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

Dectomax 10 mg/ml Solution for Injection for Cattle and Sheep
Doramax 10 mg/ml Solution for Injection for Cattle and Sheep

Date Created: September 2024

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Dectomax 10 mg/ml Solution for Injection for Cattle and Sheep Doramax 10 mg/ml Solution for Injection for Cattle and Sheep
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 and Sheep
Indication for use	**Cattle:** For treatment of infestations of gastrointestinal roundworms, lungworms, eyeworms, warbles, lice and mange mites. Gastrointestinal roundworms (adults and fourth stage larvae) • *Ostertagia ostertagi* (inc. inhibited larvae) • *O. lyrata** • *Haemonchus placei* • *Trichostrongylus axei* • *T. colubriformis* • *Cooperia oncophora* • *C. pectinata** • *C. punctata* • *C. surnabada (syn. mcmasteri)* • *Nematodirus spathiger** • *Bunostomum phlebotomum** • *Strongyloides papillosus** • *Oesophagostomum radiatum* • *Trichuris* spp.* * adults

	Lungworms (adults and fourth stage larvae) • *Dictyocaulus viviparus* Eyeworms (adults) • *Thelazia* spp Warbles (parasitic stages) • *Hypoderma bovis,* • *H. lineatum* Sucking lice • *Haematopinus eurystemus,* • *Linognathus vituli,* • *Solenopotes capillatus* Mange mites *Psoroptes bovis,* *Sarcoptes scabiei* May also be used as an aid in the control of *Nematodirus helvetianus*, biting lice (*Damalinia bovis*) and the mange mite *Chorioptes bovis*. **Sheep:** For treatment and control of *Psoroptes ovis* (sheep scab mite) and for the treatment and control of gastrointestinal roundworms and nasal bots. Mange mites • *Psoroptes ovis* Gastrointestinal roundworms (Adults and fourth stage larvae (L4) unless otherwise indicated): • *Chabertia ovina* (adults only)

	• *Cooperia curticei* (L4 only) • *C. oncophora* • *Gaigeria pachycelis* • *Haemonchus contortus* • *Nematodirus battus* (L4 only)[1] • *Ostertagia (Teladorsagia) circumcincta* * • *Oesophagostomum columbianum* • *Strongyloides papillosus* • *Trichostrongylus axei* • *Trichostrongylus colubriformis* • *Trichostrongylus vitrinus* • *Trichuris* spp (Adults only) * Inhibited larval stages (L4) including strains that are benzimidazole resistant, are also controlled. [1]For effective treatment and control of both adults and L4 larvae of *Nematodirus battus* a dose rate of 300 mcg/kg is required. <u>Lungworms</u> • *Dictyocaulus filaria* (Adults only) <u>Nasal bots (1st, 2nd and 3rd instar larvae)</u> • *Oestrus ovis*

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	03/07/2024

I. SCIENTIFIC OVERVIEW

The applications are for generic products with the reference product for GB being Dectomax 10 mg/ml and the reference product for NI being Zearl 10 mg/ml which have been authorised since 1994 and 2009 respectively.

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 doramectin and the excipients ethyl oleate, butylated hydroxyanisole and sesame oil.

The container/closure system consists of Type II glass vials, closed with chlorobutyl rubber stoppers and an aluminium cap. 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.

[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 regulatory 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.

Process validation data on the product have been presented in accordance with the relevant regulatory guidelines.

II.C. Control of Starting Materials

The active substance is doramectin, an established active substance supported by an ASMF. 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 comply with Ph. Eur.

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 appropriate to adequately control the quality of the pharmaceutical form.

II.F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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: 3 years.
Shelf life after first opening the immediate packaging: 28 days.
Store in the original package in order to protect from light.
Do not freeze. Do not refrigerate

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a Generic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10) as amended, the bioequivalence with a reference product has been demonstrated, results of pharmaco-toxicological tests are not required.

Toxicological Studies

Not applicable due to the legal basis of the product

User Safety

A user risk assessment was provided in compliance with the relevant guidelines.

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:

- Do not eat, drink or smoke while handling the product.
- Wash hands after use.
- Take care to avoid accidental self administration - seek medical attention should any specific signs be noticed.
- Advice to Medical Practitioners: In cases of accidental self injection specific symptoms have rarely been observed and therefore any cases should be treated symptomatically.

Environmental Safety

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

Phase I:
A Phase I assessment was provided. It was concluded that a Phase II ERA was required because the product is to be used for the control of parasites in animals reared on pasture.

