College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tialin 125 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys
Tialin 250 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys

Date Created: July 2018

Updated August 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0287/001/DC NL/V/0287/002/DC
Name, strength and pharmaceutical form	Tialin 125 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys Tialin 250 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys
Applicant	Dechra Regulatory B.V. Handelsweg 25 5531 AE Bladel The Netherlands
Active substance	Tiamulin hydrogen fumarate 125.0 mg Equivalent to 101.2 mg of timulin Tiamulin hydrogen fumarate 250.0 mg equivalent to 202.4 mg of tiamulin
ATC Vetcode	QJ01XQ01
Target species	Pigs, chickens and turkeys
Indication for use	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 herd 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 herd must be established before the product is used.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic and generic 'hybrid' applications in accordance with Articles 13 (1) and 13 (3) respectively of Directive 2001/82/EC, as amended.
Date of conclusion of the decentralised procedure	28th March 2018.
Date product first authorised in the Reference Member State (MRP only)	No applicable.
Concerned Member States for original procedure	Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

These applications were for:

A generic application for Tialin 125 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys. Submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended.

A generic 'hybrid' application for Tialin 250 mg/ml Solution for Use in Drinking Water for Pigs, Chickens and Turkeys. Submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended. The application was deemed a 'hybrid' based on the concentration of active substances than were to be found in the reference product. On addition to drinking water, the amount consumed by the target species is the same as that of the 125 mg/ml product, and the reference product. Therefore, an exemption from providing pharmacological or toxicological studies was permitted under section 7.1 of guideline EMA/CVMP/016/00 Rev.2.

The reference product for both products was Denagard 12.5% w/v Concentrate for Oral Solution, marketed in the UK since July 1992.

Any adverse reactions observed are indicated in the SPCs.[1] The products are 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 SPCs. The efficacy [2] of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The products contain tiamulin hydrogen fumarate at either 125.0 mg or 250.0 mg, equivalent respectively to 101.2 mg and 202.4 mg of tiamulin. The 125 mg product contains the excipients methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, citric acid monohydrate, disodium phosphate dehydrate, ethanol 96% and purified water. The 250 mg product contains all excipients except methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate.

The container/closure system consists of a white, opaque, high density polyethylene bottle of 1 litre with transparent graduated scale, closed with a white opaque, low density polyethylene screw-cap.

The product is also available in a white, opaque high density polyethylene container of 5 litres, closed with a white opaque high density polyethylene screw-cap. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservatives are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of: weighing of materials, addition of components under continuous stirring, filtration, filling of solution into bottles, followed by quality control testing.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II.C. Control of Starting Materials

The active substance is tiamulin hydrogen fumarate, an established active substance described in the European Pharmacopoeia (Ph. Eur). Additional testing is performed in line with Certificates of Suitability. 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. Batch analytical data demonstrating compliance with this specification have been provided.

All excipients are produced in line with current Ph. Eur monographs. Packaging components comply with the appropriate Commission Directive.

II.C.4. Substances of Biological Origin

Declarations have been provided that no components of animal origin are included in the product or primary packaging.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

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 sites have been provided demonstrating compliance with the specification.

Control tests on the finished product are those for: (125 mg products) appearance, pH, density, identification and assay of active substance and key excipients and periodically, microbiological quality. For the 250 mg product, all tests except identification and assay of the excipients methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate, which are not present in this product. For the 250 mg product there is an additional test: identification and assay of ethanol 96%.

II.F. Stability

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. A retest period of 3 years was established for one manufacturer, 4 years for the second

manufacturer. Real time, refrigerated and accelerated stability studies were performed on the finished product, in addition to in-use, medicated water and freeze thaw stability studies.

G. Other Information

In light of stability studies, the following storage precautions were approved:

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

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

Shelf life after dilution or reconstitution according to directions: 24 hours.

125mg product: This veterinary medicinal product does not require any special storage conditions.

250 mg product: Do not freeze.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the application, no toxicological or pharmacological studies were required. A user safety assessment and environmental safety assessment were provided.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are the same as those of the reference product, (the 250 mg product is equivalent to the 125 mg product and reference product when presented in drinking water), and are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- This product may cause skin and eye irritation. When mixing, direct contact with the skin and eyes should be avoided by wearing impermeable rubber gloves and safety glasses.
- In case of accidental eye contact, irrigate the eyes thoroughly with clean running water immediately. Seek medical advice if irritation persists.

- Contaminated clothing should be removed and any splashes on to the skin should be washed off immediately.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP[3] guidelines.

Phase I:

A Phase I exposure assessment considering tiamulin was submitted. Since the product is indicated for use in chickens, turkeys and pigs, consideration of contamination of the environment by intensively reared animals was considered.

