IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Taurador 5 mg/ml Pour-on Solution for Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0617/001 (formerly UK/V/0450/001)
Name, strength and pharmaceutical form	Taurador 5 mg/ml Pour-on Solution for Cattle
Active substances(s)	Doramectin
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Date of Authorisation	25 September 2013 (UK) 29 November 2013 (IE)
Target species	Cattle
Indication for use	For treatment 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 phlebotomum*[1] *Oesophagostomum radiatum* *Trichuris* spp[1] [1] adults 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* Mange mites *Psoroptes bovis,* *Sarcoptes scabiei,* *Chorioptes bovis* Horn fly *Haematobia irritans* Duration of activity The veterinary product protects cattle against infection or re-infection with the following parasites for the periods 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 veterinary product also controls horn flies (*Haematobia irritans*) for at least 42 days after treatment.
ATCvet code	QP54AA03
Concerned Member States	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Ireland (now RMS), Italy, Latvia, Lithuania, Luxembourg, Malta, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

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

These three products are solutions containing 5 mg/ml of doramectin. The indication is for the treatment of a variety of gastrointestinal roundworms, lungworms, eyeworms, warbles, sucking and biting lice, mange mites, and hornfly in cattle. The products are applied as a single treatment of 500 µg of doramectin/kg bodyweight, which is equivalent to 1 ml of product per 10 kg bodyweight. The products are applied topically along the mid-line of the back between the withers and tail head. Where cattle are treated collectively, dosing
should be performed by bodyweight in order to avoid under- or over-dosing. These were generic applications, and the reference product was Dectomax 5 mg/ml Pour-On Solution for Cattle, first authorised in the UK in 1997.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species, the slight reactions observed are indicated in the SPC. The products are 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. Avermectins may not be well tolerated in all non-target species. There are specific warnings in the SPC that especially dogs (collies, old English Sheepdogs and related breeds or crosses), and turtles and tortoise, along with all non-target species should not be permitted to ingest the product. The efficacy of the products 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. Composition

The products contain 5 mg/ml of doramectin and the excipients brilliant blue FCF (E133), cetearyl octanoate, isopropyl alcohol, purified water and trolamine. The container/closure system consists of 250 mL and 1 L standard high density polyethylene bottles with 28 mm polypropylene/high density polyethylene caps. Or 1 L, 2.5 L and 5 L white flat-bottomed heavy duty high density polyethylene back-packs with 38 mm white polypropylene easy peel caps. Or 10 L and 20 L high density polyethylene jerry cans with high density polyethylene caps. 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 products are an established pharmaceutical form, and their development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product
The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the products have been presented in accordance with the relevant European guidelines. Isopropyl alcohol is added to a mixing vessel, followed by cetearyl octanoate. Doramectin is then added, followed by brilliant blue FCF (E133) in purified water, and triethanolamine. Fill volume is achieved using further isopropyl alcohol, and the product is then packaged for sale.

C. Control of Starting Materials
The active substance, doramectin, an established active substance which is not described in the European Pharmacopoeia, but it is a product of fermentation, which is cited in this document. A suitable in-house specification was provided for doramectin. 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. Suitable ASMF[1] documentation were provided.

Excipients described in a pharmacopoeia are purified water and isopropyl alcohol. The specification used for triethanolamine is that of the USPNF[2].

Excipients not described in a pharmacopoeia are cetearyl octanoate and brilliant blue FCF (E133), for which suitable specifications were provided.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
A signed TSE declaration confirming that the solutions complied with the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 rev 2 of October 2003). This was considered acceptable.

E. Control on intermediate products
Not applicable.

F. 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. Tests include those for appearance, amount of active substance, doramectin-related substances, water content, specific gravity, dose uniformity and microbiological quality.

G. Stability
Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A study was presented which showed the degradation of doramectin under a variety of stress conditions. The active substance was unstable in the presence of high temperature, strong acid and light, and moderately unstable in strong alkali.

Doramectin was however stable in high humidity and oxidative conditions. Three consecutive batches of doramectin were used in accelerated and long-term stability studies, with the active substance being stored at 40°C/75% RH,

25°C/60% RH, and at 2 – 8°C in receptacles representative of the commercial packaging. A retest period of 9 months at 2 – 8°C was recommended.

For the finished products, stability data were presented for 3 commercial-scale batches, presented in the proposed sizes, in suitable containers. Storage parameters ranged from 3 months at 25°C/60 RH to 24 months at 25°C/60% RH for variously sized products. One set of stored product was retained 0 Months at 25°C/60% RH. There was an increase in related substances and water content on storage, and this is reflected in the shelf-life that was ultimately determined.

H. Genetically Modified Organisms
Not applicable.

J. Other Information

Shelf life of the veterinary medicinal products as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 3 months.
Protect from light.
Do not refrigerate.
Store in tightly closed original container.
[1] ASMF – Active Substance Master File.
[2] USPNF – United States Pharmacopeia and The National Formulary.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As these were generic applications according to Article 13, and bioequivalence with a reference product has been established, results of toxicological and pharmacological tests were not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the products to users, the environment and consumers.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

A literature search was provided which described the two modes of action of doramectin; the binding to post-synaptic glutamine-gated chloride ion channels and the increased release of GABA[1] in pre-synaptic neurons in the target parasite, both leading to subsequent paralysis and death.

Pharmacokinetics

A literature search provided data on the effect of route of administration of the active substance, and the sequestering of avermectins. No further data were required for this section.

Toxicological Studies

The applicant provided an overview of toxicological data. No additional data were required.

User Safety

The applicant provided a user safety assessment. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Persons 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 veterinary 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 accidental eye exposure occurs, flush the eyes immediately with water and get medical attention. Use only in well ventilated areas or outdoors.

Highly Flammable - Keep away from heat, sparks, open flame or other sources of ignition.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline. Further assessment was required, this is mandatory for ectoparasitacides, therefore a Phase II assessment was also provided. The assessment drew several conclusions. Acceptable PECs[2] were calculated for soil, groundwater, surface water, sediment and dung, and acceptable PNECs[3] were calculated for enchytaieds, springtails, fish, sediment dwellers, algae and *Daphnia*. Suitable soil adsorption/desorption data were also provided.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

- Doramectin is very toxic to aquatic organisms. Like other macrocyclic lactones, doramectin has the potential to adversely affect non-target 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.

III.B Residues documentation

No data were required for this section. Confirmation was provided that two excipients, brilliant blue FCF (E133), and purified water, (not seen in the reference product), would not cause additional issues to these products with regard to residues. The products are otherwise considered synonymous with the reference product.

Withdrawal Periods

Based on the data provided above, a withdrawal period of 35 days was agreed for meat and offal. The product is not to be used in lactating cows used to produce milk for human consumption, or in dry cows or pregnant dairy heifers within 60 days prior to calving.

[1] GABA – gamma-aminobutyric acid.
[2] PEC - Predicted Environmental Concentration.
[3] PNEC – Predicted No Effect Concentration.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for these products were considered equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

Although data were not required in this section, the applicant provided bibliographical references for the pharmacodynamic and pharmacokinetic properties of the active substance. These data were acceptable.

Tolerance in the Target Species of Animals

Although data were not required for this section, the applicant provided a tolerance study. These data were accepted as supporting the applications.

Resistance

There is a lack of evidence to support any resistance to doramectin by target pathogens. However, adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

There was no requirement to provide data for this section, however, the applicant provided a suitable supporting literature review.

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.