Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Maximec 5mg/ml Pour-On Solution for Cattle

Date Created: September 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Maximec 5 mg/ml Pour-On Solution for Cattle
Applicant	Bimeda Animal Health Limited 2/3/4 Airton Close Tallaght Dublin 24 Ireland
Active substance	Ivermectin
ATC Vetcode	QP54AA01
Target species	Cattle
Indication for use	For the treatment and control of gastro-intestinal nematodes, lungworms, eyeworms, warbles, chorioptic and sarcoptic mange and sucking and biting lice in beef and non-lactating dairy cattle. The product at the recommended dosage level of 500 µg ivermectin per kg bodyweight effectively controls the following parasites of cattle: Gastrointestinal roundworms (adult and fourth stage larvae): *Ostertagia ostertagi* (including inhibited stage) *Haemonchus placei* *Trichostrongylus axei* *T. colubriformis* *Cooperia spp.* *Oesophagostomum radiatum* *Strongyloides papillosus* adult *Trichuris* spp. adult Lungworms (adult and fourth stage larvae): *Dictyocaulus viviparus* Eyeworms (adult): *Thelazia* spp. Warbles (parasitic stages):

	Hypoderma bovis *H. lineatum* Mites: *Sarcoptes scabiei var. bovis* *Chorioptes bovis* Lice: *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* *Damalinia bovis* The product, given at the recommended dosage of 500 micrograms per kg bodyweight, controls infections with *Trichostrongylus axei* and *Cooperia* spp acquired up to 14 days after treatment, *Ostertagia ostertagi* and *Oesophagostomum radiatum acquired* during the first 21 days after treatment and *Dictyocaulus viviparus* (lungworm) acquired during the first 28 days after treatment. It also controls horn fly (*Haematobia irritans*) for up to 35 days after treatment.

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 conclusion of the procedure	8/7/2022

I. SCIENTIFIC OVERVIEW

The quality / safety / efficacy aspects of this product are identical to Ivomec Classic Pour-On for Cattle. The initial application for Ivomec was assessed before there was a requirement to have a public assessment report, therefore no details in this section are available.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains ivermectin and the excipients trolamine, crodamol CAP, isopropyl alcohol, FD&C Blue #1dye (E133) and purified water.

The container/closure system consists of a white high-density polyethylene flexipack. 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 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 adding the excipients and active to a tank and mixing.

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 ivermectin, 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.

All excipients, except crodamol CAP and FD&C Blue #1, are described in the Ph. Eur. which are used in other authorised products in the UK.

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 for appearance, blue dye ID, specific gravity, ivermectin assay, ivermectin identification, ivermectin impurities, volume and bioburden.

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 product as packaged for sale: 3 years.
Do not store above 25°C.
Flammable - keep away from heat, sparks, open flame or other sources of ignition.

Protect from light.
Bottles should remain upright during storage. The dosing cup should not be stored attached to the bottle when not in use. Remove the cup after each use and replace with the bottle cap. Cloudiness may result when the product is stored at temperatures below 0°C. Allowing the product to warm at room temperature will restore the normal appearance without affecting efficacy.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Not required due to the legal basis of this application.

Toxicological Studies

Not required due to the legal basis of this 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:,

- The product may be irritating to human skin and eyes and the user should be careful not to apply it to himself or other persons.
- Operators should wear rubber gloves and boots with a waterproof coat when applying the product. Protective clothing should be washed after use.
- Use only in well-ventilated areas or outdoors.
- As absorption through skin can occur, in the event of accidental skin contact the affected area should be washed immediately with soap and water.
- If accidental eye exposure occurs, flush the eyes immediately with water and get medical attention.
- Wash hands after use.

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 ivermectin unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	5 mg/l
Melting Point/Melting Range	OECD 102	99-102°C
Vapour Pressure	OECD 104	2 x 10^{-7} Pa
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	5.99

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	DT_{50} values: 16.1 to 37.1 at 20°C
Aerobic and Anaerobic Transformation in Soil	OECD 307	K_{oc} (l/kg): 12000 to 54810

Environmental effects

Study type	Species	Guideline	Endpoint	Result
Algae, Growth Inhibition Test	Algae (*P. subcapitata*)	OECD 201	EC50	>4000 µg/l
Daphnia sp. immobilisation	*Daphnia magna*	OECD 202	LC50	0.0057 µg/l
Fish, acute toxicity	Zebrafish (*Danio errio*)	OECD 203	LC50	73.3 µg/l
Earthworm subacute/reproduction	Earthworm *(E. foetida)*	OECD 220/222	NOEC	2500 µg/kg
Dung fly larvae	11 dung fly species	OECD 228	LC50	4.65 µg/kg wwt
Dung beetle larvae	Dung beetle (*Aphodius constans)*	OECD draft	LC50	880 µg/kg dwt

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. PEC values for dung were based on excretion data. The following PEC values were calculated.

