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AGENCE NATIONALE DU MEDICAMENT VETERINAIRE
8 rue Claude Bourgelat –
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FOUGERES

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Elivec 5 mg/ml pour-on solution for cattle

Date: 20 March 2018

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0313/001/DC
Name, strength and pharmaceutical form	Elivec 5 mg/ml pour-on solution for cattle
Applicant	LIVISTO Int'l, S.L. Av. Universitat Autònoma, 29 08290 Cerdanyola del Vallès (Barcelona), Spain
Active substance(s)	Eprinomectin
ATC Vetcode	QP54AA04.
Target species	Beef and dairy cattle.

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Indication for use	Treatment of infestations by the following parasites sensitive to eprinomectin: Gastrointestinal roundworms (adults and L4 larvae): *Ostertagia ostertagi* (including inhibited L4 larvae), *Ostertagia lyrata* (only adults), *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis, Cooperia sp.* (including inhibited L4), *Cooperia oncophora*, *Cooperia punctata*, *Cooperia pectinata*, *Cooperia surnabada*, *Bunostomum phlebotomum*, *Nematodirus helvetianus*, *Oesophagostomum radiatum*, *Oesophagostomum* sp. (only adults), *Trichuris discolor* (only adults); Lungworms: *Dictyocaulus viviparus* (adults and L4); Warbles (parasitic stages): *Hypoderma bovis*, *Hypoderma lineatum;* Mange mites: *Chorioptes bovis*, *Sarcoptes scabiei* var. *Bovis;* Sucking lice: *Linognathus vituli*, *Haematopinus eurysternus*, *Solenopotes capillatus*; Biting lice: *Damalinia bovis*; Flies: *Haematobia irritans.* The product protects the animals against reinfestations with: - *Nematodirus helvetianus* for 14 days. - *Trichostrongylus axei* for 21 days. - *Dictyocaulus viviparus,Haemonchus placei,Cooperia oncophora, Cooperia punctata, Cooperia surnabada, Oesophagostomum radiatum* and *Ostertagia ostertagi* for 28 days. The duration of persistent efficacy can be variable for *Cooperia spp* and *H. placei* 14 days after treatment in particular in young and lean animals at the time of treatment.

MODULE 2

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

MODULE 3

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PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	31/01/2018
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, EE, EL, ES, HU, IE, IT,LT,LV, NL, PL, PT, RO, SK, 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 5 mg/ml of eprimomectin as active substance and butylhydroxytoluene, all-rac-alpha-tocopherol and propylene glycol dicaprylocaprate 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 eprimomectin, an established active substance. 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

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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 test product is bioequivalent to the reference product, EPRINEX POUR ON 5 MG/ML marketed by MERIAL. An exemption from the requirement to provide a bioequivalence study was accepted as formulations of the tested and the reference products are similar.

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

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

Toxicological Studies

As this is a generic application according to Article 13, and bioequivalence with a 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

The applicant has not provided a user safety assessment which is acceptable given the type of application (Article 13) and because the tested product and the reference product have similar formulations.

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

Environmental Risk Assessment

The product is an ecto/endoparasiticide for cattle and the target animals are reared on pasture. Therefore a phase II has been 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 to be complete and acceptable.

Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Water solubility	OECD 105	13.5 mg/l (20°C)	
Physical-chemical properties			
Study type	Test protocol	Result	Remarks
Dissociation constants in water pKa	OECD 112	pKa = 7.16 ± 0.6 (20°C)	
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 123	$logK_{ow}$ = 4.59 (25°C)	

Environmental fate

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Soil Adsorption/Desorption	OECD 106	Mean Koc = 2956	Mean from 6 reliable Koc values coming from a proprietary study (3 values) and from a scientific publication (3 values)
Aerobic and Anaerobic Transformation in Soil	OECD 307	DT50, $_{20°C.,SFO}$ = 142, 125, 111, 152 on RefeSol 02-4, LUFA 2.2, LUFA 2.3 and LUFA 6s soils respectively $DT_{50, 20°C. geo. mean}$ = 131.6	DT50 values have been calculated based on the total extractable amount of radioactivity by LSC (major metabolites are handled as parent active substance).

