Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bovimox LA 100 mg/ml Solution for Injection for Cattle
Moxodex LA 100 mg/ml Solution for Injection for Cattle
Ridamec LA 100 mg/ml Solution for Injection for Cattle

Date Created: November 2024

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Bovimox LA 100 mg/ml Solution for Injection for Cattle Moxodex LA 100 mg/ml Solution for Injection for Cattle Ridamec LA 100 mg/ml Solution for Injection for Cattle
Applicant	EU Pharmaceuticals Ltd, 37 Geraldine Road, London, SW18 2NR
Active substance	Moxidectin
ATC Vetcode	QP54AB02
Target species	Cattle
Indication for use	In cattle weighing from 100 to 500 kg body weight, treatment and prevention of mixed infestations by the following gastro-intestinal nematodes, respiratory nematodes and certain arthropod parasites: Adult and immature gastro-intestinal nematodes: . *Haemonchus placei* . *Haemonchus contortus* . *Ostertagia ostertagi* (including inhibited larvae) . *Trichostrongylus axei* . *Trichostrongylus colubriformis* . *Nematodirus helvetianus* (adults only) . *Nematodirus spathiger* . *Cooperia surnabada* . *Cooperia oncophora* . *Cooperia pectinata* . *Cooperia punctata* . *Oesophagostomum radiatum* . *Bunostomum phlebotomum* (adults only) . *Chabertia ovina* (adults only) . *Trichuris spp.* (adults only) Adult and immature respiratory tract nematode: . *Dictyocaulus viviparus*

Warble grubs (migrating larvae)
. *Hypoderma bovis*
. *Hypoderma lineatum*

Lice:
. *Linognathus vituli*
. *Haematopinus eurysternus*
. *Solenopotes capillatus*
. *Bovicola bovis* (aid in control)

Mange mites:
. *Sarcoptes scabiei*
. *Psoroptes ovis*
. *Chorioptes bovis* (aid in control)

The veterinary medicinal product has a persistent action and protects cattle for a certain duration against infection or re-infection with the following parasites for the period indicated:

Species	**Protection period (days)**
Dictyocaulus viviparous	120
Ostertagia ostertagi	120
Haemonchus placei	90
Oesophagostomum radiatum	150
Trichostrongylus axei	90
Linognathus vituli	133

The veterinary medicinal product is effective against *Hypoderma* larvae at the time of treatment but its persistent activity against *Hypoderma* has not been evaluated. If the product is given before the end of the fly season complimentary treatment with a product effective against *Hypoderma* may be required.

Persistent efficacy periods have not been established for parasite species other than those included in the above list. Therefore, re-infection of animals on pasture contaminated by parasites other than these remains possible before the end of the 90 day minimum persistency period demonstrated for specific species.

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 8 of VMRs 2013 (Schedule 1, Para 10) as amended.
Date of conclusion of the procedure	09/09/2024

I. SCIENTIFIC OVERVIEW

These are generic applications with the reference product being Cydectin 10% LA Solution for Injection which has been marketed in the UK since 2005.

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.[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 efficacy [2] of the product was demonstrated according to the claims made in 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 moxidectin and the excipients benzyl alcohol (E1519), butylhydroxytoluene (BHT), sorbitan oleate and propylene glycol dicprylocaprate.

The container/closure system consists of a HDPE vial with a chlorinated butyl rubber stopper and an aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

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

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

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 product is manufactured in accordance with the European Pharmacopoeia and relevant guidelines.

II.C. Control of Starting Materials

The active substance is moxidectin, 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.

The excipients are listed in Ph. Eur.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 suitable for this pharmaceutical form.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable regulatory 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 regulatory guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.
Do not store above 25°C.
Keep the container in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that moxidectin is an endectocide active against a wide range of internal and external parasites and is a second generation macrocyclic lactone of the milbemycin family.

Moxidectin interacts with GABA receptors and glutamate gated chloride channels. The net effect is to open the chloride channels on the postsynaptic junction to allow the inflow of chloride ions and induce an irreversible resting state. This results in flaccid paralysis and eventual death of parasites exposed to the active substance.

The exact mechanisms of parasite resistance to moxidectin have not been elucidated. A resistance mechanism involving metabolism by p-glycoproteins and efflux from the cells by ABC transporters has been proposed for ivermectin and a similar mechanism is thought to play a role in moxidectin resistance. However, parasites resistant to ivermectin are known to show some degree but not complete cross-resistance to moxidectin. It has been proposed that the reason for the incomplete cross-resistance is that there are multiple avenues of moxidectin action in target parasites that may include receptors other than the Glutamate-gated chloride channels.

The applicant has also provided bibliographical data which show that moxidectin is absorbed following subcutaneous injection with maximum blood concentrations being achieved 24 to 48 hours post injection. The active substance is distributed throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. The depletion half-life in fat is 26 – 32 days.

Moxidectin undergoes limited biotransformation by hydroxylation in the body. The only significant route of excretion is the faeces.

Toxicological Studies

Not required due to the legal basis of the application.

