United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tauramox 5 mg/ml Pour-On Solution for Cattle

Date Created: 6th June 2018

PuAR correct as of 27/02/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0601/001/DC
Name, strength and pharmaceutical form	Tauramox 5 mg/ml Pour-On Solution for Cattle
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry Co. Down BT35 6JP Northern Ireland
Active substance(s)	Moxidectin
ATC Vetcode	QP54AB02
Target species	Cattle
Indication for use	Infections of cattle with parasites sensitive to moxidectin. For the treatment of infections caused by: - Adult and larval gastro-intestinal nematodes: *Haemonchus placei* *Ostertagia ostertagi* (including inhibited larvae) *Trichostrongylus axei* *Nematodirus helvetianus* *Cooperia oncophora* *Cooperia punctata* (adults) *Oesophagostomum radiatum* (adults) *Bunostomum phlebotomum* (adults) - Adult respiratory tract nematode *Dictyocaulus viviparus* - Warbles (migrating larvae) *Hypoderma bovis* *Hypoderma lineatum* - Lice *Linognathus vituli* *Haematopinus eurysternus* *Solenopotes capillatus* *Bovicola bovis (Damalinia bovis)* - Mange Mites *Sarcoptes scabiei*

	Psoroptes ovis *Chorioptes bovis* - Horn Flies *Haematobia irritans* The Product has a persistent effect in preventing against reinfection by: *Ostertagia ostertagi* for 5 weeks *Dictyocaulus viviparus* for 6 weeks.

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 decentralised procedure	20/01/2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Ireland

I. SCIENTIFIC OVERVIEW

This was a generic application in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference product is Cydectin 0.5% w/v Pour-on for Cattle authorised in the UK since January 1997.

The product is indicated for treatment of infections in cattle with parasites sensitive to moxidectin caused specified adult and larval gastro-intestinal nematodes, adult respiratory tract nematode, warbles (migrating larvae), lice, mange mites and horn flies. The product also has a persistent effect in preventing against reinfection by *Ostertagia ostertagi* for 5 weeks and *Dictyocaulus viviparous* for 6 weeks.

The product is for topical application of a single treatment of 500 µg/kg bodyweight equivalent to 1 ml per 10 kg bodyweight.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 5 mg moxidectin and the excipients tertiary butylhydroquinone (E319), butylhydroxyanisole (E320), isopropyl alcohol, polybutene, PPG-2 myristyl ether propionate, citric acid (anhydrous), propylene glycol and triglycerides (medium-chain).

The container/closure systems consist of either; 250 ml and 1 L fluorinated high density polyethylene single neck dispensers with high density polyethylene/polypropylene caps and coloured fluorinated high density polyethylene ball plugs, 1 L, 2.5 L and 5 L coloured fluorinated flat high density polyethylene back-packs with white polypropylene easy peel caps, or 10 L coloured high density polyethylene fluorinated jerry can with high density polyethylene 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.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European 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 simple mixing and filling process. 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 moxidectin, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is manufactured in accordance with the principles of good manufacturing practice and in accordance certificate of suitability. 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 isopropyl alcohol, butylhydroxyanisole, citric acid (anhydrous), propylene glycol and triglycerides (medium chain) are manufactured in accordance with the Ph. Eur. Tertiary Butylhydroquinone, Polybutene and PPG-2 Myristyl Ether Propionate are manufactured in accordance with the manufacturers own specifications. The excipient specifications are considered adequate to control the quality of the materials. Specifications of all packaging materials are considered satisfactory.

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 include those for: appearance, identification of the active substance, related substances of the active substance, identification and content of excipients, uniformity of mass, fill volume, viscosity, product density and microbial quality.

II.F. 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.

Stability data on the finished product have 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

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 6 months.

Store in original container.
Protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has

been demonstrated, there was no requirement for pharmacological, or toxicological data in this section. An *in vivo* bioequivalence study comparing the final product formulation of the product with the reference product was presented and is discussed in Section 4.

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

III.A Safety Documentation

Pharmacological Studies

The applicant provided a literature review of the pharmacology, pharmacokinetics and toxicology of moxidectin. However, as this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, this data was not required.