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 doramectin, unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	2.075 mg/l (pH 5.69, 20±0.5°C)
Dissociation constants in water pKa	OECD 112	No dissociation at environmentally relevant pH 1 - 12
UV-Visible Absorption Spectrum	OECD 101	245.0 nm (acidic) 245.5 nm (neutral) 245.5 nm (basic)
Melting Point/Melting Range	OECD 102	151.1 – 157.0°C
Vapour Pressure	OECD 104	9.2×10^{-6} Pa
n-Octanol/Water Partition Coefficient logP_{ow}	OECD 107	6.71

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	geometric mean DT_{50} = 30.7 days* geometric mean DT_{90} = 131.6 days
Aerobic and Anaerobic Transformation in Soil	OECD 307	geometric mean $K_F^{ads}oc$ = 4615 ml/g

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata* Growth rate	OECD 201	EC50	>472 µg/l
Daphnia sp. immobilisation	OECD 202	EC50	0.0107 µg/l
Fish, acute toxicity/ *Oncorynchus mykiss*	OECD 203	LC50	14.1 µg/l

Study type	Guideline	Endpoint	Result
Earthworm/ *Eisenia foetida,* reproduction	OECD 220/222	NOEC	0.50 mg/kg soil dwt
Dung beetle larvae *Onthophagus Taurus Emergence*	OECD draft	EC50	0.518 mg/kg wwt
Dung fly *Musca autumnalis* emergence/development	OECD 208	EC50	0.0423 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. For PECdung, no excretion profile data were available so the conservative default assumption that 100% of the dosage is excreted in one day has been used. The following PEC values represent the worst case for all target animal PECS that were calculated.

Target animal	PEC						
	Soil initial (µg/kg)	Ground water (µg/l)	Surface water (µg/l)	Sediment (µg/l)	PECdung (µg/kg)	Surface water direct excretion (µg/l)	Sediment direct excretion (µg/l)
Pasture reared cattle	1.67	0.005	0.0017	0.395	5080	0.418	4.768
Ewe	0.96	0.003	0.0010	0.232	12000	n/a	n/a

Risk Characterisation (Risk Quotient)

In the initial Tier A risk characterisation, predicted no effect concentrations (PNEC) were calculated using the assessment factors (AF) in VICH guidelines. Then they were compared with the PEC values for each target animal, as follows.

Pasture Reared Beef Cattle

Test organism	End point	AF	PNEC	PEC	RQ
Dung fly larvae	EC_{50}[1] = 0.0055 mg/kg dung wwt	100	0.055 µg/kg dung wwt	5080 µg/kg	**92364**
Dung beetle larvae	EC_{50} [2]= 0.518 mg/kg wwt	100	5.18 µg/kg dung wwt	5080 µg/kg	**981**
Earthworm	NOEC = 0.50 mg/kg soil dwt	10	50 µg/kg soil dwt	1.67 µg/kg	0.03

Test organism	End point	AF	PNEC	PEC	RQ
Algae	EC_{50} >472 µg/l	100	4.72 µg/l	0.0017	0.0004
				0.418[4]	0.09
Daphnia	EC_{50} = 0.0107 µg/l	1000	0.0000107 µg/l	0.0017	**158.9**
				0.418[4]	**39065**
Fish	LC_{50} = 14.1 µg/l	1000	0.0141 µg/l	0.0017	0.12
				0.418[4]	**29.6**
Sediment	n/a	n/a	0.00249 µg/kg dwt[3]	0.395	**158.6**
				4.768[4]	**1915**

[1] Based on a dung water content of 87.0% (water content of homogenised dung at test start); dry weight EC_{50} = 0.0423 mg/kg dung dw
[2] Based on a dung water content of 89.88% (water content of homogenised dung at test start); dry weight EC_{50} = 5.12 mg/kg dung dw
[3]With regard to sediment, there is no requirement during Tier A to undertake experimental ecotoxicity studies on sediment dwelling organisms. In the absence of experimental data, CVMP Equation 16 (together with CVMP Equations 17, 18, and 19) is used to generate a PNECsediment.
[4]Direct excretion

Pasture Reared Sheep

Test organism	End point	AF	PNEC	PEC	RQ
Dung fly larvae	EC_{50}[1] = 0.0055 mg/kg dung wwt	100	0.055 µg/kg dung wwt	12000 µg/kg	**21818**
Dung beetle larvae	EC_{50} [2]= 0.518 mg/kg wwt	100	5.18 µg/kg dung wwt	1200	**232**
Earthworm	NOEC = 0.50 mg/kg soil dwt	10	50 µg/kg soil dwt	0.96	0.02
Algae	EC_{50} >472 µg/l	100	4.72 µg/l	0.001	0.0002
Daphnia	EC_{50} = 0.0107 µg/l	1000	0.0000107 µg/l	0.001	**93.5**
Fish	LC_{50} = 14.1 µg/l	1000	0.0141 µg/l	0.001	0.07
Sediment	n/a	n/a	0.00249 µg/kg dwt[3]	0.232	**93.2**

Based on a dung water content of 87.0% (water content of homogenised dung at test start); dry weight EC_{50} = 0.0423 mg/kg dung dw
[2] Based on a dung water content of 89.88% (water content of homogenised dung at test start); dry weight EC_{50} = 5.12 mg/kg dung dw
[3]With regard to sediment, there is no requirement during Tier A to undertake experimental ecotoxicity studies on sediment dwelling organisms. In the absence of experimental data, CVMP Equation 16 (together with CVMP Equations 17, 18, and 19) is used to generate a PNECsediment.

