Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
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(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Eprinovet 5mg/ml

Pour-on solution for beef and dairy cattle

25 March 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0314/001/DC
Name, strength and pharmaceutical form	Eprinovet 5 mg/ml pour-on solution for beef and dairy cattle
Applicant	Laboratorios Calier S.A C/ Barcelonès, 26 (Pla de Ramassà) 08520 Les Franqueses del Vallès, (Barcelona) Spain
Active substance(s)	Eprinomectin
ATC Vetcode	QP54AA04
Target species	Cattle (beef and dairy cattle)
Indication for use	Treatment of infections by the following parasites sensitive to eprinomectin: **Gastrointestinal Roundworms (adults and L4 larval stages)** *Ostertagia ostertagi* (including inhibited L4 larval stages) *Ostertagia (Skrjabinagia) lyrata* (adult) *Ostertagia spp.* *Haemonchus placei* *Trichostrongylus axei* *Trichostrongylus colubriformis** *Trichostrongylus spp.* *Cooperia spp. (*including inhibited L4 larval stages*)* *Cooperia oncophora* *Cooperia punctata* *Cooperia pectinata* *Cooperia surnabada* *Bunostomum phlebotomum* *Nematodirus helvetianus* *Oesophagostomum radiatum* *Oesophagostomum spp.* (adult) *Trichuris spp.* (adult)

	* Rare in cattle **Lungworms** *Dictyocaulus viviparus* (adult and L4 larval stages) **Warbles (parasitic stages)** *Hypoderma bovis* *Hypoderma lineatum* **Lice** *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* **Biting lice** *Bovicola bovis* **Mange mites** *Chorioptes bovis* *Sarcoptes scabiei var. bovis* **Horn flies** *Haematobia irritans* Prolonged efficacy up to 7 days after application The product prevents infections with *Ostertagia spp.*, *Oesophagostomum radiatum* and *Dictyocaulus viviparus* for up to 28 days after treatment, infections with *Cooperia spp.* and *Trichostrongylus spp*. for up to 21 days after treatment, and infections with *Haemonchus placei* and *Nematodirus helvetianus* for up to 14 days after treatment. 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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 March 2020
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	BE, EL, ES, FR, IT, NL, PT, RO

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; any 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 product, Eprinovet 5mg/ml Pour-on solution for beef and dairy cattle, is a generic to the German reference product “Eprinex Pour-on 5 mg/ml Lösung zum Auftragen auf die Haut von Rindern” with the marketing authorisation holder Boehringer Ingelheim Vetmedica GmbH. The application for the reference product was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains the active substance eprinomectin (5 mg/ml) and the excipients butylhydroxytoluene, all-rac-α-tocopherol and propylene glycol octanoate decanoate.

The container/closure system consists of translucent high-density polyethylene (HDPE) bottles equipped with an integrating dosing system and two openings sealed with a polyethylene seal closed with a polypropylene screw cap (1L) or white high-density polyethylene (HDPE) bottles sealed with a wax/polyolefin seal and closed with a white polypropylene screw cap (2.5 and 5L). 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 at 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 eprinomectin an established active substance described in the US 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.

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

D. Control on intermediate products

Not applicable

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

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.

The claim of a 18 months stability after broaching is based on the demonstration of stability for a batch broached and stored 18 months at 25°C.

G. Other Information

Not applicable

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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

Warnings and precautions as listed in the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users.

III.A Safety Testing

User Safety

A comprehensive user safety assessment in compliance with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) and with the Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014) was provided. Relevant issues including hazard identification, determination of toxicological reference values (TRV), exposure, qualitative and quantitative risk assessment and risk communication are addressed.
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:

The initial predicted environmental concentration in soil (PECsoil, initial = 2.91 µg/kg and 2.09 µg/kg for intensively reared and pasture animals, respectively) is less than 100 µg/kg.

A Phase II ERA is required as the product is an endoparasiticide for cattle and the target animals are reared on pasture.

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	21.9 mg/l	
Vapour pressure	OECD 104	6.53×10^{-16} Pa at 20 °C	
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 117	logK_{ow} = 5.4	

Environmental fate			
Soil Adsorption / Desorption	OECD 106	Koc =1000 (silt loam, pH 8.2, 25% clay, Corg 1.57%) Koc =2750 (silt loam, pH 7.1, 20% clay, Corg 0.75%) Koc =4790 (sandy loam, pH 6.1, 5% clay, Corg 0.11%) K_d = 21.4 (silt loam)	

Environmental fate			
		K_d = 15.7 (silt loam) K_d = 6.4 (sandy loam)	
Aerobic and Anaerobic Transformation in Soil	OECD 307	***Parent:*** DT50, $_{20°C, DFOP}$ = 19.0 d (RefeSol 02-A, silt loam) DT50, $_{20°C, DFOP}$ = 18.1 d (LUFA 2.2, loamy sand) DT50, $_{20°C, SFO}$ = 40.1 d (LUFA 2.3, sandy loam) DT50, $_{20°C, SFO}$ = 40.2 d (LUFA 6S, clay) $DT_{50, 12°C. geo. mean}$ = 58.2 d (27.3 d 20°C) ***Total extractable radioactivity:*** DT50, $_{20°C, SFO}$ = 142.0 d (RefeSol 02-A, silt loam) DT50, $_{20°C, SFO}$ = 125.0 d (LUFA 2.2, loamy sand) DT50, $_{20°C, SFO}$ = 111.0 d (LUFA 2.3, sandy loam) DT50, $_{20°C, SFO}$ = 152.0 d (LUFA 6S, clay) $DT_{50, 12°C. geo. mean}$ = 280.8 d (131.6 d 20°C) ***Transformation product 'Unkown signal 1':*** DT50, $_{20°C, SFO}$ = 34.0 d (RefeSol 02-A, silt loam) DT50, $_{20°C, SFO}$ = 34.9 d (LUFA 2.2, loamy sand) DT50, $_{20°C, SFO}$ = 30.0 d (LUFA 2.3, sandy loam) DT50, $_{20°C, SFO}$ = 33.0 d (LUFA 6S, clay) $DT_{50, 12°C. geo. mean}$ = 70.3 d (32.9 d 20°C)	