User Safety

Due to this being a generic application, it is considered that the exposure, hazards and risks to the user are identical to those of the reference product.
A user risk assessment with supporting literature references was provided in compliance with the relevant guideline which shows that the product is safe for the user when used as recommended. Warnings and precautions as listed on the product literature are the same as for those of the reference product and are considered adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- Avoid direct contact with skin and eyes. The product may be irritating to skin and eyes and users should be careful not to apply it to themselves or to other people.
- Wear safety glasses, nitrile 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, immediately rinse the eyes thoroughly with water and seek medical attention.
- Avoid getting the product in your mouth. Do not smoke or eat whilst handling the product. Wash hands after use.
- Avoid accidental inhalation of this product. Use only in well ventilated areas or outdoors.
- Highly Flammable - Keep away from heat, sparks, open flame or other sources of ignition.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH[3] and CVMP[4] guidelines.

Phase I:
The Phase I ERA concludes that as the product is a parasiticide used in pasture animals, 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 physicochemical properties, environmental fate and effects.

Results were mainly obtained from proprietary studies. The active substance (moxidectin) was used in the assays.

Physicochemical properties

Study type	Result
Water solubility (OECD 105)	Mean solubility of 2.49 x 10^{-4} g/l in double-distilled water
Dissociation constants in water pKa	No dissociation at environmentally relevant pH (pH 4 – 9).
UV-aisible absorption spectrum	UV maxima 242 nm No adsorption >290 nm
Melting point (OECD 102)	From 111°C
Vapour pressure	1.0 x 10^{-6} Pa
n-octanol water partition coefficient logP_{ow} (OECD 123)	6.49 (25°C)

Environmental fate

Study type	Guideline	Result		
Soil adsorption	OECD 106	38 731 l/kg		
Degradation in soil (DT_{50})	OECD 307	**Soil Type**	**DT_{50} (days)**	**DT_{90} (days)**
		Sandy loam	78.6	261.0
		Sandly clay loam	139.0	461.7
		Clay loam	78.7	261.3
		Sand	133.6	444.0

[3] VICH – Veterinary International Conference on Harmonisation.
[4] CVMP - Committee for Medicinal Products for Veterinary Use.

Accounting for an average European temperature (12ºC) for the PBT assessment, adjustment of the determined DT_{50}s results in values greater than 120 days; indicating moxidectin to be persistent in soil. The DT_{90} geometric mean is <365 days (344 days) so there is no requirement to calculate the PEC_{soil} plateau.

Using the ASTM mobility classification scheme (ASTM, 2006), moxidectin is classified as being 'immobile'.

Environmental effects

Study type	Guideline	Endpoint	Result
Terrestrial organisms:			
Dung fly	OECD 228	EC_{50}	100 µg/kg_{wwt}
Dung beetle larvae *Aphodius constans*	OECD 122	LC_{50} (21 day) NOEC (sub-lethal effects)	1 g/kg_{dwt} 1.25 g/kg_{dwt}
Soil fauna *Eisenia fetida*	OECD 222	NOEC	0.8 mg/kg_{dwt}
Aquatic organisms:			
Cyprinus carpio	OECD 202	LC_{50} (96 hour) NOEC (96 hour)	0.11 µg/l 0.073 µg/l
Daphnia magna	OECD 202	EC_{50} (48 hour; immobilisation) NOEC (48 hour; immobilisation)	2 ng/l 26 ng/l
Pseudokirchneriella subcapitata	OECD 201	E_rC_{50}, E_yC_{50} (0 – 72 hour) NOEC (0 – 72 hour)[3]	>0.11 mg/l ≥1.1 mg/l

Exposure assessment (Predicted exposure concentration)

Initial PEC values have been calculated according to the standard algorithms and calculations described in EMEA/CVMP/ERA/418282/2005-Rev.1. The calculated values are summarised in the table below.

Compartment	Model	PEC
Dung	CVMP Equation 8	84.7 mg/kg_{dwt} (beef cattle)
Soil	Phase 1 screen based on worst case	4.18 µg/kg_{dwt} (beef cattle)
Groundwater	CVMP Equation 32	0.0015 µg/l
Groundwater (refined)	FOCUS PEARL	<0.000001 µg/l
Surface water – run off drainage	CVMP Equation 36	0.0005 µg/l
Surface water - run-off drainage	FOCUS STEP-3	0.58 ng/l (max) 0.21 ng/l (7 day TWA) 0.10 ng/l (21 day TWA)
Sediment - run-off drainage	CVMP Equations 10 to 13	0.37 µg/kg_{dwt} 0.97 µg/kg_{dwt}
Sediment - run-off drainage	FOCUS STEP-3	0.33 µg/kg_{dwt} (max)
Surface water - direct excretion	CVMP Equation 14	0.523 µg/l
Surface water - direct	CVMP Equation 44	0.00322 µg/l

excretion		
Sediment - direct excretion	CVMP Equation 46	2.4 µg/kg_{wwt} 6.24 µg/kg_{dwt}

As the concentration of moxidectin in groundwater is predicted to be <0.01 µg/l, an unacceptable risk to groundwater from moxidectin is not expected.

