Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bovimox 5 mg/ml Pour-on Solution for Cattle
Moxodex 5 mg/ml Pour-on Solution for Cattle
Moxidectin EU Pharmaceuticals 5 mg/ml Pour-on Solution for Cattle
Ridamec 5 mg/ml Pour-on Solution for Cattle
Unomox 5 mg/ml Pour-on Solution for Cattle

Date Created: July 2020

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Bovimox 5 mg/ml Pour-on Solution for Cattle Moxodex 5 mg/ml Pour-on Solution for Cattle Moxidectin EU Pharmaceuticals 5 mg/ml Pour-on Solution for Cattle Ridamec 5 mg/ml Pour-on Solution for Cattle Unomox 5 mg/ml Pour-on Solution for Cattle
Applicant	EU Pharmaceuticals Ltd 37 Geraldine Road London SW18 2NR
Active substance	Moxidectin
ATC Vetcode	QP54AB02
Target species	Cattle
Indication for use	Infections of cattle with parasites sensitive to moxidectin. For the treatment of infections caused by: **- Adult and larval gastro-intestinal nematodes:** *Haemonchus placei* *Ostertagia ostertagi* (including inhibited larvae) *Trichostrongylus axei* *Nematodirus helvetianus* *Cooperia oncophora* *Cooperia punctata* (adults) *Oesophagostomum radiatum* (adults) *Bunostomum phlebotomum* (adults) **- Adult respiratory tract nematode**

	Dictyocaulus viviparous **- Warbles (migrating larvae)** *Hypoderma bovis* *Hypoderma lineatum* **- Lice** *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* *Bovicola bovis (Damalinia bovis)* **- Mange Mites** *Sarcoptes scabiei* *Psoroptes ovis* *Chorioptes bovis* **- Horn Flies** *Haematobia irritans* The product has a persistent effect in preventing against reinfection by: *Ostertagia ostertagi* for 5 weeks *Dictyocaulus viviparus* for 6 weeks.

MODULE 2

The Summary of Product Characteristics (SPC) for these products are 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 applications	Generic application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedures	24/06/2020

I. SCIENTIFIC OVERVIEW

These were applications for generic products, submitted in accordance with Article 13 (1) of Directive 2001/82/EC as amended. The reference product is Cydectin 0.5% w/v Pour-On Solution for Cattle. The reference product was authorised in UK in January 1997.

The indications are as described above, and administration of the products is 500 µg moxidectin/kg bodyweight, which equates to 1 ml per 10 kg. The products are applied as a single topical application, administered along the midline of the back of the animal from withers to tailhead.

The products are 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 products can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The products are 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 SPCs. The efficacy [2] of the product was demonstrated according to the claims made in the SPCs. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contains 5 mg/ml moxidectin, and the excipients aromatic solvent, myristal propoxylate propionic ester, polybutene polymer, medium chain triglycerides,2-tert-buthylhydroquinone and butylhydroxyanisole (E320).
The container/closure system consists of fluorinated HDPE white containers with polypropylene tamper evident seals and screw fit caps placed in a carton. 1 litre 'squeeze-measure-pour' container. 2.5 litres, 3 litres or 5 litres white flexi flat-bottomed backpacks. Cartons contain 2 x 3 litres or 1 litre + 5 litres.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of preservative are justified.

The products are 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 products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of appropriate heating and mixing of the ingredients, followed by filling into packs.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is moxidectin, an established active substance described in the European Pharmacopoeia (Ph. Eur). 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.

Certificates of Suitability were provided.

Excipients described in the Ph. Eur are: butylhydroxyanisole, triglycerides, medium chain and nitrogen low oxygen. Those not monographed in a pharmacopoeia but for which specifications have been provided are: polybutene

polymer (Indopol H-1900), myristal propoxylate propionic ester (Crodamol PM) and aromatic solvent (Solvesso 100).

Suitable documentation was provided with regard to packaging.

II.C.4. Substances of Biological Origin

Moxidectin used in the manufacture of Moxidectin 5 mg/ml Pour on is of vegetative and animal origin, however it is not derived from an animal origin that is susceptible to TSE. It is from "other animal origin" silkworm pupa powder, and therefore the 'Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathies agents via human and veterinary medicinal products does not apply.

No other materials of animal origin are used in the manufacture of the finished product or of the starting materials.

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 are those for: appearance, identification of active substance and antioxidant, key excipient assay, fill volume and microbiological quality.

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.