Environmental fate			
		Transformation products >10%: *Unknown signal 1* % non-extractable residues (NER): 24 – 31%	

Effect studies					
Study type	**Test protocol**	**Endpoint**	**Result**	**Unit**	**Remarks***
Algae and or cyanobacteria, growth inhibition test / *Pseudokirchneriella subcapitata*	OECD 201	EC50	>11200	µg/l	*Both endpoints yield and growth rate*
Daphnia sp. immobilisation	OECD 202	EC50	1.67	µg/l	
Daphnia magna, reproduction	OECD 211	NOEC	0.173	µg/l	*Tier B*
Fish, acute toxicity / *Oncorhynchus mykiss*	OECD 203	LC50	503.0	µg/l	
Soil microorganisms: Nitrogen transformation test (28 days)	OECD 216	%effect	7.78 / 4.88%	%	Trigger value: 25% deviation from the control
Terrestrial Plants, growth test	OECD 208	EC50	28900.0 dry weight (*Lolium perenne*)	µg/kg	*Brassica napus* *Glycine max* *Cucumis sativus* *Solanum lycopersicum* *Lolium perenne* *Allium cepa*
Earthworm reproduction / *Eisenia fetida*	OECD 222	NOEC	>16000.0	µg/kg	dry weight

Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC or EC10	2.73 11.7 (normalised to 10% C_{org})	µg/kg	*Tier B*
Dung fly larvae / *Scathophaga stercoraria*	OECD 228	EC50	42.36 355.0	µg/kg	wet weight dry weight
Dung beetle larvae / *Aphodius constans*	OECD GD 122	EC50	325.9 970.0	µg/kg µg/kg	wet weight dry weight
Bioaccumulation in fish/*Oncorhynchus mykiss*	OECD 305 Type: aquatic exposure	BCF	Low conc.: BCFss 1.93 BCFss 1.12 (lipid normalised) High conc.: BCFss 1.91 BCFss 1.09 (lipid normalised) BCFk 1.91 BCFkLG 1.14	l/kg	

Risk characterisation

The predicted environmental concentration (PEC) for each compartment and their refinement 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)

Predicted no effect concentrations (PNEC) were calculated under consideration of the assessment factors (AF) in the respective guidelines, and compared to refined PEC values. The resulting risk quotients (RQ) for the different compartments are summarised in the following table:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	0.0173 µg/l	0.098 µg/l	5.66
groundwater	0.000167 µg/l	0.000002 µg/l	0.0012
sediment	1.17 µg/kg dwt	5.06 µg/kg dwt	4.3
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
soil	289.0	2.09 µg/kg	0.0072
dung	0.000424 µg/kg	350.0 µg/kg	825.5

The results of the assessment indicate a risk for the surface water, sediment and dung compartment.

Therefore, risk mitigation measures for the aquatic and sediment compartment, based on the excretion profile of eprinomectin, are established, i.e. treated animals should not have access to watercourses during the first 7 days after treatment.

However, appropriate risk mitigation measures for dung fauna in accordance with the Reflection paper on risk mitigation measures related to the environmental risk assessment of veterinary medicinal products (EMA/CVMP/ERAWP/409328/2010) do not exist. Hence, solely information on environmental properties and warning sentences in terms of the toxicity to dung fauna are included in the product information.

The following risk mitigation measures and information on environmental properties are included in the SPC und reflected accordingly in the package leaflet.

SPC

“4.5. Special precautions for use

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 fauna 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.

5.3. Environmental properties

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

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	1.91	not B
Persistence	$DT_{50,\ soil,\ 12\ °C}$	324.4 d	vP
Toxicity	NOEC or CMR	0.173	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted because the candidate product is considered to have essential similarity with the reference product.

MRLs

The active ingredient eprinomectin is listed in Table 1 of the Annex to Commission Regulation (EU) No. 37/2010 with the following entry:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Eprinomectin	Eprinomectin B1a	All ruminants	50 µg/kg 250 µg/kg 1500 µg/kg 300 µg/kg 20 µg/kg	Muscle Fat Liver Kidney Milk	NO ENTRY	Antiparasitic agents/Agents acting against endo- and ectoparasites

Withdrawal Periods

Based on the MRLs for the active substances, on the established withdrawal periods for the reference product, the applicant proposes the following withdrawal periods:

Cattle:	Meat and offal:	15 days
	Milk:	Zero hours

IV. CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13(3), and bioequivalence with the reference product has been demonstrated, efficacy and target animal safety studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13(3), no target animal tolerance studies were conducted.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography information provided suggests that there are no concerns on resistances for both eprinomectin and the class of macrocyclic lactones.
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.

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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

<None>