction on the temperature of storage.

III. SAFETY ASPECTS

(Safety data submitted for original product)

Introduction

This product has been authorised as a Line Extension application to add a new strength to the existing Tiamulin 2% Premix. Summaries of the information provided are presented in the sections below.

Pharmacology

Tiamulin is a diterpene antimicrobial with a pleuromutilin chemical structure similar to that of valnemulin. The activity of tiamulin is largely confined to gram-positive micro-organisms and *mycoplasma*. Tiamulin acts by inhibiting protein synthesis at the ribosomal level. In veterinary medicine, tiamulin is used for treatment and prophylaxis of dysentery, pneumonia and mycoplasmal infections in pigs and poultry. Tiamulin is not used in human medicine.

A series of tests was carried out to investigate secondary pharmacodynamic effects. Tiamulin had no effect on motility, carbiazol-induced convulsions, body temperature or pupil diameter in the mouse following oral administration of doses of up to 200 mg/kg bw. In the rat, there were no progestational, uterotrophic, diuretic or anabolic effects at oral doses of up to 100 mg/kg bw. However there was a decrease in testosterone-stimulated growth of seminal vesicles at 50 mg/kg bw; the NOEL² was 15 mg/kg bw. This effect was considered to be of doubtful significance because of the lack of effects on reproductive performance, fertility, gonadal weight or pathology in the repeated-dose toxicity and reproductive toxicity studies in rats which used dose levels of up to 20 times the NOEL for this study.

Electrocardiogram effects were observed in dogs given a single oral dose of 5 mg/kg bw but not at the lower dose of 1 mg/kg bw. A NOEL of 3 mg/kg bw/day based on this effect was established in a repeated-dose toxicity study in dogs. No electrocardiogram (ECG)³ effects were observed in rhesus monkeys given an oral dose of up to 45 mg/kg bw tiamulin nor in humans given an oral dose of up to 10.7 mg/kg bw tiamulin.

A plasma C_{max}⁴ value of 2.6 µg/ml was observed in dogs 40 to 60 minutes after an oral dose of 10 mg ³H-labelled tiamulin /kg bw. Elimination was bi-phasic with an initial elimination half-life of 5.5 hours followed by a slower elimination half-life of 7.5 days. Around 100% of the dose was recovered in excreta within 10 days of dosing with approximately 33% of this in the urine. Tiamulin underwent extensive metabolism in the liver. No antimicrobial activity was observed for 67% of the metabolites. In rats given an oral dose of 50 mg/kg bw ³H-labelled tiamulin, 92% of the dose was recovered from excreta within 2 days of dosing. In urine 15 to 30% of the dose was eliminated and 45 to 63% was eliminated via bile. Comparison with intravenous dosing

² NOEL - No observed effect level

³ ECG - An electrocardiogram is a recording of the electrical activity of the heart

⁴ C_{max} – Maximum concentration

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indicated that the oral bioavailability in rats was 95 to 100%. Rat urine contained several metabolites together with a small amount of unmetabolised tiamulin.

Toxicology

The hydrogen fumarate salt of tiamulin (tiamulin hfu) is the active substance in this product. The toxicity of tiamulin hfu was investigated as follows.

Single dose toxicity

In male and female rats, the acute oral LD₅₀⁵ values for tiamulin were 2740 and 1830 mg/kg bw, respectively. In male and female NMRI mice, the acute oral LD₅₀ values were 770 and 650 mg/kg bw. The substance was of high toxicity when administered intravenously (LD₅₀ values were 19 to 20 mg/kg bw in rats and approximately 50 mg/kg bw in mice).

Repeat dose toxicity

Twenty-six week toxicity studies in rats and dogs and a one-year toxicity study in dogs were conducted with tiamulin hfu.

No consistent toxicology was found in these studies. Rats and mice showed the liver as potential organ of toxicity whilst dogs displayed transient ECG changes.

From the repeated dose studies, the dog was identified as the most sensitive species. A NOEL of 3 mg/kg bw was established based in a one-year study in dogs.

Reproductive toxicity

A three generation study was conducted in rats and embryofetal toxicity studies were carried out with rats and rabbits. Tiamulin hfu neither affected the fertility of male and female rats nor the pre- and postnatal development of their offspring. Tiamulin hfu was neither embryotoxic nor teratogenic to rats or rabbits at maternally toxic doses.

Mutagenicity

The mutagenic potential of tiamulin hfu was investigated in two gene mutation assays *in vitro* and in an erythrocyte micronucleus test *in vivo* in mice. Based on the results of these studies it can be concluded that tiamulin hfu does not possess mutagenic activity.

