IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Maximec 5 mg/ml Pour-On solution for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0650/001/DC
Name, strength and pharmaceutical form	Maximec 5 mg/ml Pour-on solution for cattle
Active substance(s)	Ivermectin
Applicant	Bimeda Animal Health Limited 2, 3 & 4 Airton Close Airton Road Tallaght Dublin 24 Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of completion of procedure	20/10/2021
Target species	Cattle (beef and non-lactating dairy cattle)
Indication for use	For the treatment of infections with the following species of gastrointestinal roundworms, lungworms, warbles, mites and lice for beef and non-lactating dairy cattle: **Gastrointestinal roundworms (adults and fourth stage larvae):** *Ostertagia ostertagi* (including inhibited *O. ostertagi*) *Haemonchus placei* *Trichostrongylus axei* *Trichostrongylus colubriformis* *Cooperia* spp. *Oesophagostomum radiatum* *Strongyloides papillosus* (adults only) *Trichuris* spp. (adults only) **Lungworms (adult and fourth stage larvae):** *Dictyocaulus viviparus* **Eyeworms:** *Thelazia* spp. (adults) **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/kg bodyweight, has persistent activity against *Trichostrongylus axei* and *Cooperia spp* acquired during the 14 days after treatment, only if the whole herd is treated simultaneously. It also has a persistent activity against *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 has a persistent activity on horn flies (*Haematobia irritans*) for 28 days after treatment, partial efficacy may last for up to 35 days post application. Occasionally variable activity may be observed against *Haemonchus placei (L4), Cooperia spp, Trichostrongylus axei* and *Trichostrongylus colubriformis*.
ATCvet code	QP54AA01
Concerned Member States	ES, FR

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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; the slight 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 overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product is formulated as a pour-on solution and contains 5 mg/ml of ivermectin. The product includes the following excipients: crodamol CAP, trolamine, purified water, brilliant blue FCF (E133) and isopropyl alcohol.
The finished product is filled into 1 L, 2.5 L and 5 L high density polyethylene (HDPE) bottles, closed with a tamper evident, polypropylene cap.

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 for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance ivermectin is 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 has 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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. Stability

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

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing
This generic application was submitted in accordance with paragraph 1 of Article 13 of Directive 2001/82/EC, as amended. The reference product cited by the applicant is Ivomec Classic Pour-on for Cattle 5 mg/ml (VPA 10454/065/001, Boehringer Ingelheim Vetmedica GmbH). The reference product has been authorised for in excess of ten years and can therefore be accepted as a valid reference product in this generic application.

Pharmacological Studies
An exemption from the need to conduct an *in vivo* bioequivalence study in the target species was accepted in accordance with section 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies on the basis that the product is intended for systemically acting topical administration, has the same pharmaceutical form, contains the same concentration of the active substance and has comparable excipients as the reference product Ivomec Classic Pour-on for Cattle 5 mg/ml. In addition, the intended target species, route of administration and the posology of the product are the same as for the reference product.
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, results of pharmacological studies are not required.

Toxicological Studies
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, results of toxicological studies are not required.

User Safety
The applicant has provided a user safety assessment. The potential risks will be the same as those of the reference product, that is, the product may be irritating to human skin and eyes.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

Phase I

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

Phase II

A Phase II Tier A and B assessment was conducted the results of which are summarised below.

Physico-chemical properties	
Study type	**Result**
Vapour pressure	2×10^{-7} Pa
Water solubility	5 mg/ml
Dissociation constants in water (pKa)	Ivermectin does not contain any ionisable groups which are likely to predominate under environmental conditions.
n-Octanol/Water Partition Coefficient ($logP_{ow}$)	$logP_{ow}$ = 5.99

Environmental fate	
Soil Adsorption/Desorption	Koc = 16,444 L/kg
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 67 days (20°C ± 1)

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *species*	EC50	>4000	µg/l
Daphnia sp. immobilisation	EC50	0.0057	µg/l
Daphnia magna, reproduction (Tier B)	NOEC	0.0000003	µg/l
Fish, acute toxicity/ *Danio rerio*	LC50	17.21	µg/l
Earthworm/ *Eisenia andrei* reproduction	NOEC	2500	µg/kg dry weight
Sediment dwelling organism/ *Chironomus riparius*	NOEC	3.1	µg/kg dry weight
Dung fly larvae/ *Musca autumnalis*	EC50	4.07	µg/kg fresh weight
Dung beetle larvae/ *Aphodius constans*	LC50	352	µg/kg fresh weight
Bioaccumulation in fish/ *Oncorhynchus mykiss*	BCF	137	L/kg

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with guideline requirements.

Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.

The risk characterisation resulted in risk quotients below 1 for the groundwater and soil compartments indicating that the product will not pose a risk to those compartments when used as recommended.

The results of the assessment for the surface water and dung compartments indicate that a risk for the environment potentially exists for:

- dung dwelling organisms exposed to dung produced by treated pasture animals,
- aquatic invertebrates in surface waters in the case of run-off and drainage and direct excretion,
- sediment dwelling organisms in the case of direct excretion.

Consequently, the following risk mitigation measures are required for this product:
Ivermectin is very toxic for aquatic organisms and dung fauna. After treatment, potentially toxic concentrations of ivermectin may be excreted for at least 2 months. Faeces excreted on pasture by treated animals may reduce the abundance of dung fauna which may impact on dung degradation.
In case of repeated treatments with ivermectin (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.
Ivermectin - treated cattle should not have direct access to ponds, streams or ditches for at least two months after treatment.

PBT Assessment
An assessment of the compound in terms of potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent and very Bioaccumulative (vPvB) was performed.
The log P_{ow} of ivermectin was demonstrated to be 5.99.
The compound is not considered to be either PBT or vPvB.

Conclusion
Based on the data provided in the ERA, a risk to the aquatic and terrestrial environment cannot be excluded. Therefore suitable risk mitigation measures and/or advice were included in the SPC for this product.

III.B Residues Documentation

Residue Studies
No residue depletion studies were conducted and their omission was accepted because the product is accepted as being bioequivalent with the reference product and the formulations are considered to be sufficiently similar to not influence depletion of residues from the administration site. This took into account the product being the same type of solution, containing the same concentration of the active substance, similar excipients, administration to the same target species, using the same route of administration at the same dose rate as already approved for the reference product. Consequently, a similar rate and extent of absorption of the active substance from the application site is expected.

Maximum Residue Limits
Ivermectin is listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	Marker residue	Animal species	MRL	Target tissues	Other provisions
Ivermectin	22, 23-Dihydro-avermectin B 1a	All mammalian food producing species	30 µg/kg 100 µg/kg 100 µg/kg 30 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption

Withdrawal Periods
Based on the data provided above, a withdrawal period of 15 days for meat and offal in cattle is justified.
The product is not permitted for use in animals producing milk for human consumption. It is not to be used in non-lactating dairy cows including pregnant heifers within 60 days of calving.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies
An exemption from the need to conduct an *in vivo* bioequivalence study in the target species was accepted in accordance with section 7.1.b of the CVMP Guideline on the conduct of bioequivalence studies on the basis that the product is intended for systemically acting topical administration, has the same pharmaceutical form, contains the same concentration of the active substance and has comparable excipients as the reference product Ivomec Classic Pour-on for Cattle 5 mg/ml. In addition, the intended target species, route of administration and the posology of the product are the same as for the reference product.
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, results of pre-clinical studies are not required.

Tolerance in the Target Species of Animals
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, systemic tolerance studies are not required. Evidence to demonstrate target animal tolerance at the administration site is

expected for topically-applied products. It was accepted that the inclusion of the two additional excipients Brilliant Blue FCF (E133) and water will not negatively impact target animal tolerance. On the basis that the product formulation includes the same concentration of active substance, similar amounts of Crodamol CAP, isopropyl alcohol and trolamine as included in the reference product formulation, no difference in tolerance at the administration site compared to the reference product is expected.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been demonstrated, the resistance profile of the product will be the same as that of the reference product.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies
As this is a generic application according to Article 13(1), and bioequivalence with a reference product has been accepted, 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

On the basis of the original data submitted, the HPRA considered that the product demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory benefit/risk profile and therefore granted a marketing authorisation.

VI. 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 HPRA website.

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.

Changes:
None.