Target animal	PEC			
	Soil (µg/kg) dwt	Groundwater (µg/l)	Surfacewater (µg/l)	Dung
Beef cattle	4.18	0.003	0.0011 – run off	494 (µg/kg) wwt 2845(µg/kg) dwt
			0.5225 – direct excretion	

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.

Test organism	End point	AF	PNEC	PEC	RQ
Terrestrial Compartment					
Earthworms	2500 µg/kg (NOEC)	10	250 µg/kg dwt	4.18 µg/kg dwt	0.02
Dung fly larvae	4.65 µg/kg wwt (LC50)	100	0.05 µg/kg wwt	494 (µg/kg) wwt	9880
Dung beetle larvae	880 µg/kg dwt (LC50)	100	8.8 µg/kg dwt	2845(µg/kg) dwt	323
Aquatic compartment					
Surface water- run off					
Algae, Growth Inhibition	>4000 µg/l (EC50)	100	40 µg/l	0.0011 µg/l	2.75×10^{-5}
Daphnia sp. immobilisation	0.0057 µg/l (LC_{50})	1000	0.0000057 µg/l	0.0011 µg/l	193
Fish, acute toxicity	73.3 µg/l (LC50)	1000	0.0733 µg/l	0.0011 µg/l	0.02
Surface water- direct excretion					
Algae, Growth Inhibition	>4000 µg/l (EC50)	100	40 µg/l	0.5225 µg/l	0.010
Daphnia sp. immobilisation	0.0057 µg/l (LC_{50})	1000	0.0000057 µg/l	0.5225 µg/l	91667
Fish, acute toxicity	73. µg/l (LC50)	1000	0.0733 µg/l	0.5225 µg/l	7.13

No risk was identified for earthworms or algae during the initial risk characterisation; however, a risk could not be eliminated for dung fauna, fish and daphnids.

Subsequent to this, PEC refinement was carried out, as part of the Tier A refinement, and the risk characterisation was updated as follows.

Refined Tier A Risk Characterisation

<table>
<tr><th>Organism</th><th>PEC</th><th>PNEC</th><th>RQ</th></tr>
<tr><td colspan="4">Terrestrial compartment</td></tr>
<tr><td>Dung fly</td><td><table><tr><th>Day after treatment</th><th>Ivermectin residue (µg/kg) wwt</th></tr><tr><td>3</td><td>494</td></tr><tr><td>7</td><td>434</td></tr><tr><td>14</td><td>124</td></tr><tr><td>28</td><td>8</td></tr></table></td><td>0.05 µg/kg wwt</td><td><table><tr><th>Day after treatment</th><th>RQ</th></tr><tr><td>3</td><td>2470</td></tr><tr><td>7</td><td>2170</td></tr><tr><td>14</td><td>620</td></tr><tr><td>28</td><td>40</td></tr></table></td></tr>
<tr><td>Dung beetle</td><td><table><tr><th>Day after treatment</th><th>Ivermectin residue (µg/kg) dwt</th></tr><tr><td>3</td><td>2845</td></tr><tr><td>7</td><td>2480</td></tr><tr><td>14</td><td>692</td></tr><tr><td>28</td><td>49</td></tr></table></td><td>8.8 µg/kg$_{dwt}$</td><td><table><tr><th>Day after treatment</th><th>RQ</th></tr><tr><td>3</td><td>323</td></tr><tr><td>7</td><td>282</td></tr><tr><td>14</td><td>79</td></tr><tr><td>28</td><td>5.5</td></tr></table></td></tr>
<tr><td colspan="4">Aquatic compartment</td></tr>
<tr><td>Daphnia</td><td>Surface water, run-off: FOCUS global max: 0.000101 µg/l</td><td>0.0000057 µg/l</td><td>17.72</td></tr>
<tr><td>Fish</td><td rowspan="2">Surface water, direct excretion - based on maximum daily excretion at 3 days after treatment 0.0203 µg/l</td><td>00.0733 µg/l</td><td>0.28</td></tr>
<tr><td>Daphnia</td><td>0.0000057 µg/l</td><td>3561</td></tr>
<tr><td>Daphnia</td><td>Surface water, direct excretion - further refined based on sediment partitioning 0.000302 µg/l,</td><td>0.0000057 µg/l</td><td>53</td></tr>
</table>

Following PEC refinement at Tier A, a risk could not be eliminated for dung fauna or aquatic invertebrate.

Tier B

Toxicity to Dung Fauna

The calculated risk quotients indicated that the product will pose a risk to dung fauna when used as directed. At Tier B, data from field studies with ivermectin were investigated. It was noted that the dung fauna population will be impacted for a short period (*circa* one month after treatment) of the grazing season and that migration from untreated pats and surrounding fields will help maintain population levels. While this rationale was noted, it was agreed that this consideration had its uncertainties and could not be solely relied upon. It was concluded that suitable risk mitigation measures and environmental warnings would be included in the SPC and product literature.

Toxicity to Aquatic Invertebrates

During Tier B, a NOEC of 0.0003 ng/l, from a 21 day daphnid reproduction study was used to calculated the PNEC. In addition, a PNEC for sediment dwellers was calculated using the equilibrium portioning method.