Carcinogenicity

The carcinogenic potential of tiamulin hfu was evaluated in a 30 month oral study in rats and a 123 week oral study in mice.

The studies did not show any evidence of a carcinogenic potential of tiamulin hfu.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which addresses the potential routes of exposure. These are as follows:

- accidental **topical** exposure,
- accidental **ocular** exposure,
- accidental **oral** exposure, and
- **inhalational** exposure.

⁵ LD₅₀ median lethal dose – These figures are frequently used as a general indicator of a substance's acute toxicity

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Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. These are as follows:

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.

Conclusions on User Safety

The applicant proposed the inclusion of appropriate user warnings which are in line with the other Tiamulin Premix products. The proposed warnings are considered satisfactory and there are no outstanding issues on user safety.

Residues

This product has been authorised as a Line Extension application to add new strength to the existing Tiamulin 2% Premix. The applicant provided data that had been submitted previously for assessment either during the MRL procedure or during the assessment of Tiamulin 2% and 80% Premixes.

MRLs

Tiamulin is listed in Annex I of Council Regulation 2377/90. The MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8- α -hydroxymutilin	Porcine, rabbit	100 μ g/kg 500 μ g/kg	Muscle Liver	
		Chicken	100 μ g/kg 100 μ g/kg 1000 μ g/kg	Muscle Skin+Fat Liver	
	Tiamulin		1000 μ g/kg	Eggs	
	Sum of metabolites that may be Hydrolysed to 8- α -hydroxymutilin	Turkey	100 μ g/kg 100 μ g/kg 300 μ g/kg	Muscle Skin + fat Liver	
Maize starch	N/A	All food	-	-	Annex II

Withdrawal periods

Based on the information provided, withdrawal periods as indicated below are justified. These are reflected on the SPC.

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Pigs

Prevention (at 2.0 mg/kg bwt) 1 day

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

Conclusions on Consumer Safety

The studies submitted support the meat withdrawal periods for the different doses. Residue and consumer safety aspects were considered satisfactory for the granting of the marketing authorisation.

Environmental Safety

Denagard 10% Premix for medicated Feed for Pigs, Chickens, Turkeys and Rabbits is used in various species for treatment of a number of conditions. The treated animals will be housed and all will receive medicated feed. Residues of tiamulin will enter the soil environment following the spreading of slurry/manure from the treated animals. The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required in Phase II.

The risk to the environment from the use of Denagard 10% Premix for medicated Feed for Pigs, Chickens, Turkeys and Rabbits was considered to be acceptable for approval of the marketing authorisation. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Conclusions on Environmental Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

CONCLUSIONS ON SAFETY

The application is supported with respect to all safety aspects.

IV. CLINICAL ASPECTS

Introduction

The product contains 100g tiamulin hydrogen fumarate per kg in a cereal based carrier as pellets or meal.

Clinical Pharmacology

Pharmacodynamics

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

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shown an 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.

Pharmacokinetics

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 C_{max} was 1.03 µg/ml and 1.82 µg/ml respectively by microbiological assay and the T_{max} 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 0.36 µg/ml (range 0.22-0.5 µg/ml).

Rabbits

There are no pharmacokinetic data available for rabbits.

Tolerance in the Target Species

Pigs

The applicant provided details of a number of target species tolerance studies. These showed no effect on the breeding sows, boars and litters of piglets when tiamulin was fed at daily doses up to 16 mg tiamulin/kg bodyweight for differing time periods of 7-21 days. These data would imply that tiamulin has a wide safety margin.

The most recent periodic safety update report (PSUR) does not include any reports of adverse reactions even though the product has been authorised for approximately 27 years.

Other Species

Efficacy data was provided during the Article 34 referral for Tiamutin premix and associated names, the final opinion of which was converted into a Decision by the European Commission on 27 July 2010. Further information on this referral can be found on the EMA's website.

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Resistance

Efficacy data was provided during the Article 34 referral for Tiamutin premix and associated names, the final opinion of which was converted into a Decision by the European Commission on 27 July 2010. Further information on this referral can be found on the EMA's website.

Clinical Efficacy

During the referral procedure, data was provided and deemed appropriate to support the claims of the SPC for Denagard 10% Premix for Medicated Feed for Pigs, Chickens, Turkey and Rabbits.

CONCLUSIONS ON CLINICAL ASPECTS

The application is supported with respect to all clinical aspects.

PART V. OVERALL CONCLUSION ON THE PRODUCT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)