Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Taurador 10 mg/ml Solution for Injection for Cattle & Sheep

Date Created: March 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Taurador 10 mg/ml Solution for Injection for Cattle & Sheep, Solution for injection
Applicant	Norbrook Laboratories Limited, Station Works, Camlough Road, Newry, Co. Down, BT35 6JP
Active substance	Doramectin
ATC Vet code	QP54AA03
Target species	Cattle Sheep
Indication for use	**Cattle:** For treatment and control of the following harmful species of gastrointestinal roundworms, lungworms, eyeworms, warbles, lice and mange mites. <u>Gastrointestinal roundworms (adults and fourth stage larvae):</u> • *Ostertagia ostertagi (including 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 eurysternus*
- *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*.

The pharmacokinetics of this veterinary medicinal product allows protection of cattle against infection or re-infection with the following parasites for the period indicated:

Species	**Days**
Ostertagia ostertagi	35
Cooperia oncophora	21
Dictyocaulus viviparus	35
Bunostomum phlebotomum	22
Oesophagostomum radiatum	21
Trichostrongylus axei	28
Linognathus vituli	28
Psoroptes bovis	42
Haemonchus placei	28

Sheep:

For treatment and control of *Psoroptes ovis*

	(sheep scab mite) and for the treatment and control of gastrointestinal roundworms and nasal bots. <u>Mange mites:</u> • *Psoroptes ovis* <u>Gastrointestinal roundworms (Adults and fourth stage larvae (L4) unless otherwise indicated):</u> • *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	10/03/2025

I. SCIENTIFIC OVERVIEW

This is a generic application for authorisations in Great Britain (GB) and Northern Ireland (NI). The reference product for GB is Dectomax 10 mg/ml Solution for Injection for Cattle and Sheep, which has been authorised in the UK since August 1994. The reference product for NI is Dectomax Oplossing voor Injectie, 10 mg/ml voor runderen en schepen, which has been authorised in the EU since October 1995. No bioequivalence studies were supplied as the applicant claimed exemption in accordance with exemption 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/2000-Rev.4), which was accepted.

Taurador 10 mg/ml Solution for Injection for Cattle & Sheep contains 10.0 mg/ml doramectin. The indications for cattle are for the treatment and control of the various harmful species of gastrointestinal roundworms, lungworms, eyeworms, warbles, lice and mange mites. The indications for sheep are for the treatment and control of *Psoroptes ovis* (sheep scab mite) and for the treatment and control of gastrointestinal roundworms and nasal bots.

The dose for cattle is a single treatment of 1 ml (10 mg doramectin) per 50 kg bodyweight, equivalent to 200 µg/kg bodyweight, administered in the region of the neck by subcutaneous injection. The dose for sheep is a single treatment of 1 ml (10 mg doramectin) per 33 kg bodyweight, equivalent to 300 µg/kg bodyweight, administered by intramuscular injection for the treatment and control of *Psoroptes ovis* (sheep scab mite) and adult *Nematodirus battus* and a single treatment of 1 ml (10 mg doramectin) per 50 kg bodyweight, equivalent to 200 µg/kg bodyweight, administered by intramuscular injection for the control of certain other gastrointestinal nematodes and nasal bots.

The distribution category in GB and NI is POM-VPS, a veterinary medicine that may be prescribed by any Registered Qualified Person.

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 and refined sesame oil.

The container/closure system consists of a multi-dose Type II amber glass vial with nitryl rubber bungs and aluminium seal. 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 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. The manufacturing method consists of a standard process for manufacture and filling of a sterile solution.

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, not monographed in a pharmacopeia, but supplied supported by Active Substance Master Files (ASMFs). The active substance is manufactured in accordance with the principles of good manufacturing practice.

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

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 are described in the European Pharmacopoeia and comply with their respective monographs.

The applicant's specification for the vials includes tests and limits to ensure compliance with the requirements of the pharmacopoeia.

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 appropriate for this pharmaceutical form.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable regulatory guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

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

The shelf life of the veterinary medicinal product as packaged for sale is 2 years. The shelf life after first opening the immediate packaging is 6 months. The product should not be refrigerated or frozen or stored above 30°C. It should be protected from direct sunlight and stored in the original package.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of the applications, no new pharmacological or toxicological studies were required. The active substance has a well-established use in veterinary medicine and evidence is based on data regarding the reference products. No bioequivalence studies were performed to the reference products as the applicant claimed exemption from the requirement for these studies in accordance with exemption 7.1.b) of the Guideline on the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMA/CVMP/016/2000-Rev.4).

