Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A PROPOSED VETERINARY MEDICINAL PRODUCT <*Delete if authorised*>

Doramax 5 mg/ml Pour-on Solution for Cattle

Date Created: January 2021

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Doramax 5 mg/ml Pour-on Solution for Cattle
Applicant	C&H Generics Ltd, c/o Michael McEvoy and Co, Seville House, New Dock Street, Galway, Ireland
Active substance	Doramectin
ATC Vetcode	QP54AA03
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*[1] *Haemonchus placei* *Trichostrongylus axei* *T. colubriformis* *Cooperia oncophora* *C. punctata*[1] *C. surnabada*[1] *(syn. mcmasteri)* *Bunostomum phlebotomum1* *Oesophagostomum radiatum* *Trichuris* spp.[1] [1] adults <u>Lungworms</u> (adults and fourth stage larvae) *Dictyocaulus viviparus* <u>Eyeworms (adults)</u> *Thelazia* spp.

Warbles (parasitic stages)
Hypoderma bovis, H. lineatum

Biting lice
Damalinia (Bovicola) bovis

Sucking lice
Haematopinus eurystemus,
Linognathus vituli,
Solenopotes capillatus

Mange mites
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.

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	24th November 2020

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, 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 the active substance doramectin 5.0mg/ml and the excipients cetearyl octanoate, isopropyl alcohol and triethanolamine.

The container/closure system consists of high-density polyethylene (HPDE) bottles sealed with a polyethylene cap. Pack sizes of 1, 2.5, 3, 5, 6 (5+1) and 8 (5+3) 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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

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 is a relatively simple process of mixing the active substance with all the excipients, the process occurs under nitrogen.

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 doramectin 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.

An ASMF was provided, confirming the manufacture of doramectin is in compliance with the Ph. Eur. general monograph.

The active substance is packaged in double layer polyethylene bags, inside a compound membrane bag consisting of four layers (PE/PA/Al/PET). The bags are then placed inside a fibre drum and sealed.
The finished product is packaged into high density polyethylene backpacks sealed with a white polypropylene cap.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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 the active, assay doramectin, impurities, uniformity and microbial purity. The identification of the active substance, doramectin, is confirmed by the HPLC retention time and the UV spectrum.

II.F. Stability

The active substance has a 2-year retest period. The stability data are included in the ASMF.

Stability data were provided for two pilot scale batches.
Long term stability data are available for up to 48 months and accelerated stability data for up to 6 months. Both batches were observed to meet the full shelf-life speciation at all time points and in both pack sizes. The proposed 5 year shelf life is considered acceptable.

G. Other Information

An acceptable residual solvents declaration has been provided in compliance with option one of the VICH guideline.

Shelf life:	5 years
In-use shelf life:	1 year
Storage conditions:	Do not refrigerate. Protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

As this is an application for a generic product, submitted according to Article 13 (1) of Directive 2001/82/EC as amended, the applicant is not required to submit pharmacological or toxicological data on the active substance.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the generic and reference product are of the same pharmaceutical form (pour-on solution), have the same qualitative and quantitative composition with respect to the active substance (5 mg/ml doramectin) and are considered to be bioequivalent. Furthermore, the posology for both products is exactly the same; therefore, the tasks and situations that

lead to exposure and the subsequent exposure scenarios will be the same for both the reference and generic products.

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:

- People with known hypersensitivity to the active substance should avoid contact with the product.
- Do not smoke or eat while handling the product. Wash hands after use.
- The product may be irritating to human skin and eyes and users should be careful not to apply it to themselves or to other persons.
- Operators should wear rubber gloves and boots with a waterproof coat when applying the product. Protective clothing should be washed after use.
- If accidental skin contact occurs, wash the affected area immediately with soap and water. If irritation persists, seek medical attention.
- If accidental eye exposure occurs, flush the eyes immediately with clean water and get medical attention. Avoid accidental inhalation of this product, as this may cause drowsiness and dizziness.
- Use only in well ventilated areas or outdoors.
- Highly Flammable - Keep away from heat, sparks, open flame or other sources of ignition.

