MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Karimulina 125 mg/ml solution for use in drinking water for chickens, turkeys and pigs

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PRODUCT SUMMARY

EU procedure number	ES/V/0435/001/MR
Name, strength and pharmaceutical form	Karimulina 125 mg/ml solution for use in drinking water for pig, chickens and turkeys
Applicant	Laboratorios Karizoo S.A. Carrer Mas Den Pujades 11-12 Polígono Industrial La Borda Caldes De Montbui 08140 Barcelona - Spain
Active substance(s)	Tiamulin Hydrogen fumarate
ATC vetcode	QJ01XQ01
Target species	Chickens, turkeys and pigs
Indication for use	Chickens: Treatment and metaphylaxis of chronic respiratory disease (CRD) and air sacculitis caused by *Mycoplasma gallisepticum*. Turkeys: Treatment and metaphylaxis of infectious sinusitis and air sacculitis caused by *Mycoplasma gallisepticum* and *Mycoplasma meleagridis*. Pigs: Treatment of swine dysentery caused by *Brachyspira hyodysenteriae* susceptible to tiamuline..Treatment of pleuropneumonia caused by *Actinobacillus pleuropneumoniae*. Treatment of enzootic pneumonia caused by *Mycoplasma hyopneumoniae*. Secondary infection by bacteria such as *Pasteurella multocida* and *Actinobacillus pleuropneumoniae* can complicate enzootic pneumonia and require specific treatment.

PRODUCT INFORMATION

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this veterinary medicinal product (VMP) is available in the Union Product Database (UPD).

SUMMARY OF ASSESSMENT

Legal basis of original application*	MRP application in accordance with Article 18 of Regulation (EU) 2019/6 as amended.
Reference product (RP)	DENAGARD 125 mg/ml SOLUCIÓN PARA ADMINISTRACIÓN EN AGUA DE BEBIDA
Marketing authorisation holder	ELANCO GMBH
MS where the RP is or has been authorised	N/A
Marketing authorisation number	1873 ESP
EU procedure number	N/A
Date of authorisation	03/12/1983
Date of completion of the original mutual recognition procedure	21/12/2023
Date veterinary medicinal product first authorised in the Reference Member State (MRP only)	06/04/2009
Concerned Member States for original procedure	FR
Concerned Member States for subsequent recognition procedure	N/A
Withdrawn CMS during original mutual recognition procedure	N/A

*Please be aware that certain parts of the dossier may be varied and consequently be subject to protection of technical documentation – for these and other changes of referenceability to parts of the dossier, please see chapter POST-AUTHORISATION PROCEDURES

1. SCIENTIFIC OVERVIEW

The veterinary medicinal product (VMP) is produced and controlled using validated methods and tests, which ensure the consistency of the VMP released on the market.

It has been shown that the VMP can be safely used in the target species; the reactions observed are indicated in the SPC.

The VMP 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 VMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

The VMP contains Tiamulin Hydrogen fumarate (*125 mg/ml) and the excipients:* propyl parahydroxybenzoate (E216), methyl parahydroxybenzoate (E218), citric acid monohydrate (E330), disodium phosphate dihydrate, ethanol 96% and purified water .

Karimulina 125 mg/ml solution for use in drinking water for chickens, turkeys and pigs is presented in white high-density polyethylene containers of 1-L and 5-L capacity. Containers are closed with a high-density polyethylene screw cap with low-density polyethylene induction sealing.

The choice of the of preservatives are justified.

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

2.B. Description of the manufacturing method

The VMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing sit.

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

2.C. Production and control of starting materials

The active substance is Tiamulin Hydrogen Fumarate, an established active substance> <an established substance described in the European Pharmacopeia. 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 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.

2.D. Control tests carried out on isolated intermediates during the manufacturing process

Not applicable

2.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 VMP.

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.

2.F. Stability tests

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the VMP throughout its shelf life when stored under the approved conditions.

2.G. Other information

None

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. Safety tests

Pharmacological studies

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, pharmacological studies are not required.

Toxicological studies

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, toxicological studies 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 VMP.

Environmental Risk Assessment

A Phase I and Phase II environmental risk assessment (ERA) was 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 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). The data were considered to be complete and acceptable.

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	92850 mg/L at 20ºC	
Dissociation constants in water pKa	OECD 112	pKa = pKa = 4.68 at 20.3 ºC	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	Log Pow = -0.58 at 23ºC	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	geomean Koc = 391.77 ml/g Strong, nonlinear interaction between soil and substance)	

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Environmental fate			
		except for soil 7. Geomean 1/n=0.53	
Aerobic and Anaerobic Transformation in Soil	OECD 307	Loamy sand: DT50 soil, [SFO, 20ºC]= 49.0 d Sandy loam: DT50 soil, [[SFO, 20ºC]= 48.1 d Sandy clay: DT50 soil, [SFO, 20ºC]= 47.7 d Clay: DT50 soil, [SFO, 20ºC]= 48.3 d geometric mean (20°C) DT50 soil = 48.27 d Mineralisation: 17.6%, 17.1%, 17.7% and 16.9% AR for loamy sand, sandy loam sandy clay and clay soil at Day 120, respectively Bound residues after extraction: 33.8%, 36.6%, 38.6% and 36.6% AR for loamy sand, sandy loam sandy clay and clay soil (max at D 120) Relevant metabolites: 2 degradation products were identified in all four soils by its retention time (RT). A proposal of structure is included in the full study report (Fig 24), no further discussion on elucidation method or biological activity. Maximum values of degradation products: loamy sand 18.8% ,16.0% AR at Day 60 to 33.2 %,17.2% AR by Day 120 (1.50,8.50 RT respectively) sandy loam 20.7%,16.2% at Day 60 to 47.1%,3.3% AR by Day 120 (1.50, 8.50 RT) sandy clay 25.4%,44.7% AR at Day 60 to 9.8%, 2.1% AR by Day 120 (1.50,8.50 RT) clay soil 23.3% , 16.3% AR at Day 60 to 40.6% ,2.4 % AR by Day 120 (1.50,8.50 RT)	For each of the 4 soils. Information on soils used

