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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DENAGARD 101,2 mg/ml, solution for use in drinking water for rabbits

DATE : 11/06/2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0336/001/DC
Name, strength and pharmaceutical form	DENAGARD 101,2 mg/ml SOLUTION FOR USE IN DRINKING WATER FOR RABBITS
Applicant	LILLY FRANCE 24 Boulevard Vital Bouhot 92200 Neuilly Sur Seine
Active substance(s)	Tiamulin (as hydrogen fumarate)
ATC Vetcode	QJ01XQ01
Target species	Rabbits
Indication for use	Reduction of mortality due to epizootic rabbit enteropathy (ERE) when associated with infections by *Clostridium perfringens* susceptible to tiamulin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17/04/2019
Concerned Member States for original procedure	IT, ES, PT

I. SCIENTIFIC OVERVIEW

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 potential adverse reactions observed are indicated in the SPC.
The product is safe for the user, the consumer of foodstuffs from treated animals when used as recommended. The active substance is very persistent in soil and toxic for terrestrial plants and cyanobacteria. Suitable warnings and precautions are indicated in the SPC.
The efficacy of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 101.2 mg/ml tiamulin (as hydrogen fumarate) and the following excipients: propyl parahydroxybenzoate, methyl parahydroxybenzoate (E218), ethanol 96%, water purified, citric acid monohydrate and disodium phosphate dehydrate.
The packaging of the finished product is as described on the SPC. 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.

B. Method of Preparation of the Product

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

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

C. Control of Starting Materials

The active substance is tiamulin hydrogen fumarate, an established substance described in the European Veterinary Pharmacopoeia. 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. 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 site have been provided demonstrating compliance with the specification.

G. 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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.
An in-use shelf-life and a shelf-life after dilution in drinking water as detailed on the SPC have been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL) (*for pharmaceuticals only)*

This is a generic application according to Article 13, the cited reference product is CEVAMULINE SOLUTION LAPIN (Ceva santé animale). As bioequivalence with the reference product has been demonstrated, results of safety and residues tests are not required.

The safety aspects of this product are identical to the reference product.

Warnings and precautions as listed on the product literature are the similar as those of the reference product and are adequate to ensure safety of the product to users and the consumers. Some specific warnings are included in regards of the risk to the environment.

III.A Safety Testing

Pharmacological Studies
As this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated, it is accepted that results of pharmacological studies are not provided.

Toxicological Studies
As this is a generic application according to Article 13, and bioequivalence with the reference product has been demonstrated, results of toxicological tests are not required.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature have been improved compared to those of the reference product.

Environmental Risk Assessment

A Phase I and phase II environmental risk assessment (ERA) were provided according to the CVMP/VICH guidelines.

Phase I:

A Phase II ERA is required as the Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 1154 µg/kg) is greater to 100 µg/kg and no mitigations exist that alter the PECsoil.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

<table>
<tr><td colspan="4">Physical-chemical properties</td></tr>
<tr><td>Study type</td><td>Test protocol</td><td>Result</td><td>Remarks</td></tr>
<tr><td>Water solubility</td><td>OECD 105</td><td>65 g/L (20°C)</td><td>Study performed before adoption of the OECD guideline</td></tr>
<tr><td>Dissociation constants in water pKa</td><td>OECD 112</td><td>pKa1 = 4.3 ± 0.03, pKa2= 7.64 ±0.03</td><td>Study performed before adoption of the OECD guideline</td></tr>
<tr><td>n-Octanol/Water Partition Coefficient logP_{ow}</td><td>OECD 107</td><td>logK_{ow} =-0.35</td><td></td></tr>
<tr><td colspan="4">Environmental fate</td></tr>
<tr><td>Soil Adsorption/Desorption</td><td>OECD 106</td><td><table><tr><th>Soil</th><th>Kf (mL/g)</th><th>Koc (mL/g)</th></tr><tr><td>Clay</td><td>75.0</td><td>24808</td></tr><tr><td>Loamy sand</td><td>7.8</td><td>1018</td></tr><tr><td>Silt loam</td><td>74.4</td><td>3698</td></tr><tr><td>Silt loam</td><td>87.8</td><td>3464</td></tr><tr><td>Mean</td><td></td><td>8247</td></tr></table>As only 4 soils have been tested, the lowest Koc value (1018) has been used in the</td><td>Study performed before adoption of the OECD guideline.
Reliability 2</td></tr>
</table>