Environmental Safety

A Phase I and II environmental risk assessment (ERA) in accordance with current guidance were provided. The environment will be exposed via spreading of manure from treated animals onto land and via direct excretion onto pasture and into surface waters. Despite the $PEC_{soil\ initial}$ being less than the trigger value (100 µg/kg), a Phase II ERA was required as the product is an ecto- and endo-parasiticide.

The applicant submitted numerous proprietary, GLP-compliant studies in Phase II of the ERA, together with several references from the published literature.

Proprietary study data relating to each of the required physicochemical properties of the active substance; doramectin, were provided, except for information on molecular weight which has been sourced from published literature. These data were considered satisfactory for use in the ERA.

In respect of environmental behaviour, proprietary degradation and adsorption/desorption studies in soil were provided. The results of these studies indicate that doramectin is moderately persistent (DT_{50} = 30.7 days) and slightly immobile (K_{OC} = 46215 ml/g) in soil. Additionally, metabolism data from the

published literature were cited and indicate that the majority of the active substance or its metabolites are excreted in faeces, with approximately 43% of the excreted residues comprising unchanged parent product and the major metabolite, 3”-O-desmethyl-doramectin.

Proprietary ecotoxicological effects studies were submitted in Tier A of the Phase II assessment. These studies were conducted in accordance with the appropriate OECD guidelines and are acceptable for use in the ERA. In accordance with current guidance no data on the toxicity of doramectin to terrestrial plants and microorganisms, or sediment dwellers, were provided.

Concerning the risk characterisation, at Tier A, risks to dung organisms, fish (following direct excretion into surface water), aquatic invertebrates (following exposure via drainage/run-off and direct excretion), and the groundwater ecosystems have been identified. A proprietary bioaccumulation study in fish (in accordance with OECD GL 305) was provided. The BCF is below the trigger value (1000) and, therefore, a secondary poisoning assessment was not required.

With regard to mitigation of the risk to dung organisms and fish (following direct excretion), the applicant cited a number of references form the published literature in support of the argument that the adverse effects of doramectin on these populations were acute and localised (temporally and spatially), and the respective populations are able to recover due to the brief, temporal nature of exposure and the presence of unexposed populations of organism in the immediate vicinity which could facilitate the recovery of the affected populations in dung or surface water (downstream of exposure).

A PBT assessment was conducted, the conclusions of which are that doramectin is neither sufficiently persistent (DT_{50} at 12°C <120 days) nor bioaccumulative (BCF_{SSL} <2000 l/kg) to be classified as a PBT substance, this conclusion was supported.

The environmental precautions and warnings contained in the SPC reflect the outcome of the recent Article 35 referral on doramectin-containing injectables and pour-ons for cattle (EMEA/V/A-35/81). These mitigation measures relate to the risk identified for dung organisms and aquatic organisms and are supported. The disposal advice contained in the SPC is in line with current guidance and was considered acceptable.

III.B.2 Residues documentation

No residue depletion data were provided due to the legal base of the application. The applicant is claiming exemption from the requirement for bioequivalence

studies in accordance with the bioequivalence guideline (EMA/CVMP/016/00-Rev 2).

Withdrawal Periods

The proposed withdrawal period following the use of the generic product is the same as that for the reference product on the basis that the two products have been shown to be comparable and bioequivalence has been demonstrated:

Based on the data provided, a withdrawal period of 35 days for meat and offal and Not permitted for use in lactating animals producing milk for human consumption are justified.

IV. CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and similarity with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.I. Pre-Clinical Studies

As this is a generic application according to Art. 13 (1) of Directive 2001/82/EC, as amended, preclinical studies are not required.

Tolerance in the Target Species

Due to the similarity of generic and reference formulations, studies on target animal tolerance are not required. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.II. Clinical Documentation

As this is a generic application according to Art. 13 (1) of Directive 2001/82/EC, as amended, clinical studies are not required.

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.

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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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