The Phase I decision tree was followed to Question 17. The initial predicted environmental concentration (PEC) for tiamulin (and tiamulin hydrogen fumarate), in soil, exceeded the trigger value of 100 µg/kg for some of the treatment scenarios, as follows:

Intensively-reared species

Treatment	$PEC_{soil\ initial}$ (µg/kg)	
	Tiamulin	Tiamulin hydrogen fumarate
Weaner pig (to 25 kg)	309.3	382.3
Fattening pig (22 – 125 kg	209.8	259.3
Sow (with litter)	74.49	92.06
Laying Hen	105.4	129.5
Replace Layer	199.8	245.6
Broiler Breeder	56.79	69.81

As a result, a Phase II assessment was provided to cover the relevant treatment scenarios for chickens (pullets, breeders, layer hen), pigs and turkeys (breeders, layer hen).

It is noted that the treatment scenarios ‘broilers’ and ‘poults’ were removed for chickens and turkeys, respectively, and therefore are not supported under the target species.

[3] Committee for Medicinal Products for Veterinary Use

Phase II Tier A:

A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines, including studies on physicochemical properties, environmental fate and effects.

Studies were carried out using either tiamulin or tiamulin hydrogen fumarate*.

Physicochemical properties

Study type	**Result**
Molecular weight	493.7
Water solubility	0.3608 mg/l
Dissociation constants in water pKa*	7.64
Vapour Pressure*	1.99 x 10^{-5} Pa at 25°C
n-Octanol/Water Partition Coefficient $logP_{ow}$ (OECD 107)*	4.614. A $logP_{ow}$ >4, indicates a potential for bioaccumulation

A $logP_{OW}$ of 4.614 indicates a potential risk for bioaccumulation, which was addressed using a bioconcentration fish study (see below).

Environmental fate and behaviour

Study type	**Result**
Soil adsorption (OECD 106)*	K_{OC} value of 627.22 (arithmetic mean of 7 soils)
Degradation in soil (OECD 307)*	DT_{50} value of 108 days at 20°C (geometric mean from 3 soils considering both tiamulin and its transformation products)

The above findings indicate tiamulin to be moderately mobile in soil, and very persistent in some soils.

Environmental effects

Study type	**Result**
Algae (OECD 201)* *Anabena flos-aquae*	E_yC_{50} (yield) = 0.0947 mg test item/l. E_rC_{50} (growth rate) = 0.1206 mg test item/l.
Daphnia magna (OECD 202)*	EC_{50} 48 hour: 46.44 mg/l (37.59 mg/l)**
Zebra fish (OECD 203)*	LC_{50} 96 hour: 15 mg/l (12.14 mg/l)**

Study type	Result
Soil micro-organisms: Nitrogen Transformation Test (28 days). (OECD 216)*	% effect at. 1127 µg/kg and 11 268 µg/kg (1109 µg/kg and 11 090 µg/kg active). Equivalent to 1xPEC and 10xPEC led to a <25% difference with control group
Terrestrial Plants, Growth Test/*Species* (OECD 208)* *Allium cepa* *Avena sativa* *Zea mays* *Phaseolus aureus* *Brassica rapa* *Lactuca sativa* *Helianthus annuus* *Beta vulgaris*	The most sensitive endpoint from the species tested is shoot fresh mass of *Brassica rapa*. The NOEC was found to be 2.40 mg/kg dry soil. The EC_{10} was calculated to be 4.99 mg/kg dry soil. The EC_{50} values varied from 7 to 158 mg/kg dry soil.
Earthworm reproduction* (OECD 222)	NOEC for reproduction of 66.1 mg/kg dry soil (53.5)**. EC_{50} for reproduction of 94.6 mg/kg dry soil respectively for use in the risk assessment.

**as tiamulin

Exposure assessment (Predicted exposure concentration)
PEC values for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken following the proposed use of the product. The following PEC values were calculated for 'weaner pigs' which is considered to be the worst case scenario.

	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)*
PEC	309.3	6.91	2.30

* Based on PECgroundwater/3

An unacceptable risk to groundwater (PEC>0.1 µg/l) was indicated at Tier A. Further refinement based on FOCUS modelling was provided at Tier B.

Risk Characterisation (Risk Quotient)
Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for the worst case scenario, as follows.

Aquatic organism	*PNEC* (µg/l)	*PEC* (µg/l)	RQ
Algae (*Anabena flos-aquae)*	E_rC_{50} (growth rate): 1.21	2.30	**1.9**
Daphnia magna	EC_{50} 48 hour: 37.59	2.30	0.06
Zebra fish (Freshwater acute toxicity test)	LC_{50} 96 hour: 12.14	2.30	0.02

For aquatic organisms, a risk (RQ>1) is indicated in the surface water compartment regarding cyanobacteria.

