



Veterinary
Medicines
Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

DECENTRALISED PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

EpriMole 5 mg/ml Pour-on Solution for Beef and Dairy Cattle

Date Created: 21st December 2016

**PuAR correct as of 26/06/2018 when RMS was transferred to IE.
Please contact the RMS for future updates.**

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0519/001/DC																																																																								
Name, strength and pharmaceutical form	EpriMole 5 mg/ml Pour-on Solution for Beef and Dairy Cattle																																																																								
Applicant	Merial Animal Health Limited PO Box 327, Sandringham House Harlow Business Park Harlow Essex CM19 5TG																																																																								
Active substance(s)	Eprinomectin																																																																								
ATC Vetcode	QP54AA04																																																																								
Target species	Cattle (beef and dairy cattle)																																																																								
Indication for use	<p>Indicated for the treatment and control of the following parasites:</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left;">PARASITE</th> <th style="text-align: center;">ADULT</th> <th style="text-align: center;">L4</th> <th style="text-align: center;">Inhibited L4</th> </tr> </thead> <tbody> <tr> <td colspan="4">Gastrointestinal</td> </tr> <tr> <td colspan="4">Roundworms:</td> </tr> <tr> <td><i>Ostertagia</i> spp.</td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>O. lyrata</i></td> <td style="text-align: center;">◆</td> <td></td> <td></td> </tr> <tr> <td><i>O. ostertagi</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> </tr> <tr> <td><i>Cooperia</i> spp.</td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> </tr> <tr> <td><i>C. oncophora</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>C. pectinata</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>C. punctata</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>C. surnabada</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>Haemonchus placei</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>Trichostrongylus</i> spp.</td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>T. axei</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>T. colubriformis</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>Bunostomum phlebotomum</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>Nematodirus helvetianus</i></td> <td style="text-align: center;">◆</td> <td style="text-align: center;">◆</td> <td></td> </tr> <tr> <td><i>Oesophagostomum</i></td> <td style="text-align: center;">◆</td> <td></td> <td></td> </tr> </tbody> </table>	PARASITE	ADULT	L4	Inhibited L4	Gastrointestinal				Roundworms:				<i>Ostertagia</i> spp.	◆	◆		<i>O. lyrata</i>	◆			<i>O. ostertagi</i>	◆	◆	◆	<i>Cooperia</i> spp.	◆	◆	◆	<i>C. oncophora</i>	◆	◆		<i>C. pectinata</i>	◆	◆		<i>C. punctata</i>	◆	◆		<i>C. surnabada</i>	◆	◆		<i>Haemonchus placei</i>	◆	◆		<i>Trichostrongylus</i> spp.	◆	◆		<i>T. axei</i>	◆	◆		<i>T. colubriformis</i>	◆	◆		<i>Bunostomum phlebotomum</i>	◆	◆		<i>Nematodirus helvetianus</i>	◆	◆		<i>Oesophagostomum</i>	◆		
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spp.		
<i>O. radiatum</i>	◆	◆
<i>Trichuris</i> spp.	◆	
Lungworm:		
<i>Dictyocaulus viviparus</i>	◆	◆
Warbles (parasitic stages)		
<i>Hypoderma bovis</i>		
<i>H. lineatum</i>		
Mange mites		
<i>Chorioptes bovis</i>		
<i>Sarcoptes scabiei</i> var. <i>bovis</i>		
Lice		
<i>Linognathus vituli</i>		
<i>Haematopinus eurysternus</i>		
<i>Damalinia bovis</i>		
<i>Solenopotes capillatus</i>		
<p>While mite and louse numbers decline rapidly following treatment, due to the feeding habits of the parasites, in some cases several weeks may be required for complete eradication.</p>		
PROLONGED ACTIVITY		
Applied as recommended, the product controls reinfections with:		
Parasite*	Prolonged Activity	
<i>Dictyocaulus viviparus</i>	Up to 28 days	
<i>Ostertagia</i> spp.	Up to 28 days	
<i>Oesophagostomum radiatum</i>	Up to 28 days	
<i>Cooperia</i> spp.	Up to 21 days	
<i>Trichostrongylus</i> spp.	Up to 21 days	
<i>Haemonchus placei</i>	Up to 14 days	
<i>Nematodirus helvetianus</i>	Up to 14 days	
<p>*The following parasite species are included within each of the relevant genera: <i>Ostertagia ostertagi</i>, <i>O. lyrata</i>, <i>Cooperia oncophora</i>, <i>C. punctata</i>, <i>C. surnabada</i>, <i>Trichostrongylus axei</i>, <i>T. colubriformis</i>.</p>		

	<p>For best results the veterinary medicinal product should be part of a programme to control both internal and external parasites of cattle based on the epidemiology of these parasites.</p>
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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

www.gov.uk/check-animal-medicine-licensed

MODULE 3

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	10/10/2016
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	BE, BG, HR, CZ, DE, IE, IT, LU, NL, PL, PT, RO, SK, ES

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, submitted in accordance with Article 13 (1) of Directive EC 2001/82/EC as amended. The reference product is Eprinex Pour-on for Beef and Dairy Cattle (Eprinomectin) authorised in the UK since July 1997. Bioequivalence was accepted based on 7.1.d) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2) as the product is identical in formulation to the reference product.