III.A Safety Documentation

Pharmacological Studies

Doramectin is a fermentation-derived antiparasitic agent which belongs to the avermectin class and is closely related structurally to ivermectin. Both compounds share a wide spectrum of antiparasitic activity and produce a similar paralysis in nematodes and parasitic arthropods. This mode of action is due to avermectin binding where the physiological response is an increase in membrane permeability to chloride ions. The subsequent influx of chloride ions results in hyperpolarisation and paralysis. Doramectin is exceptionally well-tolerated in mammals, where receptor/channel complexes are localised in the Central Nervous System (CNS). Poor penetration of large molecular weight compounds, such as avermectins, through the blood-brain barrier suggests that high systemic concentrations would be required before neurological function is affected.

Maximum plasma concentration of doramectin occurs in cattle 3 days after subcutaneous administration. In sheep the maximum plasma concentration of doramectin occurs 2 days after intramuscular administration. An elimination half-life of around 6 days for cattle, by the subcutaneous route, and 4.5 days for sheep, by the intramuscular route, results in sustained doramectin concentrations which protect cattle and sheep from parasitic infection and re-infection for extended periods following treatment.

Toxicological Studies

Due to the legal basis of the application, no new toxicological studies were conducted, but the applicant provided the following bibliographical toxicity data regarding the active substance:

- Single Dose Toxicity
    - In rats the oral LD_{50} (the dose at which a substance is lethal for 50% of animals tested) in females is 500 - 1000 mg/kg and in males the oral LD_{50} is 1000 - 2000 mg/kg. in rats the dermal LD_{50} is >2000 mg/kg and the inhalation LD_{50} is 0.54 mg/l (4 hrs).
- Repeated Dose Toxicity

- The oral toxicity reference value for dogs with sub chronic administration, for 3 months, is 0.1mg/kg/day. In rats the oral toxicity reference value for sub chronic administration, for 3 months, is 2mg/kg/day.

- Reproductive Toxicity, including Teratogenicity:
  - In rats the oral no observable effect level (NOEL) is 0.3 mg/kg/day.
  - For developmental toxicity the oral NOELs in rats is >6mg/kg/day, in mice is 3mg/kg/day and in rabbits is 0.75mg/kg/day.
- Mutagenicity
  - No data is available to indicate the active substance present at greater than 0.1% is mutagenic or genotoxic
- Carcinogenicity
  - The active substance is not considered to be a carcinogen.

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:

- Take care to avoid accidental self-administration. If any adverse effects are noticed following accidental self-administration, seek medical advice and show the package leaflet or the label to the physician.
- This veterinary medicinal product can be irritating to eyes. Avoid accidental contact with the eyes, including hand-to-eye contact. In the case of accidental contact with the eyes rinse with plenty of water.
- The veterinary medicinal product may cause embryotoxicity and toxic effects to newborns via breastfeeding. Pregnant and breastfeeding women should therefore take special care when handling this veterinary medicinal product.
- Do not eat, drink or smoke while handling the product.
- Wash hands after use.
- Advice to medical practitioners: In case 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.

The product is a ectoparasiticide, 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 doramectin unless indicated otherwise.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	2.22 mg/l
Dissociation constants in water pKa	Calculation	No dissociation at environmentally relevant pH 4 - 9 based on structure
UV-Visible Absorption Spectrum	Published literature – endpoint values	UV maxima: 245 nm Published source
Melting Point/Melting Range	Published literature – endpoint values	116 - 119°C Published source
Vapour Pressure	Calculation	1.0×10^{-6} Default, worst-case for modelling, assuming no loss through volatilisation.
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 123	6.74 Bioaccumulation considered as the $logP_{ow}$ >4.

Environmental fate

Study type	Guideline	Result
Soil Adsorption/Desorption	OECD 106	Geometric mean K_{oc} 29078 l/kg. Classified as immobile.
Aerobic and Anaerobic Transformation in Soil	OECD 307	Geometric DT_{50} (20°C) of 99 days. Geometric DT_{50} (12°C) of 327 days Classified as very persistent.

Environmental effects

Study type	Guideline	Endpoint	Result
Algae, Growth Inhibition *Pseudokirchneriella subcapitata*	OECD 201	EC50	≥20 mg/l
Daphnia sp. immobilisation	OECD 202	EC50	49 ng/l
Fish, acute toxicity/ *Cyprinus carpio*	OECD 203	LC50	2.3 µg/l
Earthworm*/Eisenia Andrei* subacute/reproduction	OECD 220/222	NOEC	8.4 mg/kg

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. The following PEC values were calculated. Treatment of beef cattle represents the worst-case scenario for environmental exposure.