Terrestrial organism	PNEC (µg/kg)	PEC (µg/kg)	Individual RQ
Nitrogen transformation	At 28 days: <25% difference with control.		
Terrestrial plants	EC_{50} 70	309.3	**4.42**
Earthworms	NOEC 5350	309.3	0.06

An unacceptable risk for plants is indicated at Tier A and further refinement at Tier B was required.

Tier B refinement:

Potential for bioaccumulation in fish
The findings from an OECD 305 study (BCF value of 17) indicate that tiamulin is unlikely to have a significant potential for bioaccumulation. In addition, the secondary poisoning assessment indicated no significant potential for secondary poisoning.

Risk to groundwater
As the initial PEC for groundwater exceeded the 0.1 µg/l drinking water standard that has been established in the EU, it was refined using the groundwater model FOCUS PEARL. Results demonstrated that the 80th percentile annual average concentration of tiamulin in leachate was <0.1 µg/l for all soils; confirming that appropriate use of the product will not pose a risk to drinking water.

Risk to plants and cyanobacteria
Due to revision of the intended treatment scenarios, provision of information on the excretion/metabolism of tiamulin in pigs, and refinement of the risk to plants from treated chicken manure using the species sensitivity distribution (SSD) method (and ETX 2.1 program), the risk to plants and cyanobacteria, following the use of the test product as recommended, could be refined to an acceptable level. As a result, the product is not expected to pose a risk for the environment when used as recommended. Since tiamulin was shown to be very persistent in some soil types, appropriate wording is included under the environmental properties section of the SPC and product literature, as follows:

- Tiamulin is very persistent in soil.

III.B.2 Residues documentation

Due to the nature of the application, and bioequivalence having been established with the reference product, no residue data were required.

MRLs

Tiamulin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues. The marker is the sum of metabolites that may be hydrolysed to 8-a-hydroxymutlin.

MRLs are listed below:

	Porcine	Turkey	Chicken
Muscle	100 µg/kg	100 µg/kg	100 µg/kg
Liver	500 µg/kg	300 µg/kg	1000 µg/kg
Fat / skin	-	100 µg/kg	100 µg/kg

Withdrawal Periods

Withdrawal agreed were the same as those of the reference product:

Pigs

Meat and offal: 2 days (8.8 mg tiamulin hydrogen fumarate for the 125 mg product: (equivalent to 0.07 ml solution); for the 250 mg product: (equivalent to 0.035 ml solution)/kg body weight)
Meat and offal: 4 days (20 mg tiamulin hydrogen fumarate for the 125 mg product: (equivalent to 0.16 ml solution); for the 250 mg product: (equivalent to 0.08 ml solution)/kg body weight)

Chickens (pullets, breeders, layer hen)
Meat and offal: 2 days
Eggs: Zero days

Turkeys (breeders, layer hen)
Meat and offal: 6 days

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant submitted bibliographical references, and MIC data were submitted for target pathogens. The SPC reflects the required information.

Pharmacokinetics

A biowaiver claimed in accordance with EMA/CVMP/016/00-Rev.2 confirmed that no further data were required.

Tolerance in the Target Species

The SPC reflects appropriate warnings.

Resistance

Bibliographical data were submitted showing reviews reflecting the type and incidence of resistance to the active substance which might be expected. The SPC reflects appropriate warnings.

IV.II. Clinical Documentation

Due to the nature of the application, no further data were required.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics the benefit/risk profile of the products is favourable.

MODULE 4

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

Summary of change (Application number	**Section updated in Module 3**	**Approval date**
Addition of a manufacturer responsible for batch release including batch control/testing. Addition of a secondary packaging site of the finished product. Addition of a primary packaging site of the finished product. Addition of a manufacturing site of the finished product. (UK/V/0650/IB/001/G)	N/A	25 September 2018
Change in RMS from UK to NL	Module 1 updated	30 August 2018
Change in the QPPV (IE/V/xxxx/IA/102/G)	N/A	1 February 2019
MAH transfer from Dechra Limited to Dechra Regulatory B.V.	Module 1 updated	1 March 2019
CEP update from an already approved manufacturer (NL/V/0287/001-002/IA/002)	N/A	2 May 2019
Deletion of a manufacturing site, CEP update from an already approved manufacturer (NL/V/0287/001-002/IA/003/G)	N/A	25 March 2021

Deletion of a manufacturing site (NL/V/0287/001-002/IA/004)	N/A	17 January 2022
Changes in shape or dimension of the container of closure (immediate packaging), Change in immediate packaging of the finished product (NL/V/0287/001-002/IB/005/G)	N/A	20 January 2022
One-off alignment of the product information with version 9.0 of the QRD templates (NL/V/0287/001-002/A/006)	N/A	26 May 2023