IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Doramax 5 mg/ml Pour-on Solution for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0669/001/MR
Name, strength and pharmaceutical form	Doramax 5 mg/ml Pour-on Solution for Cattle
Active substance	Doramectin
Applicant	Chanelle Pharmaceuticals Manufacturing Limited IDA Industrial Estate Dublin Road Loughrea County Galway Ireland
Legal basis of application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of first authorisation	09 April 2021
Date of completion of the mutual recognition procedure	09 February 2022
Target species	Cattle
Indication for use	For treatment of infestations of gastrointestinal roundworms, lungworms, eyeworms, warbles, sucking and biting lice, mange mites and hornfly in cattle. Gastrointestinal roundworms (adults and fourth stage larvae) *Ostertagia ostertagi* (inc. inhibited larvae) *O. lyrata* (adults only) *Haemonchus placei* *Trichostrongylus axei* *T. colubriformis* *Cooperia oncophora* *C. punctata* (adults only) *C. surnabada (syn. mcmasteri)* (adults only) *Bunostomum phlebotomum* (adults only) *Oesophagostomum radiatum* *Trichuris* spp (adults only) Lungworms (adults and fourth stage larvae) *Dictyocaulus viviparus* Eyeworms (adults) *Thelazia* spp Warbles (parasitic stages) *Hypoderma bovis,* *H. lineatum* Biting lice *Damalinia (Bovicola) bovis* Sucking lice *Haematopinus eurystemus,* *Linognathus vituli,* *Solenopotes capillatus* Mangemites *Psoroptes bovis,* *Sarcoptes scabiei,* *Chorioptes bovis* Horn fly *Haematobia irritans*

	Duration of activity Following product administration, efficacy against re-infection with the following parasites persists for the period indicated: Species / Days *Ostertagia ostertagi* / 35 *Cooperia oncophora* / 28 *Dictyocaulus viviparus* / 42 *Linognathis vituli* / 49 *Oesophagostomum radiatum* / 21 *Damalinia (Bovicola) bovis* / 42 *Trichostrongylus axei* / 28 *Solenopotes capillatus* / 35 The product also controls horn flies (*Haematobia irritans*) for at least 42 days after treatment.
ATC vet code	QP54AA03
Concerned Member States	BE, CZ, DE, FR, HU, NL, PL, RO, SL

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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 contains the active substance doramectin (5 mg/ml) and the excipients cetearyl octanoate, triethanolamine and isopropyl alcohol.
The product is packaged in 1 L, 2.5 L, 3 L, 5 L, 6 L (containing 5 L + 1 L pack sizes) and 8 L (containing 5 L + 3 L pack sizes) high-density polyethylene containers with tamper evident caps.
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 is doramectin, which has no monograph in the European Pharmacopoeia (Ph. Eur.). 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. The active substance is manufactured in accordance with the principles of good manufacturing practice.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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 (pharmaceuticals)
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 Zearl 5 mg/ml pour-on solution for injection (VPA10047/029/001 – Elanco Animal Health, Eli Lilly and Company Limited). 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 of the CVMP Guideline on the conduct of bioequivalence studies.
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 in compliance with the relevant guideline. The potential risks will be identical to 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	9.2×10^{-6} Pa (20°C)
Water solubility	2.075 mg/l (pH 5.69, 20 ± 0.5 °C)
Dissociation constants in water pKa	None could be determined at pH 1-12 at 20°C
n-Octanol/Water Partition Coefficient logP_{ow}	logK_{ow} = 6.71

Environmental fate	
Soil Adsorption/Desorption	Koc = 4615 ml/g K_d = 53.6 ml/g
Aerobic and Anaerobic Transformation in Soil	DT_{50} = 30.7 days (20 ± 2°C)

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapitata*	EC_{50}	472	µg/l
Daphnia sp. immobilisation	EC_{50}	0.0213	µg/l
Fish, acute toxicity/ *Oncorhynchus mykiss*	LC50	14.1	µg/l
Soil microorganisms: Nitrogen transformation test (28 days)	% effect	<25%	
Earthworm/*Eisenia foetida* reproduction	NOEC	500	µg/kg dry weight
Sediment dwelling organism/ *Chironomus riparius*	NOEC	9.03	µg/kg dry weight
Dung fly larvae/ *Musca autumnalis*	EC50	5.5	µg/kg wet weight
Dung beetle larvae/ *Onthophagus taurus*	EC50	518	µg/kg wet weight
Bioaccumulation in fish/ *Oncorhynchus mykiss*	BCF	347	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:

Doramectin 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 doramectin (and products of the same anthelmintic class) in cattle.
The risk to aquatic ecosystems will be reduced by keeping treated cattle away from water bodies for two to five weeks 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 K_{ow} of doramectin was demonstrated to be 6.71.
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 provided.

MRLs
Doramectin 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
Doramectin	Doramectin	All mammalian food producing species	40 µg/kg 150 µg/kg 100 µg/kg 60 µg/kg	Muscle Fat Liver Kidney	No entry

Withdrawal Periods
It is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended, with a topical route of administration. The withdrawal periods are the same as those for the reference product, as follows:
Meat and offal: 35 days.
Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition.

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 of the CVMP Guideline on the conduct of bioequivalence studies (EMA/CVMP/016/2000-Rev.3).
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. Given that the product includes the same concentration of active substance and the same excipients in similar amounts as the reference product, no difference in tolerance at the administration site is expected between candidate and reference products.
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 updated 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

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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.