Target animal	PEC		
	Soil (µg/kg)	Groundwater (µg/l)	Surfacewater (µg/l)
Beef cattle	1.81	0.00088	0.00029 (runoff) 0.00171 (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.

Beef cattle

Test organism	End point	AF	PNEC	PEC	RQ
Algae, Growth Inhibition	≥0.20 mg/l	100	≥2.0 µg/l	0.00029 µg/l 0.00171 µg/l	0.000145 0.00085
Daphnia sp. immobilisation	49 ng/l	1000	0.000049 µg/l	0.00029 µg/l 0.00171 µg/l	5.9 35
Fish, acute toxicity	2.3 µg/l	1000	0.0023 µg/l	0.00029 µg/l 0.00171 µg/l	0.13 0.74
Earthworm reproduction	8.4 mg/kg	10	840 µg/l	1.81 µg/kg	0.002

A literature review of the ecotoxicological effects of doramectin on dung fauna was performed; however, in the absence of appropriate endpoint data, RQ values could not be calculated for these species in Tier A. The CVMP Article 35 referral for doramectin-containing injectable and pour-on veterinary medicines used in food-producing mammals concludes that doramectin is toxic to dung fauna and recommends appropriate warning statements and risk mitigation measures. Given the well-established risks identified for doramectin toward dung fauna, a Tier B assessment and generation of new ecotoxicological data were not considered necessary. The warning statements and risk mitigation measures recommended by the Article 35 referral for dung fauna have been applied by the applicant, and therefore, assessment concluded in Tier A.

As the RQs for *daphnia* via runoff and direct excretion were >1, further assessment of environmental risks, including those for sediment species were required.

In the Tier B assessment, the risk characterisation for *daphnia* was refined using a PNEC calculated from a 21-day reproduction NOEC (OECD 211). Although no unacceptable risks were identified from the refined risk characterisation (RQs <1), a warning statement recommended by the Article 35 referral for doramectin, highlighting the toxicity aquatic organisms was included in the SPC and product literature. Furthermore, to address risks identified for aquatic invertebrates via direct excretion in Tier A, and to comply with the Article 35 referral for doramectin, appropriate risk mitigation measures were included, directing users to keep treated cattle away from watercourses for five weeks.

A PNEC derived from a 28-day NOEC for *Chironomus riparius* emergence (OECD 218) was used for the risk characterisation of sediment-dwelling species. When compared to a sediment PEC value, no unacceptable risks were identified (RQ <1).

As doramectin has a $logP_{ow}$ >4, the potential for bioaccumulation was assessed via an OECD 305 study in zebrafish. The bioconcentration factor (BCF) derived from this study was below the trigger value of 2000 l/kg, and therefore, doramectin was not considered to be a bioaccumulative substance. While doramectin did not fulfil the bioaccumulative criteria of the persistent, bioaccumulative, and toxic (PBT) assessment, and is thus, not considered a PBT substance, the applicant concluded that it was persistent (DT_{50} >120 days) and potentially toxic, based on the EC_{50} generated for *daphnia*. This conclusion is supported.

The environmental warnings and risk mitigation measures included in the SPC and product literature align with those recommended by the Article 35 referral for products containing doramectin and are considered appropriate.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted due to the legal basis of this application. It is accepted that the withdrawal periods for the product are the same as those for the reference products.

MRLs

Doramectin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for meat and offal. However, the active substance has a restriction preventing its use in animals producing milk for human consumption. The marker substance is doramectin.

MRLs are listed below:

	All Mammalian Food Producing Species
Muscle	40 µg/kg
Liver	100 µg/kg
Kidney	60 µg/kg
Fat	150 µg/kg
Milk	N/A

Withdrawal Periods

Based on the data provided, a withdrawal period of 70 days for meat and offal in cattle and sheep are justified. The product is not permitted for use in lactating animals producing milk for human consumption. Therefore, it should not be used in pregnant cows or heifers, which are intended to produce milk for human consumption, within 2 months of expected parturition or pregnant ewes, which are intended to produce milk for human consumption, within 70 days of expected parturition.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

As this application is for a generic product, and bioequivalence with the reference product is accepted, no new pharmacological or tolerance studies are not required.

Resistance

Resistance to doramectin and other avermectins has been reported *in Psoroptes ovis* in cattle (Europe) and sheep (UK) and in gastro-intestinal nematodes, especially *Haemonchus* spp (outside Europe/UK)., *Cooperia* spp. and *Ostertagia ostertagi* in cattle (Europe including the UK) and *Teladorsagia* spp., *Trichostrongylus* spp. and *Haemonchus* spp. in sheep (Europe including the UK).

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

As this application is for a generic product and bioequivalence with the reference product is accepted, no new clinical data is provided.

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)