Effect studies				
Study type	Test protocol	Endpoint Result	Unit	Remarks*
Algae and or cyanobacteria, growth inhibition test/*species*	OECD 201	72h EC50 (growth) = 0.1489 mg/l (n) THF 0.1206 mg/l (n) Tiamulin base 72h ErC10 (growth)= 0.1073 mg/l (n) THF 0.0869 mg/l (n) Tiamulin base 72h NOECr (growth)= 0.039 mg/l (n) THF 0.0316 mg/l (n) Tiamulin base	µg/l	Nominal concentration
Daphnia sp. immobilisation	OECD 202	EC50= 27.59 mg/L	µg/l	
Fish, acute toxicity/*species*	OECD 203	LC50= 13 mg/L	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect ≤ 25% of control	µg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	*S. lycopersicum* EC50 (dry weight) = 5.78 mg/kg	µg/kg	8 species tested Dicotyledonous: *Solanum lycopersicum* (tomato)-*Solanaceae* *Beta vulgaris* (beet)-*Chenopodaceae* *Daucus carota* (carrot)-*Apiaceae* *Cucumis sativus* (cucumber)-*Cucurbitaceae* *Linum usitatissimum* (flax)-Linaceae Monocotyledoneous *Allium cepa* (onion)-*Liliaceae* *Avena sativa* (oat)-Poaceae *Triticum aestivum* (wheat)-Poaceae
Tier B 6 species: (list names)	OECD 208	NOEC (shoot height) = 0.29 mg/kg EC10 (dry weight) = 0.32 mg/kg	µg/kg	Plants, chronic effects, same test as for acute effects *A. cepa* (long term, NOEC) *C. carota* (long term, EC10)
Earthworm reproduction	OECD 222	Tier A endpoint	µg/kg	

		NOEC (weight, mortality, reproduction)= 836 mg/kg EC10 and EC50 (weight, mortality, reproduction)= 836 mg/kg		

*add information on analytical verification of test substance (nominal (n) or measured (m)), on exposure (e. g. semi-static, flow-through, sediment spiked, etc.), on test substance (salt, base), and on test medium (e. g. Corg content)

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:

Weaner pig

Compartment	PNEC	PEC	RQ
surface water	3.9 (NOEC)	94.34	**19.57**
groundwater	0.76	54.68	0.38*
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	113.2 (SSD)	1737.8	**15.3**

*The conclusion for groundwater covers the risk for broiler chicken.

Broiler chicken

Compartment	PNEC	PEC	RQ
surface water	3.9 (NOEC)	47.36	**9.82**
groundwater			
soil microorganisms: Nitrogen transformation test	<>25% difference in N transformation	NA	NA
soil	113.2 (SSD)	887.0	**7.8**

The risk characterisation resulted in risk quotients (RQs) below 1 for the groundwater compartment indicating that the product will not pose a risk to those compartments 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 and that the following risk mitigation measures are required for this VMP:

Special precautions for the protection of the environment:

The use of this veterinary medicinal product poses a risk to aquatic organisms and to terrestrial plants.

Environmental properties

Tiamulin is very persistent in soil.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Log Kow < 3	(v)B/not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	104 d	not P*
Toxicity	NOEC	NOEC > 0.01	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

**The substance is classified as P in soil based on the available public information on the substance*.

3.B. Residues documentation

Residue tests

The applicant has not submitted residues data on the basis that bioequivalence with the reference product has been demonstrated.

Maximum Residue Limits

Tiamulin is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Tiamulin	Sum of metabolites that may be hydrolysed to 8-αhydroxymutilin	Porcine	100 µg/kg 500 µg/kg	Muscle Liver	
		Chicken	100 µg/kg 100 µg/kg 1000 µg/kg	Muscle Skin+Fat Liver	
	Tiamulin	Chicken	1000 µg/kg	Eggs	
	Sum of metabolites that may be Hydrolysed to 8-α-hydroxymutilin	Turkey	100 µg/kg 100 µg/kg 300 µg/kg	Muscle Skin + fat Liver	

The excipients listed in section 2. of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

Withdrawal Periods

Based on the data provided, the following withdrawal periods were established:

Chickens:
Meat: 6 days
Eggs: Zero days

Turkeys:
Meat: 6 days

Eggs: Not for use in birds producing or intended to produce eggs for human consumption.

Pigs:
Meat: 4 days

4. EFFICACY DOCUMENTATION (preclinical studies and clinical trials)

As this is a generic application according to Article 18 of Regulation (EC) 2019/6 and bioequivalence with a reference VMP has been demonstrated, efficacy studies are not required. The efficacy claims for this VMP are equivalent to those of the reference VMP.

4.A. Pre-Clinical Studies

No pre-clinical studies were performed.

Development of resistance and related risk in animals

The bibliography provided suggests that the product is effective when used according to the product information.

Adequate warnings and precautions appear on the product literature.

Tolerance in the target species of animals

The product literature accurately reflects the type and incidence of adverse effects, which might be expected.

4.B. Clinical trials

No clinical trials were performed.

Absence of clinical trials was adequately justified

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the VMP 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 VMP for humans and the environment is acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the VMP. The current SPC is available in the Union Product Database (UPD).

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 VMP.

None.