Based on the calculation of risk quotients (RQ) from the Phase II Tier A risk assessment, the evaluation for doramectin indicates no unacceptable risk to

earthworms, algae, or fish from drainage or run-off, and no risk to algae from direct excretion, when the product is used as proposed (RQ <1).

However, an environmental risk cannot be ruled out for the following:

- Dung organisms (such as dung fly larvae and dung beetles);
- Fish, due to direct excretion;
- Aquatic invertebrates and sediment-dwelling organisms, due to run-off, drainage, or direct excretion.

Additionally, due to the log K_{OW} value exceeding 4, the potential for bioaccumulation and secondary poisoning must also be considered.

Tier B
A proprietary bioaccumulation study in fish, conducted according to OECD Guideline 305, was submitted. The results showed that the bioconcentration factor (BCF) was significantly below the threshold value of 1000, indicating that the substance is not bioaccumulatve and a secondary poisoning assessment is not necessary.

To refine the risk assessment for dung organisms, the applicant referenced several published studies, arguing that the adverse effects of doramectin on these populations are acute and localised, both in time and space. The applicant suggested that dung organisms are expected to recover from such impacts due to their adaptability, supported by the diversity of their life cycles and behaviours, such as the migration of unexposed populations from untreated pastures. While the applicant's rationale is acknowledged, the conclusion of the risk assessment remains that doramectin is toxic to dung fauna upon exposure. It was noted that the CVMP conducted an Article 35 referral in 2013 (EMEA/V/A-35/81) regarding doramectin-containing injectable and pour-on veterinary medicines used in food-producing mammals. This procedure concluded that doramectin is toxic to dung fauna and that effective risk mitigation measures could not be established. As a result, warning statements were recommended by the Committee and these have been included in the SPC and product literature for this product.

Regarding the risk to aquatic invertebrates, the applicant argued that further chronic data are not necessary in this case. This is due to both the analytical difficulties specific to the active substance and the high likelihood that any additional acute or chronic Daphnia studies would still indicate a risk. The omission of further study data is considered acceptable in this instance, as providing it would not have any meaningful impact or benefit on the risk assessment for this trophic level. Since a risk to aquatic invertebrates remains, the applicant has agreed to include risk mitigation measures (RMM) in line with those recommended during the Article 35 class referral.

Regarding the risk to fish from direct excretion into surface water, the applicant refined the exposure assessment based on the metabolism of the active substance in the animal. This resulted in a revised risk quotient (RQ) of less than

1, indicating an acceptable risk to fish due to direct excretion into surface water by beef cattle.

To address the risk identified at Tier A to sediment organisms, the applicant has provided a GLP-compliant Chironomid study conducted in accordance with OECD guideline 218 (2004). The applicant has applied the correct assessment factor in deriving the PNEC (from the most sensitive endpoint, $NOEC_{emergence}$) and, regarding the risk from run-off/drainage into surface water, the refined RQs for all categories of target species are below the threshold which would indicate a risk (i.e. RQ values are <1).

Concerning direct excretion into surface water, a risk remained despite further refinements; therefore, risk mitigation is required. The precautions proposed for aquatic invertebrates are also considered applicable for sediment organisms.

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

Risk Mitigation Measures
The following warnings have been agreed upon for inclusion in the Summary of Product Characteristics (SPC) and product literature:

Special precautions for the protection of the environment:

- Doramectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments.
- Like other macrocyclic lactones, doramectin has the potential to adversely affect nontarget organisms. Following treatment, excretion of potentially toxic levels of doramectin may take place over a period of several weeks. Faeces containing doramectin excreted onto pasture by treated animals may reduce the abundance of dung feeding organisms which may impact on the dung degradation.

- 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 and sheep.

- The risk to aquatic ecosystems will be further reduced by keeping treated cattle away from water bodies for five weeks after treatment.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because due to this veterinary medicinal product having the same pharmaceutical form and a formulation which is essentially similar to that of the reference product

MRLs

Doramectin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues.

MRLs are listed below:

	All mammalian food producing species
Muscle	40 µg/kg
Liver	150 µg/kg
Kidney	100 µg/kg
Fat / skin	60 µg/kg
Milk	N/A

Withdrawal Periods

Based on the data provided, a withdrawal period of 70 days for meat and offal for cattle. However, as there is no MRL set for milk and, therefore, the veterinary product is contraindicated for use in animals producing milk for human consumption.

IV. CLINICAL DOCUMENTATION

As this is a Generic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10) as amended, and bioequivalence with a reference product has been demonstrated, efficacy 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.

(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)