TIER A Risk Characterisation (Risk Quotient)

The PNEC values were compared with the PEC value to derive RQ values. Initial PNEC values have been calculated according to VICH guidelines.

Organism	PEC	PNEC	RQ
Dung fly	Dung 84 700 µg/kg_{dwt}	4.7 µg/kg_{dwt}	**18 021**
Dung beetle		10 µg/kg_{dwt}	**8 470**
Earthworms	Soil 4.18 µg/kg_{dwt}	80 µg/kg	0.052
Algae	Surface water *run-off drainage* 0.5 ng/l	>1100 ng/l	0.0005
Daphnia		0.026 ng/l	**19**
Fish		0.110 ng/l	**4.545**
Algae	Surface water *direct excretion* 523 ng/l	>1100 ng/l	0.48
Daphnia		0.026 ng/l	**20 115**
Fish		0.110 ng/l	**4754**
Daphnia	FOCUS refined Surface water *run-off drainage* 0.58 ng/l	0.026 ng/l	**22**
Daphnia	FOCUS refined Surface water *direct excretion* 3.2 ng/l	0.026 ng/l	**123**
Fish		0.110 ng/l	**29**

TIER B Risk Characterisation (Risk Quotient)

As the findings from a fish bioconcentration study, in accordance with OECD 305, estimated a bioconcentration factor value of >2000 l/kg, moxidectin is considered to fulfil the bioaccumulation criterion.

The assessment for persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances demonstrated moxidectin to be a PBT substance.

An assessment for secondary poisoning was provided which indicates an acceptable risk for top predators from consumption of contaminated fish.

As the RQ values for aquatic invertebrates, fish (surface water, direct excretion) and dung were >1 further assessment of the environmental risk was required. The findings from a chironomid study in line with OECD 218 and a *Daphnia magna* study in line with OECD guideline 211 determined NOECs of 235 µg/kg

and of 3.1 ng/l, respectively. These values were compared with the relevant aquatic PEC values and a risk remained. As a result, risk mitigation wording and information on environmental properties, pertaining to moxidectin, aquatic organisms and dung fauna, was required for the SPC and product literature for this product.

Agreed environmental safety information is as follows.

SPC Section 4.5.iii 'Other precautions regarding impact on the environment'

Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance; therefore, exposure of the environment to moxidectin must be limited to the extent possible. Treatments should be administered only when necessary and should be based on faecal egg counts or evaluation of the risk of infestation at the animal and/or herd level.

Like other macrocyclic lactones, moxidectin has the potential to adversely affect non-target organisms:

- Faeces containing moxidectin excreted onto pasture by treated animals may temporarily reduce the abundance of dung feeding organisms. Following treatment of cattle with the product, levels of moxidectin that are potentially toxic to dung fly species may be excreted over a period more than 2 weeks and may decrease dung fly abundance during that period. It has been established in laboratory tests that moxidectin may temporarily affect dung beetle reproduction; however, field studies indicate no-long term effects. Nevertheless, in case of repeated treatments with moxidectin (as with products of the same anthelmintic class) it is advisable not to treat animals every time on the same pasture to allow dung fauna populations to recover.

- Moxidectin is inherently toxic to aquatic organisms including fish. The product should be used only according to the label instructions. Based on the excretion profile of moxidectin when administered as the pour-on formulation, treated animals should not have access to watercourses during the first week after treatment.

5.3 Environmental properties

Moxidectin fulfils the criteria for a (very) persistent, bioaccumulative and toxic (PBT) substance. In particular, in acute and chronic toxicity studies with algae, crustaceans and fish, moxidectin showed toxicity to these organisms, yielding the following endpoints:

Organism		**EC_{50}**	**NOEC**
Algae	*S. capricornutum*	>86.9 µg/l	86.9 µg/l
Crustaceans (Water fleas)	*Daphnia magna* (acute)	0.0302 µg/l	0.011 µg/l
	Daphnia magna	0.0031 µg/l	0.010 µg/l

	(reproduction)		
Fish	*O. mykiss*	0.160 µg/l	Not determined
	L. macrochirus	0.620 µg/l	0.52 µg/l
	P. promelas (early life stages)	Not applicable	0.0032 µg/l
	Cyprinus carpio	0.11 µg/l	Not determined

EC_{50}: the concentration which results in 50% of the test species individuals being adversely affected, i.e. both mortality and sub-lethal effects.
NOEC: the concentration in the study at which no effects are observed.

This implies that when allowing moxidectin to enter water bodies, this may have a severe and lasting impact on aquatic life. To mitigate this risk, all precautions for use and disposal must be adhered to.

III.B.2 Residues documentation

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, data from toxicological, pharmacological or clinical studies were not required. However, due to differences in the formulation between the test and reference product (use of isopropyl alcohol instead of an aromatic solvent), which may have an impact on the distribution of the product in terms of residues of a topically applied product, the findings from a confirmatory meat residue depletion study have been provided.

Residue Studies

The applicant has conducted residue depletion studies in cattle which confirm that residues of moxidectin in muscle and fat are below the MRL in all treated animals by day 9. This shows that residues at the site of application are not likely to exceed the MRLs for those tissues and supports the 14 day meat and offal withdrawal period authorised for the reference product. The analytical method was High-Performance Liquid Chromatography with Fluorescence Detection. The method was fully validated.

As bioequivalence between the reference product and the test product has been demonstrated, the applicant is entitled to use the same milk withdrawal period as for the reference product.

MRLs

Moxidectin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk. The marker substance is moxidectin.

MRLs are listed below:

	Bovine
Muscle	50 µg/kg
Liver	100 µg/kg

Kidney	50 µg/kg
Fat / skin	500 µg/kg
Milk	40 µg/kg

Withdrawal Periods

Based on the data provided, a withdrawal period of 14 days for meat and offal in cattle and 6 days (144 hours) for milk are justified.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applicant conducted an *in vivo* bioequivalence study comparing the plasma levels of moxidectin in cattle following the topical administration of a test product of moxidectin pour-on to the reference product. The study design was a two period, two treatment, two sequence crossover involving 32 cattle randomly assigned to two groups. The test and control products were administered once during each period. Blood samples were taken from each animal for moxidectin determination at several timepoints post-administration. Following extraction from plasma samples, moxidectin levels were determined by HPLC with fluorescence detection. The lower limit of quantification (LOQ) WAS 0.25 ppb. Kinetic parameters C_{max}[5] *and* AUC_t[6] were calculated for each animal and analysed. Ninety percent confidence intervals were determined at 0.8 to 1.25 for AUC_t and 0.7 to 1.43 for C_{max}. Results showed that the 90% confidence intervals for C_{max} and AUC_t fell entirely within the limits of 0.8 to 1.25 and therefore bioequivalence can be concluded.

Tolerance in the Target Species

The applicant conducted and supplied results of a target animal safety study using multiples of the recommended dose of the product in the target species. The results showed the product was well tolerated and there were no adverse effects. However, as the product was concluded to be bioequivalent to the reference product following an *in vivo* bioequivalence study, there is no requirement for safety studies and therefore this study was viewed as supportive only.

Resistance

The applicant provided a literature overview of the status of resistance to moxidectin. Section 4.4 of the proposed SPC contains appropriate general warnings relating to the prudent use of anthelmintics, in accordance with

[5] Observed maximum drug plasma concentration
[6] Area under the curve.

EMEA/CVMP/EWP/170208/2005 (Guideline on the summary of product characteristics for anthelmintics):
Care should be taken to avoid the following practices because they increase the risk of development of resistance and could ultimately result in ineffective therapy:

- too frequent and repeated use of anthelmintics from the same class, over an extended period of time.
- under dosing, which may be due to underestimation of bodyweight, misadministration of the product, or lack of calibration of a dosing device (if any).

Suspected clinical cases of resistance to anthelmintics should be further investigated using appropriate tests (e.g. faecal egg count reduction test). Where the results of the test(s) strongly suggest resistance to a particular anthelmintic, an anthelmintic belonging to a different pharmacological class and having a different mode of action should be used.
Partial cross-resistance between ivermectin and moxidectin has been reported in nematode parasites. Cases of resistance to moxidectin have been reported in gastrointestinal nematode parasites of cattle, in the EU and elsewhere. Therefore use of this product should be based on local (regional, farm) epidemiological information about susceptibility of parasites, local history of treatments and recommendations on how to limit further selection for resistance to anthelmintics.

IV.II. Clinical Documentation

As this was an application made in accordance with Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been demonstrated, no clinical data are 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 Characteristic 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)