The target species are beef and dairy cattle. The product is indicated for the treatment and control of parasites including gastrointestinal roundworms, lungworm, warbles, mange mites and lice. For a full description of the parasite species the product is indicated for please refer to Section 4.9 of the SPC¹. For best results the product should be part of a programme to control both internal and external parasites of cattle based on the epidemiology of these parasites. The product is for topical administration only.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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.¹ 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 efficacy² of the product was demonstrated according to the claims made in

¹ SPC – Summary of product Characteristics.

² Efficacy – The production of a desired or intended result.

the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 5.0 mg of eprinomectin and excipients butylhydroxytoluene (E321) and propylene glycol octanoate decanoate.

The container consists of a HDPE bottle containing 250 ml or 1 litre of product, or a back-pack containing 2.5 litre or 5 litre of product. The closure system consists of an induction sealed tamper evident HDPE screw on cap. The cap contains a screw on dosing device capable of delivering measured amounts of the product. The 250 ml bottle uses a 25 ml dispenser and the 1 litre bottle uses a 50 ml dispenser. The dispenser is a screw-on, squeeze and pour measuring chamber. The 2.5 litre and 5 litre back-packs are designed for use with a suitable automatic dispensing gun.

The choice of the formulation and the absence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple solubilisation process. The excipients and active substance are mixed together to form a solution and then filtered into a holding tank. The solution is then transferred to filling equipment from which the bottles are filled, capped, and induction sealed. The bottles are then labelled and packaged into cartons.

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

II.C. Control of Starting Materials

The active substance is eprinomectin, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice. The specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Both the excipients, butylated hydroxytoluene and propylene glycol octanoate decanoate are described in the European Pharmacopoeia.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product include: eprinomectin assay, appearance, clarity and related substances.

II.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. A re-test period for the active substance of 24 months, when stored in the commercial packaging at 2-8 °C and protected from light.

Stability data were provided confirming that that the product is stable in-use once the bottle has been opened and therefore an in-use shelf life was not considered necessary.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after first opening the immediate packaging: see expiry date.
Keep the bottle in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACOTOXICOLOGICAL)

As this is a generic application according to Article 13 (1) and bioequivalence with a reference product has been established, results of pharmacological and toxicological tests are not required. Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment, and to consumers.

III.A Safety Documentation

User Safety

The product is qualitatively and quantitatively identical to the reference product with the same indication, route of administration and dose rate. Therefore, the applicant proposed user safety warning as for the reference product which is considered acceptable.

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

- This product may be irritating to skin and eyes and may cause hypersensitivity.
- Avoid skin and eye contact with the product during treatment and when handling recently treated animals.
- Individuals with known hypersensitivity to the active substance or to any of the excipients should avoid contact with the product.
- Users should wear rubber gloves, boots and a waterproof coat when applying the product.
- If accidental eye exposure occurs, flush eyes immediately with water and seek medical advice if irritation persists.
- If accidental skin contact occurs, wash the affected area immediately with soap and water.
- Should clothing become contaminated, remove as soon as possible and launder before re-use.
- This product may be toxic after accidental ingestion. Avoid accidental ingestion of the product by hand to mouth contact.
- Do not smoke, eat or drink while handling the product.
- In the event of ingestion, wash out mouth with water and seek medical advice.
- Wash hands after use.

Environmental Safety

An environmental risk assessment (ERA) was conducted in accordance with VICH³ and CVMP⁴ guidelines.

Phase I

As the product is an ectoparasiticide used on pasture animals, a Phase II ERA was required (Question 16 VICH decision tree).

Phase II Tier A

A Phase II Tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines; including studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substance eprinomectin.

Physicochemical properties

Study type	Guideline	Result	Remarks
Water solubility	OECD 105	3.5(±0.2) µg/l (pH 7.26±0.09)	Published data
Dissociation constants in water pKa	OECD 112	No pKa between 3 and 10	
UV-Visible Absorption Spectrum	OECD 101	244 nm	
Melting Point/Melting Range	OECD 102	163 - 166°C	
Vapour Pressure	OECD 104	4 ±1 x 10 ⁻⁶ torr (22.5±0.9°C) Equiv. to 4.3 x 10 ⁻⁴ Pa	
n-Octanol/Water Partition Coefficient logP _{ow}	OECD 123	- pH 4: 5.51 - pH 7.1: 5.61 - pH9: 5.56	Bespoke study logP _{ow} >4, indicates bioaccumulative potential

³ VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

⁴ Committee for Medicinal Products for Veterinary Use

Environmental fate

Study type	Guideline	Result	Remarks
Soil Adsorption/ Desorption	OECD 106	K _{oc} : 1000 to 9208 (6 soils) Geometric Mean = 3710	Published Slightly mobile in soil
Aerobic and Anaerobic Transformation in Soil	OECD 307	A range of degradation rates were observed in four soil types DT ₅₀ s: 10.9 to 67 days at 20±2°C (geometric mean: 28 days) For PBT assessment (worst case) DT ₅₀ : >120 days at 12°C using Arrhenius equation	Bespoke study Persistent in soil (at 12°C)

