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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DOXINYL, 500 mg/g powder for use in drinking water for pigs, chickens and turkeys

DATE: 30/09/2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0406/001/DC
Name, strength and pharmaceutical form	DOXINYL, 500 mg/g powder for use in drinking water for pigs, chickens and turkeys
Applicant	LIVISTO Int'l, S.L. Av. Universitat Autònoma, 29 08290 Cerdanyola del Vallès (Barcelona), Spain
Active substance(s)	Doxycycline
ATC Vetcode	QJ01AA02.
Target species	Pigs (pigs for fattening), chickens (broiler and chicken for reproduction) and turkeys (turkey for meat production and turkey for reproduction)
Indication for use	Pigs: treatment of clinical respiratory infections caused by Mycoplasma hyopneumoniae and Pasteurella multocida susceptible to doxycycline. Chickens and turkeys: treatment of clinical respiratory infections associated with Mycoplasma gallisepticum susceptible to doxycycline.
Concerned Member States for original procedure	AT, CZ, DE, EL, ES, HU, IT, PL, PT, RO, SK

MODULE 2

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

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 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. Composition

The product contains the active substance doxyxycline as hyclate at a concentration of 500 mg/g and citric acid and silica colloidal anhydrous as excipients.
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 doxycycline as hyclate, 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.

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

A re-test period for the active substance is set in the dossier, 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 as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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, results of pharmacological tests are not required.

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

Toxicological Studies

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

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

User Safety

Although this is a generic application according to Article 13 and bioequivalence with the reference product has been demonstrated a brief user risk assessment was submitted. As bioequivalence is accepted, this approach can be accepted.

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) were provided according to the CVMP/VICH guidelines.

Phase I:

The Phase I assessment showed that the initial predicted environmental concentration in soil (PECsoil initial = 887 µg/kg) is greater than 100 µg/kg and

no mitigations exist that alter the PECsoil. Therefore, a Phase II ERA was provided.

Target animal	Number of animals raised/place	BW (kg)	Nitrogen produced in 1 year per place (kg.N.y-1)	Housing factor	PEC (µg/kg)
Fattening pig	3	65	7.5	1	589
Turkey	2.7	6.5	0.9	1	552
Broiler breeder	1	1.7	0.69	1	56
Broiler	90	1	0.23	1	887

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	143 g/l	20°C, pH 2.1
Dissociation constants in water pKa	OECD 112	pKa = 3.12	20°C
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	logK_{ow} = -0.63	22°C

Environmental fate			
Soil Adsorption/ Desorption	OECD 106	Koc = 18535, 872478, 29412, 177273, 138381	The calculated Freundlich exponents were below the recommended

Environmental fate			
			range of 0.7 – 1.1 (for 3/5 soils) Consequently, the lowest Koc value (138381) obtained from the two reliable values has been used in the ERA.
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT_{50,\ 20°C.\ SFO}$= 8.8, 22.8, 33.6 and 37.4 d $DT_{50,\ 20°C.\ geo.\ mean}$ = 22.41 d	Unlabelled compound was used. The results represent dissipation half-life values

Effect studies (doxycycline base)					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/ *Anabaena flos-aquae*	OECD 201	EC50	91.72	µg/l	
Daphnia sp. immobilisation	OECD 202	EC50	72.76	mg/l	
Fish, acute toxicity/ *Oncorhynchus mykiss*	OECD 203	LC50	82.1	mg/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 NOEC	34 (*Spinacia oleracea)* 19.09 (*Spinacia oleracea)*	mg/kg	8 species: *Brassica napus, Pisum sativum, Helianthus annuus, Spinacia oleracea, Cucumis sativus and Zea mays, Allium cepa, Avena sativa.*
Earthworm reproduction	OECD 220	NOEC	842.9	mg/kg dw	

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:

Tier A

Compartment	**PNEC**	**PEC**	**RQ**
surface water (algae)	0.9172 µg/l	0.027 µg/l	0.029
groundwater	0.9172 µg/l	0.08 µg/l	0.087
soil microorganisms: Nitrogen transformation test	<>25% difference in N transformation	NA	NA

Soil (terrestrial plants)	340 µg/kg	887 µg/kg	2.6

Tier B

Compartment	PNEC	PEC	RQ
Soil (terrestrial plants)	1909 µg/kg	887 µg/kg	0.46

The risk characterisation resulted in risk quotients below 1 for the surface water, groundwater and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended.

Persistence, **Bioaccumulation** and **Toxicity (PBT) assessment:**

Taking into account its very low Log Kow value (-0.63), it is accepted that doxycycline is not a PBT substance.

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, residue depletion studies are not required.

MRLs

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

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
doxycycline	All food producing species	100 µg/kg 300 µg/kg 300 µg/kg	Muscle Fat Liver	For fin fish the muscle MRL relates to "muscle and skin in natural proportions"	Agents-infectious agents/ Antibiotics	2015/151 of 30/01/2015

		600 µg/kg	kidney	MRLs for fat, liver and kidney do not reply to fin fish. For porcine and poultry species the fat MRL relates to "skin and fat in natural proportions" Not for use in animals from which milk or eggs are produced for human consumption.		

Withdrawal Periods

The same withdrawal periods as for the reference product are applicable.

Pigs:	Meat and offal:	4 days.
Chickens:	Meat and offal:	5 days.
Turkeys:	Meat and offal:	12 days.

Not authorised for use in laying birds producing eggs for human consumption.

Do no use within 4 weeks of the start of the laying period.

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

Pharmacology

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

Tolerance in the Target Species of Animals

This is an application for a hybrid product and the applicant has demonstrated bioequivalence with the reference product. No tolerance data was provided. It is accepted that the tolerance in the target species of the generic is comparable to those of the princeps.

Resistance

The applicant has documented the current state of resistance to doxycycline.

Adequate warnings and precautions appear on the product literature.

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.