DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CITRAMOX 100 mg/g powder for use in drinking water for pre-ruminant calves, broilers and pigs [ES, PT]

KARIMOX 100 mg/g powder for use in drinking water for pre-ruminant calves, broilers and pigs [EL]

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0415/001/MR
Name, strength and pharmaceutical form	CITRAMOX 100 mg/g powder for use in drinking water for pre-ruminant calves, broilers and pigs [ES, PT] KARIMOX 100 mg/g powder for use in drinking water for pre-ruminant calves, broilers and pigs [EL]
Applicant	LABORATORIOS KARIZOO, S.A.
Active substance(s)	Amoxicillin
ATC Vetcode	QJ01CA04
Target species	Cattle (pre-ruminant), chicken (broiler) and pig.
Indication for use	Treatment of infections caused by bacteria sensitive to amoxicillin; colibacillosis, salmonellosis (except in broilers), streptococci, staphylococci.

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	Mutual Recognition application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition decentralised>procedure	28/01/2022
Date product first authorised in the Reference Member State (MRP only)	08/06/2016
Concerned Member States for original procedure	EL, PT

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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 amoxicillin 100 mg (equivalent to 114.78 mg amoxicillin trihydrate) as substance active and silica colloidal anhydrous, lactose monohydrate and sucrose as excipients.

The container/closure system is thermosealed bags made of polyester, aluminium and low density polyethylene (LDPE) complex.

The choice of the formulation has been justified.

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 Amoxicillin trihydrate, an established active substance described in the European 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.

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.

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

A re-test period to the active substance is included in some of the CEPs and, in case a re-test period is not include in the corresponding CEP, it is confirmed that the active substance will be fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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.

The proposed in-use shelf-life period of 3 months for the medicinal product and 24 hours shelf-life after dilution in drinking water have been supported with appropriate data according to current guidelines.

G. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL

As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, results of safety tests are not required.

The safety and residue 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 and consumers.

III.A Safety Testing

Pharmacological Studies

As this is a generic application according to Article 13(1), and bioequivalence with the reference product has been demonstrated, results of pharmacological tests are not required.

Toxicological Studies

As this is a generic application according to Article 13(1), and bioequivalence with the reference product has been demonstrated, results of toxicological tests are not required.

User Safety

An user safety assessment has not been presented. Since the candidate product has the same composition in active substances and excipients than the reference product, it is assumed that the risks for the user will be similar to those associated with the use 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:

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. However, it was demonstrated that amoxicillin was not stable in soil and cattle and pig manure. As such, the Phase II assessment was carried out on the primary degradation product of amoxicillin, amoxicillin penicilloic acid (APA).

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	79.9 g/l	
Dissociation constants in water pKa	OECD 112	pK1= 8 pK2= 10,1	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	LogKow= -2,2 (main component) LogKow= (-0,51)-(0,46) (minor components/impurities)	

Environmental fate			
Soil Adsorption/Desorption	OECD 106	Refesol 01-A: Koc = 68,6 Refesol 02-A: Koc = 87 Refesol 03-G: Koc = 56 Refesol 04-A: Koc = 44,7 Refesol 06-A: Koc = 77,4 Mean Koc = 66,7 cm^3/g	

Environmental fate			
Aerobic and Anaerobic Transformation in Soil	OECD 307	Refesol 01-A : DT50= 1,7 d Refesol 02-A: DT50= 1,4 d Refesol 03-G: DT50= 1,3 d Refesol 04-A: DT50= 2 d Geometric mean (20°C): 1,6 d Mineralization: 82,1 % 4 minor transformation products	

Effect studies				
Study type	**Test protocol**	**Endpoint**	**Result**	**Remarks**
Cyanobacteria, growth inhibition test/ *Anabaena flos-aquae*	OECD 201	EC50	EC50 (growth) = 172 mg/l	
Daphnia sp. immobilisation	OECD 202	EC50	EC50 = 1000 mg/l	
Fish, acute toxicity/*species*	OECD 203	LC50	LC50 = 1000 mg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	≤ 25% of control	
Terrestrial Plants, growth test (most sensitive specie: *Lactuca sativa*)	OECD 208	EC50 NOEC	EC50 = 1000 mg/kg NOEC= 1152 mg/kg	Species tested: *Avena sativa*; *Allium cepa; Lactuca sativa*; *Brassica alba*; *Solanum lycopersicum*; *Phaseolus aureusotal*
Earthworm	OECD 208	EC10 or NOEC	NOEC (mortality) ≥ 2000 mg/kg NOEC (weight) ≥ 2000 mg/kg NOEC	

			(reproduction)≥ 2000 mg/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:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	>1 µg/L	63.3 µg/L	0.063
groundwater	NA	0.000	NA
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	11.52 µg/L	984.1 µg/L	0.085

The risk characterisation resulted in risk quotients (RQs) below 1 for the surface water, and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended. Concentration in groundwater was below the action limit of 0.1 µg/L.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	Kow < 4	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	< 120 d	not P
Toxicity	NOEC	1000 mg/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13(1), and bioequivalence with the reference product has been demonstrated, results of residue depletion tests are not required.

MRLs

The active substance amoxicillin is an allowed substance as described in table 1 of the annex to Commission Regulation (EU) No 37/2010.

MRLs are listed below:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues
Amoxicillin	Amoxicillin	All food producing species	50 µg/kg	Muscle
			50 µg/kg	Fat
			50 µg/kg	Liver
			50 µg/kg	Kidney
			4 µg/kg	Milk

Withdrawal Periods

The same withdrawal periods than the reference product are proposed:

Broilers:
- Meat and offal: 6 days
- Eggs: Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 4 weeks of the start of the laying period.

Pigs:
- Meat and offal: 10 days

Pre-ruminant calves:
- Meat and offal: 2 days

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, 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(pharmaceuticals only)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, pharmacodynamics, pharmacokinetics and tolerance studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, clinical 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).