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test <i>Pseudokirchneriella subcapita</i>	OECD 201	EC ₅₀ (72 hour)	>3.4 mg/l
<i>Daphnia</i> sp. immobilisation	OECD 202	EC ₅₀ (48 hour)	0.45 µg/l
Fish, acute toxicity <i>Lepomis macrochirus</i>	OECD 203	LC ₅₀ (96 hour)	0.37 mg/l
Earthworm subacute <i>Eisenia fetida</i>	OECD 222	NOEC	19 mg/kg
Dung fly larvae <i>Musca autumnalis</i>	OECD 228	EC ₅₀ NOEC	41.64 µg/kg 26.62 µg/kg
Dung beetle larvae <i>Onthophagus gazelle</i> (Fabricus) <i>Euoniticellus intermedius</i> (Reiche)	OECD draft	NOEC	64.7 µg/kg

Exposure assessment

Predicted exposure concentration (PEC) values for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Outputs	Value		Source
	Intensive	Pasture	
PEC _{soil} (µg/kg)	2.91 µg/kg	2.09 µg/kg	CVMP Equation 1, 2
PEC _{dung} (µg/kg)	n/a	79 300 µg/kg	CVMP Equation 8
PEC _{groundwater} (µg/l)	0.0111	0.0080	CVMP Equation 32 - 35
PEC _{surface water} (µg/l) indirect	0.0037 µg/l	0.0027 µg/l	CVMP Equation 31, 36
PEC _{sediment} (µg/l) indirect	0.72 µg/kg	0.50 µg/kg	CVMP Equation 16 - 18, 37
PEC _{surface water} (µg/l) direct	n/a	0.52 µg/l	CVMP Equation 44
PEC _{sediment} (µg/l) direct	n/a	2.26 µg/kg	CVMP Equation 45

As the initial PEC_{groundwater} is below the threshold of 0.1 µg/l, further refinement was not necessary.

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the worst case PEC values derived above, as follows.

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	EC ₅₀ (72 hour)	100	34 µg/kg	0.52 µg/l	<1
<i>Daphnia</i> sp. immobilisation	EC ₅₀ (48 hour)	100	0.00045 µg/l		>1
Fish, acute toxicity	LC ₅₀ (96 hour)	1000	0.37 µg/l		<1
Earthworm reproduction	NOEC	10	1900 µg/kg	2.91 µg/kg	<1
Dung fly larvae	EC ₅₀	100	0.4164 µg/kg	79 300 µg/kg	>1

As the RQ values for *Daphnia*, fish and dung fauna were >1, further assessment of the environmental risk and consideration of risk mitigation measures were required.

Phase II Tier B and risk mitigation

At Tier B, findings from a chronic *Daphnia* study in accordance with OECD 211 were presented and a NOEC value from the existing fish study was used to calculate a revised PNEC for comparison with the PEC as shown below.

Test species	End point	AF	PNEC	PEC	RQ
<i>Daphnia magna</i> reproduction	NOEC (21 day) 0.028 µg/kg	10	0.0028 µg/l	0.52 µg/l	>1
Fish, juveniles	NOEC 0.14 µg/kg	10	0.014 µg/l		<1

At Tier B the RQ value for *Daphnia* remained above 1; indicating a risk.

Eprinomectin was deemed to not fulfil the bioaccumulation criterion and therefore, is not considered a PBT substance.

As a result, appropriate risk mitigation and environment properties wording was required, as follows:

Other precautions

- Eprinomectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.
- The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of eprinomectin (and products of the same anthelmintic class) in cattle.
- The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for two to four weeks after treatment.

Environmental properties

- Like other macrocyclic lactones, eprinomectin has the potential to adversely affect non-target organisms.
- Following treatment, excretion of potentially toxic levels of eprinomectin may take place over a period of several weeks.
- Faeces containing eprinomectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.
- Eprinomectin is very toxic to aquatic organisms and may accumulate in sediments.

Disposal advice

- Dangerous to fish and aquatic life.
- Do not contaminate surface waters or ditches with the product or used container.
- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

It is concluded that the risk to the environment from the use of the product is acceptable when used as recommended in the SPC, following all precautions.

III.B.2 Residues documentation

Residue Studies

As essential similarity to the reference product has been accepted, no residues depletion studies have been provided, which is acceptable. The proposed methods of administration and dosage regime for use in the food producing target species are identical to the reference product and therefore, the same withdrawal period is proposed and considered acceptable.

Withdrawal Periods

This product is quantitatively and qualitatively identical to the reference product with the same indications, administration route and dose rate. Therefore the

same withdrawal period to that of the reference product, of 15 days for meat and offal is justified.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1) and bioequivalence with a reference product has been established on the basis of being of identical formulation to the reference product ((7.1.d) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/00-Rev 2)), efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

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 benefit/risk profile of the product is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed