FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Distocur 34 mg/ml Oral suspension for cattle and sheep

Distocur.vet (DK, NO, SE)

Date: 27/10/2016

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products
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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0312/001/MR
Name, strength and pharmaceutical form	Distocur 34 mg/ml Oral suspension for cattle and sheep. Distocur.vet (DK, NO, SE)
Applicant	MERIAL 29 AVENUE TONY GARNIER 69007 LYON FRANCE
Active substance(s)	Oxyclozanide
ATCvet code	QP52AG06
Target species	Cattle and sheep
Indication for use	Treatment of infections caused by the adult stage of Fasciola hepatica, sensitive to oxyclozanide. Elimination of gravid tapeworm segments (Moniezia spp.).

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	application in accordance with Article13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	17/10/2016
Date product first authorised in the Reference Member State (MRP only)	13/05/2015
Concerned Member States for original procedure	AT, BE, DE, DK, HR, HU, IE, IT, LU, NL, NO, PL, PT, RO, SE, SI, UK

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 34 mg/ml of oxyclozanide and methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate as preservatives, aluminium and magnesium silicate, carmellose sodium as suspending agents, sodium laurilsulfate as wetting agent and citric acid monohydrated and sodium citrate as buffering agent. Water purified is also used as solvent.

The container/closure system is a polyethylene vial fitted with a polyethylene stopper. 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 oxyclozanide, 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

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 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

The application is made in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic application). The applicant has conducted a bioequivalence study in cattle.

The tested product has been shown to be bioequivalent to the reference product, Zanil suspension, following oral administration at a dose rate of 10 mg oxyclozanide/kg bodyweight in calves.

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

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the safety profile will be the same as that of the reference product.

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

Ecotoxicity

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP[1] guidelines.

Phase I

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline. The product is indicated for use in cattle and sheep. Therefore, consideration of contamination of the environment by pasture and intensively reared animals was considered. The initial predicted environmental concentration (PEC) for oxyclozanide in soil, exceeded the trigger value of 100 µg/Kg in some cases of intensively reared animals (see below):

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PECsoil for intensively reared animals

Target animal	Dose (mk/kg/day)	Ad (number of treatment)	Number of animals raised/place	BW (kg)	Nitrogen produced in 1 year per place (kg.N.y-1)	Housing factor	PEC (µg/kg)
Calves	10	2	1.8	140	10	1	115
Cattle (0-1 year)	10	2	1	200	18	0.5	101
Cattle (>2 years)	10	2	1	450	35	0.5	117
Dairy cow	10	2	1	425	60	0.5	64

PECsoil for pasture animals

Parameter	Beef cattle	Dairy cow	Sheep (ewe)	Lambs
Individual dose (D) mg/kg BW	10	10	15	15
Number of day of treatment (Ad), d	2	2	2	2
Body weight (BW) kg/animal	330	600	80	36
Stocking density (SD), animals/ha	9.5	3.5	15	25
Fraction of herd treated (Fh)	1	1	1	1
PECsoil (µg/kg)	83	56	48	36

[1] Committee for Medicinal Products for Veterinary Use

As a result and also because the product is also an endoparasiticide, a phase II assessment for the relevant scenarios for cattle and sheep was provided.

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 acceptable.

Study type	**Test protocol**	**Result**	**Remarks**
Water solubility	OECD 105	3.1 mg/l	NO
Dissociation constants in water pKa	OECD 112	Not determined	NO
n-Octanol/WaterPartition Coefficient logP_{ow}	OECD 107	logK_{ow} = 4.49	NO

Environmental fate and behaviour			
Soil Adsorption/Desorption	OECD 106	**Soil type** / **Kf** / **Kf,oc** / **1/n**: Loamy sand 127 5862 0.82; Clay 24.2 2467 0.98; Sandy loam 43.1 2462 0.79	The lower Koc from this study has been used in the risk assessment.
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50, $_{20°c., SFO}$ = 80.4, 1.55, 1.97, 1.81 for Loamy sand, silt loam, sandy clay loam and clay loam soils respectively Highest $DT_{50, 12°C}$ > 120 days Transformation products >10%: *Decarbonylated oxyclozanide and partially dimerised oxyclozanide*	

Environmental effects					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test/*Desmodesmus subspicatus*	OECD 201	EC50	3.9	mg/l	
Daphnia sp. immobilisation	OECD 202	EC50	0.73	mg/l	
Fish, acute toxicity/*Brachydario rerio*	OECD 203	LC50	0.54	mg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	% effect	<25% at 10	mg/kg	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	>1000	mg/kg	*Only 3 plants have been tested (Triticum aestivum; Lactuca sativa; Sinapis alba).The RQ was compared to 0.1 value*
Earthworm reproduction	OECD 222	NOEC	16.4	mg/kg	
Dung fly larvae/*Scathophaga stercoraria*	OECD 228	EC50	>1000	mg/kg	
Dung beetle larvae/*Aphodius constans*	OECD GD 122	EC50	>1000	mg/kg	
Bioaccumulation in fish/*Oncorhyncus mykiss*	OECD 305	BCF	<60	l/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:

Terrestrial compartment

Taxonomic level	PECsoil (µg/kg)	Endpoints	AF	Risk Quotient
Nitrogen transformation	117	≤25% of control	-	No effects were observed at > 10 x PEC
Terrestrial plants	117	EC_{50} : 1000 mg/kg	100	0.017
Earthworm	117	NOEC: 16.4 mg/kg	10	0.07

No significant risk for the terrestrial compartment is expected.