Effect studies					
Study type	Test protocol	Endpoint	Result	Unit	Remarks*
Algae growth inhibition test/ Desmodesmus subspicatus	OECD 201	EC50	>5.29	mg/l	Limit test, geometric mean measured concentration
Daphnia sp. immobilisation	OECD 202	EC50	0.13	µg/l	Static test, geometric mean measured concentration
Daphnia magna, reproduction	OECD 211	NOEC	>59.71	ng/l	Tier B, semi-static test, TWM of the measured concentrations.

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Fish, acute toxicity/ Oncorhynchus mykiss	OECD 203	LC50	136.7	µg/l	Static test, nominal concentration
Earthworm reproduction	OECD 222	NOEC	5	mg/kg	
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	2.73	µg/kg	Tier B, static test, measured concentrations
Dung fly larvae/ Scathophaga stercoraria L.	OECD 228	EC50	0.339	mg/kg	
Dung beetle larvae/ Aphodius constans	OECD GD 122	EC50	2.12	mg/kg	
Bioaccumulation in fish/ Oncorhynchus mykiss	OECD 305	BCF_{SSL}	1.09	l/kg	flow-through conditions

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 (direct excretion)	0.0059 µg/L	0.0292 µg/L	4.89
Sediment (direct excretion)	0.27 µg/kg	1.678 µg/kg	6.15
soil	0.5 mg/kg	0.0034 mg/kg (plateau)	0.007
dung	0.0039 mg/kg (dung fly larvae)	0.47 mg/kg	120

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Risk mitigation measures

As RQ are higher than 1 for surface water and dung compartments, the following information on environmental properties has been included in the product literature:

4.5 iii) Other precautions

Eprinomectin is very toxic to aquatic organisms, is persistent in soils and may accumulate in sediments.

Faeces containing eprinomectin excreted onto pasture by treated animals may temporarily reduce the abundance of dung feeding organisms. Following treatment of cattle with the product, levels of eprinomectin that are potentially toxic to dung fly species may be excreted over a period of more than 4 weeks and may decrease dung fly abundance during that period. In case of repeated treatments with eprinomectin (as with products of the same anthelmintic class) it is advisable not to treat animals every time on the same pasture to allow dung fauna populations to recover.

Eprinomectin is inherently toxic to aquatic organisms. The product should be used only according to the label instructions. Based on the excretion profile of eprinomectin when administered as the pour-on formulation, treated animals should not have access to watercourses during the first 7 days after treatment.

Environmental properties

Like other macrocyclic lactones, eprinomectin has the potential to adversely affect non-target organisms. See section 4.5 iii) other precautions. .

PBT assessment

A bioaccumulation study in fish according to OECD 350 has been performed.
Bioaccumulation factor (BCF) is less than 1000.

The active is considered as very persistent but as not bioaccumulative.

III.B Residues documentation

Residue Studies

As the candidate product has a similar formulation than the reference product, contains same excipients in similar amounts and is indicated in the same species at the same regimen dosage, the results of residue studies are not required.

MRLs

a. active substances

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

EPRINOMECTIN (ADI: 5 µg/kg)

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Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Eprinomectin B1a	Bovine	50 µg/kg 250 µg/kg 1 500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	No entry	Antiparasitic agents/ Agents against endo and ectoparasites	37/2010 of 22.12.2009

b. excipients

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

Excipient	MRL status	ADI
Butylhydroxytoluene	Table 1, no MRL required	-
All rac Alpha Tocopherol	Table 1, no MRL required	-
Propylene glycol dicaprylocaprate	Table 1, no MRL required	

Withdrawal Periods

The withdrawal periods of the reference product will be applied to the tested product: Meat and offal: 15 days. Milk: zero hours.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has not provided a tolerance study which is acceptable because the tested product and the reference product are bioequivalent and their formulations are similar.

IV.B Clinical Studies

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 of the tested product are based on the reference product documentation.

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.

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