Test organism	**Endpoint**	**PNEC**
Daphnia	0.0003 ng/l (NOEC)	0.00000003 µg/l
Sediment dwelling invertebrate	Daphnia PNEC 0.0000057 µg/l & CVMP Equation 17	0.0045 µg/kg wwt

These PNECs were compared to appropriate PECs, as specified below:

Scenario	**PEC**	**PNEC**	**RQ**
Surface water, run-off	FOCUS 21-day TWAC 0.000013 µg/l.	0.00000003 µg/l	433
Surface water, direct excretion	refined based on sediment partitioning 0.000302 µg/l		10,067
Sediment, run-off	Worst-case FOCUS global max 0.127500 (µg/l)	0.0045 µg/kg wwt 0.0017 µg/kg dwt	28.33
Sediment, direct excretion	PEC sediment (µg/kg) Day 3: 0.0924 Day 14: 0.0233 Day 28: 0.0014		54 14 0.82

As a risk could not be eliminated, the risk characterisation was further refined by considering toxicity data from a study that investigated the chronic toxicity of ivermectin-fortified dung to *Daphnia magna* and *Chironomus riparius* in a sediment/water test system.

Test organism	**Endpoint**	**PNEC**
Daphnia magna	0.031 µg/l (NOEC)	0.0031 µg/l
Chironomus riparius	0.46 µg/kg wwt (NOEC) 1.20 µg/kg dwt (NOEC)	0.046 µg/kg wwt 0.12 µg/kg dwt

The above PNEC was compared to appropriate PECs for surface water (run-off) and surface water (direct excretion). The resulting risk characterisation is presented below:

Scenario	**PEC**	**PNEC**	**RQ**
Surface water, run-off	Worst case FOCUS global max: 0.000101 µg/l	0.0031 µg/l	0.033
Surface water, direct excretion	0.000302 µg/l at peak excretion		0.097
Sediment, run-off	Worst case FOCUS global max: 0.127500 µg/kg dwt	0.12 µg/kg dwt	1.063
Sediment, direct excretion	PEC sediment Day 3: 0.0924 µg/kg Day 14: 0.0233 µg/kg Day 28: 0.0014 µg/kg	0.046 µg/kg wwt	2 0.51 0.03

Based on the data provided, there is a risk to aquatic invertebrates. Although there is some evidence that the risk to daphnids may be reduced to an acceptable level when considering sediment partitioning and binding of ivermectin to faeces, a risk cannot be completely excluded. Furthermore, a risk to sediment dwellers was present for up to 14 days post treatment. Therefore, it was agreed that suitable risk mitigation measures and environmental warnings would be included in the SPC and product literature.

Bioaccumulation

As the log K_{OW} is greater than 4 (5.99), there is a potential for bioaccumulation to occur. To address this, the applicant has submitted a proprietary fish bioconcentration study. Results from the study gave a bioconcentration factor (BCF) of 137, indicating that ivermectin is not bioaccumulative.

PBT Assessment

The applicant has followed the CVMP guideline on the assessment of persistent, bioaccumulative and toxic (PBT) substances. The findings from this assessment confirm that ivermectin is not a PBT substance, because ivermectin does not classify as bioaccumulative or persistent; however, it does classify as toxic.

Risk mitigation measures and environmental warnings

Based on the conclusions above the following risk mitigation were agreed:

Other precautions
This product is very toxic to aquatic organisms, sediment dwelling organisms, and dung insects. Long-term effects on dung insects caused by continuous or repeated use cannot be excluded.

Treated cattle should not have direct access to ponds, streams or ditches for 14 days after treatment. The risk to aquatic ecosystems and dung fauna can be reduced by avoiding too frequent and repeated use of this product and other products of the same anthelmintic class. Therefore, the repetition of treatment in a pasture during a season should be performed only in the absence of alternative treatment and on veterinary advice.

Environmental Properties
Ivermectin is moderately persistent in soil and may accumulate in sediments.

Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products
EXTREMELY DANGEROUS TO AQUATIC ORGANISMS AND DUNG FAUNA. Do not contaminate surface waters or ditches with product or used container. Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

III.B.2 Residues documentation

Residue Studies

Not required due to the legal basis of the application.

MRLs

Ivermectin is listed in Table 1 of Regulation 37/2010and MRLs have been established for edible tissues. The marker substance is 22, 23-dihydroavermecin B1a.

MRLs are listed below:

	All mammalian food producing species
Muscle	30
Liver	100
Kidney	30
Fat / skin	100
Milk	Not for use in animals from which milk is produced for human consumption

Withdrawal Periods

Based on the data provided, a withdrawal period of 15 days for meat in mammalian food producing species. Do not use in animals producing milk for human consumption. Do not use in non-lactating dairy cows including pregnant heifers within 60 days of calving.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Not required due to the legal basis of the application.

Tolerance in the Target Species

Tolerance studies were not required because of the legal basis of the application.

Resistance

The bibliography / information provided are supportive.
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 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)