Dung compartment

Taxonomic level	PECdung (mg/kg dw)	Endpoints	AF	Risk Quotient
Dung beetle	111	EC_{50} > 1000 mg/kg	100	<11.1
Dung fly	111	EC_{50} > 1000 mg/kg	100	<11.1

The results of the dung fauna studies showed very low toxicity of oxyclozanide (EC50>1000 mg/kg). However as a risk to dung fauna can not be totally excluded (RQ<11) a risk mitigation has been included in the SPC (see below)

Aquatic compartment ground water

With a Koc value of 2462 and a maximum PECsoil value (cattle >2 years) of 117 µg/kg, the PECgw will be equal to 0.67 µg/L.
As raw PECgw is higher than 0.1 µg/L, application of a more advanced model (metamodel) has been used.
With a Kom of 1428 (2462/1.724) and a DT50 of 80 days the following relationship is true:
Kom> -5.9 + 6.5 DT50

PECgw refined is less than 0.1 µg/l.

Aquatic compartment run off scenario

Taxonomic level	PECsw (µg/l)	Endpoints (mg/l)	AF	Risk Quotient
Daphnia magna	0.22	EC_{50} 48h : 0.73	1000	0.3
Brachydario rerio	0.22	LC_{50} 96h : 0.54	1000	0.43

Desmodesmus subspicatus	0.22	EC_{50} 72h: 3.9	100	0.014

All risk quotient values are < 1. Therefore, no significant risk for the aquatic compartment following run-off scenario is expected.

Aquatic compartment direct excretion scenario

Taxonomic level	PECsw (µg/l)	Endpoints (mg/l)	AF	Risk Quotient
Daphnia magna	10.5	EC_{50} 48h : 0.73	1000	14.4
Brachydario rerio	10.5	LC_{50} 96h : 0.54	1000	19.4
Desmodesmus subspicatus	10.5	EC_{50} 72h: 3.9	100	0.27

Based on initial PECsw, potential risk for fish and daphnia endpoints is expected. The PECsw has been refined based on the partitioning of the compound between water and sediment.

Aquatic compartment direct excretion scenario (refined based on partitioning)

Taxonomic level	PECsw (µg/l)	Endpoints (mg/l)	AF	Risk Quotient
Daphnia magna	0.92	EC50 48h : 0.73	1000	1.26
Brachydario rerio	0.92	LC50 96h : 0.54	1000	1.7
Desmodesmus subspicatus	0.92	EC50 72h: 3.9	100	0.02

The risk characterisation resulted in risk quotients slightly higher than 1 for the surface water in direct excretion scenario. For precaution, risk mitigation has been included in the SPC (see below). In addition, the applicant committed to provide a fish early-life-stage test and a Daphnia reproduction study.

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	< 60	not B
Persistence	$DT_{50,\ compartment,\ 12\ °C}$	> 120 days	P

Toxicity	EC50	>0.01 mg/l	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		

Conclusion

The results of the environmental risk assessment indicate that a risk for the environment cannot be totally ruled out and that the following risk mitigation measures are required for this product:

Section 4.5 iii) Other precautions
Oxyclozanide is toxic to dung fauna and aquatic organisms. The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of oxyclozanide in cattle. The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for 5 days after treatment.

Section 5.3 Environmental properties
Faeces containing oxyclozanide excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on dung degradation.
Oxyclozanide is toxic to aquatic organisms. Oxyclozanide is persistent in soils.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted, as the candidate product is administered orally in the same species at the same regimen dosage and bioequivalence with the reference product has been demonstrated. Therefore, the results of residue studies are not required.

MRLs

The active substance is included in table 1 of the MRL regulation 470/2009, as follows:

Marker residue	Animal Species	MRL	Target Tissues	Therapeutic Classification	Regulation
oxyclozanide	All ruminants	20 µg/kg 20 µg/kg 500 µg/kg 100 µg/kg	Muscle Fat Liver Kidney	Antiparasitic agents/ Agents against endoparasites	37/2010 of 22.12.2009

		10 µg/kg	Milk		

The MRL status of excipients of the product is indicated in the following table:

Excipient	MRL status	ADI
Methyl parahydroxybenzoate (E 218)	Table 1, no MRL required	-
Propyl parahydroxybenzoate	Table 1, no MRL required	-
Aluminium and magnesium silicate	Table 1, no MRL required	-
Carmellose sodium (E 466)	Table 1, no MRL required	-
Sodium laurilsulfate	Table 1, no MRL required	-
Citric acid monohydrate (E 330)	Table 1, no MRL required	-
Sodium citrate (E 331)	Table 1, no MRL required	-
Purified water	Out of scope	

Withdrawal Periods

Based on the data provided above, a withdrawal period of 14 days for meat and offal and 4.5 days for milk are justified.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

The application is made in accordance with Article 13(1) of Council Directive 2001/82/EC (as amended), a generic application. The product is bioequivalent with the reference product Zanil suspension based on AUC_{last} and $C_{max.}$ As bioequivalence with the reference product has been demonstrated, the results of pre-clinical and clinical trials are not required.

Tolerance in the Target Species of Animals

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of tolerance studies are not required.

Resistance

An overview of the level of resistance to in target pathogens based on recent bibliographical data has been submitted. It can be concluded that resistance to oxyclozanide is limited.

IV.B Clinical Studies

As this is a generic application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been demonstrated, the results of clinical studies are not required.

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

Summary of change **FR/V/0312/001/DX/006**	**Approval date**
This application is a variation (extension) to add sheep as a new food producing target species to the marketing authorisation of Distocur 34 mg/ml Oral suspension for cattle.	05/06/2019