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, drink, or eat while handling the product.
Wash hands after use.
If accidental skin contact occurs, wash the affected area with soap and water.
If accidental eye exposure occurs, immediately rinse the eyes thoroughly with water.
If skin or eye irritation persists, seek medical attention.
Take care to avoid self-injection.
In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.
Advice to medical practitioners: In case of accidental self-injection: Treat symptomatically.

Environmental Safety

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

Phase I:
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 (at20 ± 1°C)
Dissociation constants in water pKa	OECD 112	A very weak base with a pK_a 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	4.69×10^{-20}
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	>6 at 20°C

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	Geo mean: 1230 ml/g (20-25˚C)
Aerobic and Anaerobic Transformation in Soil	OECD 307	Highest DT_{50} value: 87.3 days (20˚C)

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/*Species*	OECD 201	EC50	>29.1 mg/l
Daphnia sp. immobilisation	OECD 202	EC50	0.263 µg/l
Fish, acute toxicity/*Species*	OECD 203	LC50	0.849 µg/l
Earthworm/*Species* subacute/reproduction	OECD 220/222	NOEC	1.03 mg/kg soil
Dung fly larvae	OECD 228	EC50	1.47 mg test item/kg dung $_{dwt}$
Dung beetle larvae	OECD draft	EC50	2.00 mg/kg dung $_{dwt}$

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.

Target animal	PEC					
	Soil (µg/kg)	**Groundwater (µg/l)**	**Surface water (µg/l)**	**Surface water, direct excretion (µg/l)**	**Dung mg/kg (fw)**	**Sediment, direct excretion (µg/kg dwt)**
Cattle	4.18	0.0032	0.0011	1.05	25.4	12.38

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.

Cattle

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition. Surface water, run off	EC_{50} >29.1 mg/l	100	<291 µg/l	0.0001860 µg/l	<6.41 x 10^{-7}
Algae, Growth Inhibition. Surface water, direct excretion				1.05 µg/l	0.004
Daphnia sp. immobilisation	EC_{50} = 0.000263 µg/l	-	0.248 µg/kg dwt	12.38 µg/kg dwt	**49.9**
Fish, acute toxicity	LC_{50} = 0.849 µg/l	1000	0.000849 µg/l	1.05 µg/l	**1237**
Earthworm reproduction	56-day reproduction NOEC 1.03 mg/kg soil dwt	10	103 µg/kg soil dwt	4.18	0.0406
Dung fly larvae	EC_{50} = 0.21 mg/kg wet dung	100	0.0021 µg/kg dung wwt	25.4 mg/kg wwt	**12 095**
Dung beetle larvae	LC_{50} = 1.45 mg/kg wwt	100	14.5 µg/kg wwt	25.4 mg/kg wwt	**1752**

Where the RQ value was >1, further assessment of the environmental risk was required.

PEC Refinement & Tier B
The applicant refined the RQ for dung beetles and flies, which resulted in a risk to dung beetles when exposed to dung excreted 1-3 days post treatment and ≥4 days post treatment. The applicant provided refined RQ values for surface water and sediment following direct excretion, however these values remained above 1 and thus, an unacceptable risk to the environment was still identified.

A risk was determined for dung fauna and aquatic species. The applicant refined the risk by applying results from an excretion profile study. Results indicate that moxidectin present in field excretion is lower than the calculated reasonable worst-case calculations, nevertheless, a risk to dung or aquatic fauna could not be discarded.

As the octanal water partition co-efficient was >4, the applicant correctly considered bioaccumulation. Results from a proprietary OECD 305 study indicate that the substance is bioaccumulative (BCF_{SSL}= 2665 l/kg_{wwt}). Secondary poisoning was considered by the applicant and no risk was indicated for fish and earthworm eating predators.

Regarding the PBT assessment, based on data provided in the dossier, the active substance is persistent, bioaccumulative and toxic. These findings are not entirely in agreement with the outcome of a recent Article 35 referral conducted by the CVMP involving all VMPs containing moxidectin for food producing species, where it was concluded that moxidectin classifies as very persistent, bioaccumulative and toxic. Nevertheless, the substance still classifies as PBT and the warnings which were agreed during the 2017 Article 35 referral for moxidectin containing veterinary medicines used in cattle, sheep and horses still apply.

III.B.2 Residues documentation

Residue Studies
BCF
Not required due to the legal basis of the application.

MRLs

Moxidectin is listed and MRLs have been established for edible tissues/milk.

MRLs are listed below:

	Bovine
Muscle	50 µg/kg
Liver	100 µg/kg
Kidney	50 µg/kg
Fat	500 µg/kg
Milk	40 µg/kg

Withdrawal Periods

Based on the data provided, a withdrawal period of 108 days for meat in cattle. Not permitted for use in lactating animals producing milk for human consumption or industrial purposes or within 80 days of expected parturition.
The withdrawal period is based solely on a single injection at the ear site of injection.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Not required due to the legal basis of the application. Bioequivalence was established with regard to the reference product.

Tolerance in the Target Species

Not required due to the legal basis of the application.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Not required due to the legal basis of the application.

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 products are 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.

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