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
		ERA	
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 22°C.,\ FO}$ = 47.8, 51.9, 61.4 and 97.1 d for sand, sandy loam, silty clay loam and silt loam soils The geometric mean of 62 d have been used in the ERA	Study performed before adoption of the OECD guideline. Reliability 2

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae and or cyanobacteria, growth inhibition test/*Synechoccus leopoliensis*	OECD 201	EC50	6.10	µg/l	
Daphnia sp. immobilisation	OECD 202	$EC50_{24h}$	69000	µg/l	Study performed before adoption of the OECD guideline. Reliability 2
Fish, acute toxicity/*Oncorhyncus mykiss*	OECD 203	LC50	6040	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25%	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	35 000	µg/kg	3 species: (*Lepidium sativum, Brassica rapa and Avena sativa*)
Terrestrial Plants, growth test	OECD 208	EC50	5 000	µg/kg	6 species: (*Beta vulgaris, Cucumis sativus, Glycine*

Physical-chemical properties					
Study type	**Test protocol**	**Result**			**Remarks**
					max, Helianthus annuus, Allium cepa and Avena sativa)
Earthworm/*Eisenia fetida*	OECD 222	NOEC	178 000	µg/kg	

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Endpoint	**PNEC**	**PEC**	**RQ**
Algae	0.06 µg/l	14.12 µg/l	235
Daphnia	69 µg/l	14.12 µg/l	0.20
Fish	6 µg/l	14.12 µg/l	2.35
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Earthworm	17800 µg/kg	1154 µg/kg	<1
Terrestrial plants	50 µg/kg	1154 µg/kg	23

The risk characterisation resulted in risk quotients (RQs) below 1 for the daphnia and earthworm reproduction endpoints indicating that the product will not pose a risk to those endpoints when used as recommended.

PECsoil and PECwater have been refined taking into account high metabolism (Fa=0.1) in target species and using FOCUS SWASH model.

Endpoint	PNEC	$PEC_{refined}$	RQ
Algae	0.06 µg/l	0.077 µg/l	1.28
Fish	6	0.077 µg/l	<1
Terrestrial plants	50 µg/kg	115 µg/kg	2.3

The risk characterisation resulted in RQS higher than 1 for algae and terrestrial plants indicating a risk to those endpoints.

Taking into account the overall benefit/risk analysis and the fact that the product is intended for a minor species, the product has been accepted with the following RMMs included in the SPC :

4.5 iii) other precautions

Tiamulin is very persistent in soil.

Tiamulin is toxic for terrestrial organisms (plants) and for aquatic organisms (blue-green algae).

5.3 environmental properties

Tiamulin is very persistent in soil.

Tiamulin is toxic for terrestrial organisms (plants) and for aquatic organisms (blue-green algae).

PBT assessment

Tiamulin does not fulfil PBT criteria.

III.B Residues documentation

Residue Studies

No data was provided.

Given the legal basis of the application, and the fact that the product is orally administered at the same dose as the reference product, it is accepted that a residue depletion study is not required.

MRLs

a. active substances

The active substance, tiamulin, is included in table 1 of the MRL regulation 37/2010, as follows

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Sum of metabolites that may be hydrolysed to 8-α-hydroxymutilin	Porcine, **rabbit**	100 µg/kg 500 µg/kg	Muscle Liver	No entry	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009
	Chicken	100 µg/kg 100 µg/kg 1000 µg/kg	Muscle Skin + fat Liver			
	Turkey	100 µg/kg 100 µg/kg 300 µg/kg	Muscle Skin + fat Liver			
Tiamulin	Chicken	1000 µg/kg	Eggs			

An acceptable daily intake (ADI) was defined for tiamulin. It is 30 µg/kg bw (*i.e*. 1800 µg/person).

b. excipients

The MRL status of excipients of the product DENAGARD 125 MG/ML, ORAL SOLUTION FOR RABBITS is indicated in the following table.

Excipient	MRL status
Methylparahydroxybenzoate (E218)	Covered with food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)
Propylparahydroxybenzoate	Table 1 for all species, no MRL required
Ethanol 96%	Table 1 for all species, no MRL required
Citric acid monohydrate	Covered with food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)
Disodium phosphate dehydrate	Covered with food additives (substance with a valid E number approved as additives in foodstuffs for human consumption)
Purified water	Out of scope list

The composition of the product DENAGARD 125 MG/ML, ORAL SOLUTION FOR RABBITS is acceptable according to the European Regulation (EC) 470/2009.

Withdrawal Periods

Given the legal basis of the application, Article 13(1) generic, and the fact that the product is orally administered at the same dose as the reference product, it is accepted that the withdrawal period agreed for the reference product can be applied to the new generic product as bioequivalence between the two products is accepted.

Rabbit
Meat and offal: 2 days

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

It is a generic application for a marketing authorisation in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC. The cited reference product is CEVAMULINE SOLUTION LAPIN (Ceva santé animale).

Pharmaceutical form

The test and the reference products have the same pharmaceutical form : solution for use in drinking water.

Active substance qualitative and quantitative composition

The test and reference products have the same qualitative and quantitative composition in active substance: 101.2 mg of tiamulin (as hydrogen fumarate) per mL of product.

Bioequivalence studies

The omission of bioequivalence studies is justified according to section 7.1.c) of the Guidelines for the conduct of bioequivalence studies for veterinary medicinal products (EMEA/CVMP/016/00-Rev.2).

If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved reference veterinary medicinal product presented as an aqueous oral solution at time of administration, bioequivalence studies may be waived if the excipients contained in it do not affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), solubility (e.g. co-solvents) or in-vivo stability of the active substance. Any differences in the amount of excipients should be justified by reference to other data, otherwise an in vivo bioequivalence study will be required. The same

requirements for similarities in excipients apply for oral solutions as for biowaivers according to the relevant criteria.

The exemption 7.1.c is acceptable. Therefore the applicant is not required to perform a bioequivalence study.

Tolerance in the Target Species of Animals

This is an application for a generic product and the applicant has demonstrated bioequivalence with the reference product. No tolerance data were provided. It is accepted that the tolerance in the target species of the generic is comparable to that of the reference product.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The applicant was invited to comment on the current resistance situation, *e.g.* changes in the level of resistance of target pathogens against the active substance, tiamulin, based on recent information from published literature.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

No clinical studies were provided on the basis of demonstration of bioequivalence with the reference product *CEVAMULINE SOLUTION LAPIN*.
As such the efficacy is the same as that of the reference product.

The following indication for use in rabbits was accepted:

> "Reduction of mortality due to epizootic rabbit enteropathy (ERE) when associated with infections by *Clostridium perfringens* susceptible to tiamulin."

The following warnings were added together with adequate warnings and precautions were stated in the SPC for prudent use of this antimircrobial product :

> "Before installing a treatment, the management and sanitary conditions at the farm should be evaluated against the risk of an outbreak of the disease. Treatment should be initiated in case of historical cases of epizootic enteropathy in the herd and as soon as a first case of mortality due to enteropathy caused by *Clostridium perfringens* is confirmed."

The posology is the same of the reference product that is 16 mg of tiamulin per kg body weight per day, for 10 days in drinking water (i.e. 16 ml of solution per 100 kg body weight per day, for 10 days).

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V. OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

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

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 veterinary Heads of Agencies website (www.HEVRA.org).