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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

SURRICOXX 400 MG/ML SOLUTION FOR USE IN DRINKING WATER FOR CHICKENS, TURKEYS, DUCKS AND GUINEA FOWLS

DATE: 05/02/2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0422/001/DC
Name, strength and pharmaceutical form	SURRICOXX 400 mg/mL Solution for use in drinking water for chickens, turkeys, ducks, and guinea fowls 400.0 mg amprolium / mL Solution for use in drinking water
Applicant	VMD N.V. Hoge Mauw 900 2370 Arendonk, Antwerp BELGIUM
Active substance(s)	Amprolium (as hydrochloride)
ATC Vetcode	QP51AX09
Target species	Chickens (broilers, pullets, layers, breeder hens), turkeys, ducks and guinea fowls
Indication for use	Treatment of intestinal coccidiosis caused by *Eimeria* spp. susceptible to amprolium

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	Article 13(3) hybrid application of Directive 2001/82/EC as amended
Date of completion of the original decentralised procedure	16/12/2020
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, BG, CZ, DE, EE, EL, ES, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SK, UK

I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC (a “hybrid” veterinary medicinal product). The reference veterinary medicinal product is NEMAPROL, which has been authorized in France since 17/02/1992.
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 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 400 mg of amprolium (as hydrochloride) and excipients benzyl alcohol and purified water.

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.
The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post-authorisation.

C. Control of Starting Materials

The active substance is amprolium hydrochloride, an established active substance described in the British 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 as detailed In 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 & toxicological studies

As this is a hybrid application according to Article 13 (3) of Directive 2001/82/EC, and bioequivalence with a reference product has been demonstrated, results of pharmacological and toxicological tests were not required.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline, which shows that the risk-mitigation measures of the reference product are not considered to be in line with the outcome of the user safety assessment. An update of the risk-mitigation measures has been implemented by the applicant.
Warnings and precautions as listed in 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 (PECsoil initial = 1242 µg/kg) is greater/equal 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	487 g/L at pH 7	
Dissociation constants in water pKa	OECD 112	pKa = 4.80	
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	$logK_{ow}$ at pH 5 = -2.64 $logK_{ow}$ at pH 7 = -2.44 $logK_{ow}$ at pH 9 = -1.12	

Environmental fate		
Soil Adsorption/Desorption	OECD 106	Koc = 4325, 619, 2968, 7493, 1039, 176, 6467 K_d =99, 17, 80, 217, 18, 17, 129 pH =4.3, 5.9, 7.3, 4.4, 3.6, 3.2, 7.3 OC =2.3,2.7,2.7,2.9,1.7,9.4,2 %clay=19.1,22.4,44.4,33,11,11.7,52
Aerobic and Anaerobic Transformation in Soil	OECD 307	$DT50_{20°, SFO}$ =337, 15.6, 13.8, 28.6 pH =3.7, 5.3, 5.6, 7.5

Environmental fate		
		OC =1.01,5.37,5.13,2.16 %clay=6, 21, 23, 33

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks**
Algae and or cyanobacteria, growth inhibition test/ *Anabaena flos aqua*	OECD 201	EC50	43	mg/l	
Daphnia sp. immobilisation	OECD 202	EC50	200	mg/l	
Fish, acute toxicity/ *Brachydanio rerio*	OECD 203	LC50	1351	mg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25% 0, 2, 20	mg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	1841, >1565, 2096 7207 1675 6914 >1500 >1500 >1500	mg/kg	*S. saccharatum* *Zea mays* *R. sativus* *Brassica rapa* *Medicago sativa* *Brassica napus* *Glycine max* *Daucus carota* *S. lycopersicon*
Earthworm reproduction/ *Eisenia fetida*	OECD 222	NOEC	46.4	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) from 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	200 µg/l (*D. magna*)	10.6 µg/l	0.053
Groundwater	>1.0 µg/l	<0.01 µg/l (metamodel)	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil	4.64 mg/kg (earthworm)	4.14 mg/kg (plateau)	0.89

The risk characterisation resulted in risk quotients (RQs) 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.

The following information on environmental properties needs to be included in the product literature: "amprolium is a very persistent substance."

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	log Kow <0	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	716 d	(v)P
Toxicity	NOEC	>0.1 mg/L	Not T
PBT-statement :	The compound is considered as vP		

III.B Residues documentation

Residue Studies

As this is an application according to Article 13(3), and bioequivalence with a reference product has been demonstrated, residue depletion studies are not required.

MRLs

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

Pharmacologically active Substance	Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification
Amprolium	Not applicable	Poultry	No MRL required	Not applicable	For oral use only	No entry

Withdrawal Periods

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

Species	Tissues	Withdrawal periods
Chickens, turkeys, ducks, and guinea fowls.	Meat & offal	0 days
	Eggs	0 days

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

This application was submitted in accordance with Article 13(3) of Directive 2001/82/EC (a “hybrid” veterinary medicinal product). The reference veterinary medicinal product is NEMAPROL containing amprolium as active substance.

Bioequivalence is granted according to exemption 7.1.c) of the guideline (EMEA / CVMP / 016 / 2000-Rev 3). Additionally, a comparative dissolution study in water was provided.

As this is an 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

As bioequivalence with the reference product has been shown and as the product is intended to be used in the drinking water at the same dose than the reference product, it can be accepted that the tolerance in the target species of this VMP should not be different to that of the reference product.

Resistance

The applicant has documented the current state of resistance to amprolium. Adequate warnings and precautions appear in the product literature.

IV.B Clinical Studies

This hybrid application is made according to Article 13(3) of Directive 2001/82/EC, as amended by Directive 2004/28/EC. As bioequivalence with the reference product can be assumed, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

In addition, the applicant conducted two palatability studies in order to demonstrate the adequate uptake of medicated water, according to Guideline EMA/CVMP/EWP/206024/2011. Both palatability studies demonstrated that the water consumption between test and reference product was equivalent according to the guideline requirements.

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.