G. Other Information

Shelf life of the veterinary medicinal products as packaged for sale: 2 years.

Shelf life after first opening the immediate packaging: 6 months.

Do not store above 25°C. Protect from frost.

Shake vigorously before use.

Keep the container in the outer carton in order to protect from light.

Store the container in an upright position

Fluorinated HDPE white containers with polypropylene tamper evident seals and screw fit caps placed in a carton

1 litre 'squeeze-measure-pour' container

2.5 litres, 3 litres or 5 litres white flexi flat-bottomed backpacks

Cartons containing 2 x 3 litres or 1 litre + 5 litres.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the applications, pharmacological and toxicological studies were not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:,

- This product can cause skin and eye irritation. Avoid direct contact with skin and eyes. Do not smoke, eat or drink when handling this product.
- Wear impermeable rubber gloves and protective clothing during use.
- Wash hands or any exposed area after use.
- In the event of eye contact, flush the eye with copious amounts of clean water and seek medical advice

Environmental Safety

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

Phase I:

Although the PECsoil calculation was below the trigger threshold of 100 µg/kg, the product is a parasiticide used in pasture animals and 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 physico-chemical properties, environmental fate and effects. Studies were carried out using the active substance moxidectin, unless indicated otherwise.

Physico-chemical properties

Study type	**Guideline**	**Result**
Water solubility	OECD 105	31.4 mg/l
Dissociation constants in water pKa	OECD 112	A very weak base with a pKa of <2
UV-Visible Absorption Spectrum	OECD 101	UV maxima: 242 in acetonitrile
Melting Point/Melting Range	OECD 102	145 – 154°C
Vapour Pressure	OECD 104	4.69 x $10^{-2.0}$
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	>6 5.4

Environmental fate

Study type	**Guideline**	**Result**
Soil Adsorption/Desorption	OECD 106	A mean K_{oc} of 18 850 l/kg was calculated and the moxidectin can be classified as 'immobile'

Study type	Guideline	Result
Aerobic and Anaerobic Transformation in Soil	OECD 307	Half-life ranged from 13.8 to 87.3 days at 20°C and showed that moxidectin may be persistent in soil.

Environmental effects

Study type	Guideline	Endpoint
Algae, Growth Inhibition ***Pseudokirchneriella subcaptiata Hindak***	**OECD 201**	**EC50** >100 mg/l (nominal) or >29.1 mg/l (actual). Acceptable.
Daphnia sp. Immobilisation ***Magna straus***	**OECD 202**	**EC50** 0.263 µg/l. Acceptable.
Fish, acute toxicity ***Oncorhynchus mykiss***	**OECD 203**	**LC50** *0.849 µg/l (nominal value, geometric mean), considered acceptable. The NOEC for mortality at 96 hours was 600 µg/l.*
Earthworm/Species subacute/ Reproduction ***Eisenia fetida***	**OECD 220/222**	**NOEC** 1.03 mg/kg soil. Acceptable
Dung fly larvae ***Musca autumnalis***	**OECD 228**	1.47 mg test item/kg dung dry weight. Acceptable

Study type	Guideline	Endpoint
Dung beetle larvae (Published literature)	**OECD draft**	**EC50** 3.63-5.40 $mg/kg_{dw\ from}$ two studies. Dung fly results, (more sensitive species), were accepted as key result for all dung fauna.

Exposure assessment (Predicted exposure concentration)
PEC value 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. (Pasture animals considered as most significant).

Target animal	PEC		
	$Soil_{initial}$ (µg/kg)	**Groundwater (µg/l)**	**Surfacewater (µg/l)**
Pasture animals			(Direct excretion onto waterways)
Dairy cow	1.40	0.0011	0.350
Beef cattle	2.09	0.0016	0.523
Intensively reared animals			
Calf	2.86		
Cattle (0 - 1 years)	2.52		
Cattle (>2 years)	2.91		
Dairy cow	1.61		

Risk Characterisation (Risk Quotient)

Using the assessment factors (AF) in VICH guidelines predicted no effect concentrations (PNEC) were calculated and compared with the PEC values for each target animal as follows:

	PEC	PNEC	RQ
Soil			
Dung fly larvae, 19 d	12.7 mg/kg dung wet weight	0.0021 mg/kg dung wet weight	**6048**
Dung beetle larvae	12.7 mg/kg dung wet weight	0.0145 mg/kg dung wet weight	**876**
Earthworm reproduction, 56 days	0.00291 mg/kg soil dry weight	0.103 mg/kg soil dry weight	0.03
Groundwater			
$PEC_{groundwater}$ values calculated are below the trigger value of 0.1 µg/l			
Surface water, run-off, drainage			
Algae, growth inhibition, 72 hour	0.0005 µg/l	>291 µg/l	$<1.7 \times 10^{-6}$
Daphnia, acute, 48 hour		0.000263 µg/l	**1.9**
Fish, acute, 96 hour		0.000849 µg/l	0.5
Surface water, run-off, drainage			
Algae, growth inhibition, 72 hour	0.523 µg/l	>291 µg/l	0.002
Daphnia, acute, 48 hour		0.000263 µg/l	**1989**
Fish, acute, 96 hour		0.000849 µg/l	**616**
Sediment (Run-off/drainage)			
Endpoint derived from the study with *Daphnia magna*	0.49 $\mu g/kg_{dwt}$	0.248 $\mu g/kg_{dwt}$	**2.0**

The RQs for aquatic invertebrates exposed to moxidectin via run-off and drainage were slightly above the trigger value of 1 (1.9 (surface water) and 2.0 (sediment)). These were calculated assuming 100% moxidectin excretion. The exposure was expected to be lower when taking into account that only up to 58% of the administered dose was found to be excreted over up to 28 days. Therefore refinement calculations following direct excretion are presented in Tier B. A Tier B assessment was also conducted for fish and dung organisms.

Although a risk remains for moxidectin excreted directly into water, in line with guidance, the SPC and packaging carry extensive warnings.

The risk for secondary poisoning was calculated using bioconcentration factors determined from an OECD 305 study in fish (2665 l/kg). Moxidectin is considered to be bioaccumulative in fish. However, based on the low predicted environmental concentrations of moxidectin, no risk for secondary poisoning was found in the aquatic food chain. A secondary poisoning assessment for predators in the terrestrial food chain was conducted using a calculated value for earthworms (3015 l/kg) and found to be of an acceptable risk.

An assessment was also conducted by the applicant in line with appropriate guidance, concluding that the moxidectin meets the criteria for all three categories. This is in agreement with the Article 35 referral conducted by CVMP involving all VMPs containing moxidectin for food producing species (EMEA/V/A/116). This referral concluded that these medicines might have a long-term impact on the environment. In line with the outcome of the referral the applicant included the recommended measures to mitigate the environmental risks in the SPC and product literature.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the products were exempt from bioequivalence studies.

MRLs

Moxidectin is included in Annex I of 37/2010 (EMEA/MRL/906/04-Final) for food producing animals of the species bovine, ovine and equine:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Moxidectin	Moxidectin	Bovine Ovine Equidae	50 µg/kg 500 µg/kg 100 µg/kg 50 µg/kg	Muscle Fat Liver Kidney	No entry
		Bovine Ovine	40 µg/kg	Milk	

The applicant has also included an MRL Summary Report (EMA/CVMP/243810/2018) for the aromatic solvent (solvent naphtha, light aromatic) to indicate that it has a 'No MRL Required' entry.

An entry in Annex II of Reg: 2034/96 for butylated hydroxyanisole (E-number 320) has also been provided (EMEA/CVMP/765/99-Rev.23). Polybutene polymer, 2-tert-butylhydroquinone, medium chain triglyceride and myristal propoxylate propionic ester all have entries on the 'out of scope' list.

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified:

Meat and offal: 14 days.
Milk: 6 days (144 hours).

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmcodynamics

Due to the legal basis of the applications, no data were required in this section.

Pharmacokinetics

As the test and reference products are intended for topical administration and are systemically active, the applicant claims exemption from providing *in vivo* bioequivalence studies due to having the same pharmaceutical form, and being quantitatively and qualitatively identical in terms of the active substance, and quantitatively and qualitatively similar in terms of excipients. The applicant claimed test and reference products were identical in terms of concentration of moxidectin, dissolution profile, crystalline form, and particle size distribution with identical manufacturing process (see Part II). Therefore, bioequivalence studies have not been provided in accordance with the legal base. The SPC reflected that of the reference product.

Tolerance in the Target Species

Due to the legal basis of the applications, no data were required in this section.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

Due to the legal basis of the applications, no data were required in this section.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics the benefit/risk profile of the products 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 SPCs are 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 these products are available on the Product Information Database of the Veterinary Medicines Directorate website.

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