DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Karimulina 1000 mg/g granules for use in drinking water for pigs, chickens and turkeys

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0336/001/DC
Name, strength and pharmaceutical form	Karimulina 1000 mg/g granules for use in drinking water for pigs, chickens and turkeys
Applicant	LABORATORIOS KARIZOO, S.A. Pol. Ind. La Borda, Mas Pujades 11-12 08140 Caldes de Montbui Spain
Active substance(s)	Tiamulin hydrogen fumarate
ATC vet code	QJ01XQ01
Target species	Pigs, chickens and turkeys.
Indication for use	**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.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13(3) Hybrid application of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 29/07/2020
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	CY, DE, HU, IT, PL, PT

I. SCIENTIFIC OVERVIEW

This was an hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended. Karimulina 1000 mg/g is the generic veterinary medicinal product and contains tiamulin hydrogen fumarate as active substance for use in drinking water. The product is indicated for the treatment of several defined diseases in pigs, chickens and turkeys associated with tiamulin sensitive pathogens. The reference product is Denagard 450 mg/g authorised in Spain since 1982. Bioequivalence between generic and reference product can be assumed.

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 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. Qualitative and quantitative particulars

The product contains tiamulin hydrogen fumarate as active substance and it is formulated without excipients

The container/closure system is a folding carton of 125 g and 1 kg with inner layer (paper/PE/Alu/HPPE).

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 active substance described in the European. 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.

Scientific data and/or certificates of suitability issued by the EDQM 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.

D. Control on intermediate products

NA

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 site have been provided demonstrating compliance with the specification.

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.

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.

G. Other Information

NA

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

As this is a hybrid application according to Article 13 (3), and bioequivalence with a 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 same as those of the reference product and are adequate to ensure safety of the product to users, the environment and the consumers.

III.A Safety Testing

Pharmacological Studies

As this is a hybrid application according to Article 13 (3), and bioequivalence with a reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

As this is a hybrid application according to Article 13 (3), and bioequivalence with a 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. The user warnings proposed are in accordance with those of the reference product.

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

Environmental Risk Assessment

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

Phase I:

Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 868.9 µg/kg and 1108.7 µg/kg for Weaner pig and Broiler,

respectively) is greater to 100 µg/kg and no mitigations were submitted that alter the PECsoil. Therefore, Phase II ERA is required.

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. The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	92.85 g/L	Valid
Dissociation constants in water pKa	OECD 112	4.68 at 20.3ºC	Valid
Dissociation constants in water pKa	QSAR Toolbox version 4.4	pka: pka1= 3.55/-; pka2=14.4/9.51	Valid
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	$logP_{ow}$ = -0.58 (23ºC)	Valid
UV absorption spectrum	OECD 101	14172-18703 (200-206 nm)	Valid
Vapour pressure	OECD 104	2.15 (20ºC) 3.21 (25ºC)	Valid
Molecular mass	The Merck Index	609.82 g/mol	Valid

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Loam: Koc = 232.86 mL/g (pH = 4.32; Corg = 2.3%) Loam: Koc = 305.16 mL/g (pH = 5.87; Corg = 2.7%) Clay: Koc = 1227.39 mL/g (pH = 7.26; Corg = 2.7%) Clay loam: Koc = 929.94 mL/g (pH = 4.37; Corg = 2.9%) Loamy sand: Koc = 218.97 mL/g (pH = 3.6; Corg = 1.7%) Loamy sand: Koc = 56.17 mL/g (pH = 3.24; Corg = 9.4%) Clay: Koc = 1420.05 mL/g (pH = 7.27; Corg = 2%)	Valid

Environmental fate			
		meanKoc = 391.77 mL/g	
Aerobic and Anaerobic Transformation in Soil	OECD 307	Sandy clay: $DT50\ soil, [SFO], [20]$ = 45 Loamy sand: $DT50\ soil, [SFO], [20]$ = 47 Sandy loam: $DT_{50\ soil, [SFO], [20]}$ = 52 Clay: $DT_{50\ soil, [SFO], [20]}$ = 46 geometric mean (20°C): $DT_{50\ soil}$ = 48 d Bound residues (after acid and base extraction): 33.8%, 36.6%, 38.6% and 36.6% AR for loamy sand, sandy loam sandy clay and clay soil. Relevant metabolites: Two degradation products.	Valid

Effect studies				
Study type	**Test protocol**	**Endpoint**	**Result**	**Remarks***
Cyanobacteria, growth inhibition test/*species*	OECD 201	EC50	148.7 µg THF/L	*Tier A Results based on nominal concentration*
Cyanobacteria, growth inhibition test/*species*	OECD 201	EC10 NOEC	107.1 µg THF/L 39 µg THF/L	*Tier B Results based on nominal concentration*
Daphnia sp. immobilisation	OECD 202	EC50	---	Post authorization study commitment.
Fish, acute toxicity/*Danio rerio*	OECD 203	LC50	13 mg THF/l	Tier A Static test. Results based on measured concentration. Static test.
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	≤ 25% of control at 22174 mg THF/kg soil	Trigger value: 25% deviation

				from the control
Terrestrial Plants, growth test	OECD 208	EC50	Solanum Lycopersicum = 5780 µg THF/kg Beta vulgaris =17740 µg THF/kg Daucus carota = 32620 µg THF/kg Cucumis sativus = 11200 µg THF/kg Linum usitatissimum = 27780 µg THF/kg Allium cepa= 22590 µg THF/kg Avena sativa = 40630 µg THF/kg Triticum aestivum = 5780 µg THF/kg	Tier A
Terrestrial Plants, growth test	OECD 208	NOEC	Solanum Lycopersicum = 840 µg THF/kg Beta vulgaris = 2440 µg THF/kg Daucus carota = 7070 µg THF/kg Cucumis sativus = 2440 µg THF/kg Linux usitatissimum = 2050 µg THF/kg Allium cepa = 2440 µg THF/kg Avena sativa = 7070 µg THF/kg Triticum aestivum = 2440 µg THF/kg	*Tier B*
Terrestrial Plants, growth test	SSD	HC_5LL	113.2 µg THF/kg	*Tier C*
Earthworm/*Enchytraeidae* reproduction	OECD 222	NOEC	NOEC (mortality)= 836 mg THF/kg NOEC (weight) = 836 mg THF/kg NOEC (reproduction) = 836 mg THF/kg	Tier A

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:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	10.7 µg THF/kg (based on Cyanobacteria EC10 = 107.1 µg THF/kg and AF = 10)	Worst-case FOCUS PECsw for weaner pig = 19.15 µg/L Worst-case FOCUS PECsw for Broiler = 24.85 µg/L	**1.8** **2.3**
groundwater	0.15 µg THF/kg (based on Cyanobacteria EC50 = 148.7 µg THF/kg and AF = 1000)	Weaner pig PEC gw= 0.097699 µg/L Broilers PECgw = 0.143626 µg/L	0.065 0.096
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil (terrestrial plants)	0.1132 mg/kg (based on HC5LL = 0.1132 Mg/kg and AF = 1)	Weaner pig = 869 µg/kg Broiler = 1108.7	**7.7**

		µg/kg	**9.8**

The risk characterisation resulted in risk quotient (RQ) below 1 for the groundwater compartment indicating that the product will not pose a risk to this compartment when used as recommended.

The results of the assessment for the surface water and soil compartments indicate that a risk for the environment is indicated. The following information on environmental properties needs to be included in the product literature '*Tiamulin Hydrogen Fumarate is toxic for terrestrial plants and aquatic organisms*'.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	LogKow = 0.58	not B
Persistence	$DT_{50, soil, 12 °C}$	110 d	not P
Toxicity	NOEC	0.039 mg THF/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because bioequivalence with the reference product has been demonstrated.

MRLs

Tiamulin hydrogen fumarate is listed in table 1 of the Annex to Commission Regulation (EU) No 37/2010.

MRLs are listed below:

Pharmacologically Active substance	**Marker residue**	**Animal species**	**MRLs (µg/kg)**	**Target tissues**
Tiamulin hydrogen fumarate	**Sum of metabolites that may be hydrolysed to 8-α-hydroximutilin**	**Porcine**	**100** **500**	**Muscle** **Liver**
		Chicken	**100** **100** **1000**	**Muscle** **Skin+Fat** **Liver**
	Tiamulin	**Chicken**	**1000**	**Eggs**
	Sum of metabolites that may be hydrolysed to 8-α-	**Turkey**	**100** **100** **300**	**Muscle** **Skin+Fat** **Liver**

	hydroximutilin			

There are no excipients in the formulation.

Withdrawal Periods

Based on the data provided above, the following withdrawal periods are justified:

Pigs
Meat and offal: 2 days (dose 8.8 mg tiamulin hydrogen fumarate/kg bw)
Meat and offal: 4 days (dose 20 mg tiamulin hydrogen fumarate/kg bw)

Chickens
Meat and offal: 2 days
Eggs: Zero days

Turkeys
Meat and offal: 6 days

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is an hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Resistance

The bibliography / information provided suggests that there is not currently a potential risk on the development of resistance from microorganisms involved in the pathologic processes of the claimed indications.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

As this is an hybrid application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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 and the environment is acceptable.

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.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.

None