IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Robonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle

PRODUCT SUMMARY

EU Procedure number	IE/V/0542/001 (formerly UK/V/0444/001)
Name, strength and pharmaceutical form	Robonex 5 mg/ml Pour-On Solution for Beef and Dairy Cattle
Active substances(s)	Eprinomectin
Applicant	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal basis of application	Hybrid application (Article 13(3) of Directive No 2001/82/EC)
Target species	Cattle
Indication for use	Indicated for the treatment and prevention of the following parasites Gastrointestinal Roundworms (adults and fourth stage larvae): *Ostertagia* spp., *Ostertagia lyrata* (adult), *Ostertagia ostertagi* (including inhibited *O. ostertagi*), *Cooperia* spp. (including inhibited *Cooperia* spp), *Cooperia oncophora, Cooperia pectinata, Cooperia punctata, Cooperia surnabada, Haemonchus placei, Trichostrongylus* spp., *Trichostrongylus axei, Trichostrongylus colubriformis, Bunostomum phlebotomum, Nematodirus helvetianus, Oesophagostomum* spp. (adult), *Oesophagostomum radiatum, Trichuris* spp (adult). Lungworms (adults and fourth stage larvae): *Dictyocaulus viviparus* Warbles (parasitic stages): *Hypoderma bovis, H. lineatum* Mange Mites: *Chorioptes bovis, Sarcoptes scabiei* var *bovis* Lice: *Damalinia bovis* (biting lice), *Linognathus vituli* (sucking lice), *Haematopinus eurysternus* (sucking lice), *Solenopotes capillatus* (sucking lice). Horn Flies: *Haematobia irritans*. Prolonged Activity Applied as recommended, the product prevents reinfections with: Parasite * Prolonged Activity *Dictyocaulus viviparus* up to 28 days *Ostertagia* spp up to 28 days *Oesophagostomum radiatum* up to 28 days *Cooperia* spp up to 21 days *Trichostrongylus* spp up to 21 days *Haemonchus placei* up to 14 days *Nematodirus helvetianus* up to 14 days *The following parasite species are included within each of

	the relevant genera: *Ostertagia ostertagi, O. lyrata, Cooperia oncophora, C. punctata, C. surnabada, Trichostronglus axei, T. colubroformis*.
ATCvet code	QP54AA04
Date of completion of the original decentralised procedure	23 January 2013 (UK) 01 March 2013 (IE)
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States	France, Ireland (now RMS)

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

This application is a generic (hybrid) application submitted in accordance with Article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference product is Eprinex Pour-On Solution for Beef and Dairy Cattle, marketed in the UK from July 1997. Indications for this product are for the treatment and control of intestinal roundworms, lungworms, warbles, mange mites and lice, with evidence for prolonged activity against some roundworms. The recommended dose is 1ml per 10kg body weight. 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. 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 of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition
The product contains the active ingredient eprinomectin and excipients butylated hydroxytoluene (E321), cetearyl ethylhexanoate, isopropyl myristate, propylene glycol dicaprylocaprate, denatonium benzoate, and isopropyl alcohol.
The container/closure system consists of a translucent 250 mL and 1L HDPE container with integral squeeze measure pour system and white HDPE screw caps, with white 1L, 2.5L and 5L HDPE backpacks and white polypropylene screw caps also available. The particulars of the containers and controls performed are provided and conform to the regulation.
The product has an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product
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 European guidelines. The process involves simple mixing and dissolution of the ingredients in a nitrogen atmosphere. In-process controls are limited to visual assessment of the dissolution of the ingredients and. considering the simplicity of the proposed manufacturing method, the details provided are considered appropriate.

C. Control of Starting Materials
The active substance is eprinomectin, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice (GMP) and the active substance specification is considered adequate to control

the quality of the material. Batch analytical data from two batches demonstrating compliance with this specification have been provided, along with an Active Substance Master File (ASMF).

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products
There are no intermediate products.

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, including HPLC, water content, specific gravity tests and a visual method for product appearance have been provided. Batch analytical data from two batches of 600L supplied from the proposed production site demonstrating compliance with the specification.

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

H. Genetically Modified Organisms
Not Applicable.

J. Other Information
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 3 months.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

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 product to users, the environment and consumers. No new clinical documentation data were required for this application. Data were however provided for a bioequivalence study and a tolerance study, in order to support this generic 'hybrid' application.

III.A Safety Testing
Pharmacological Studies
Pharmacodynamics
Bibliographical data was provided showing that eprinomectin acts by binding selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve or muscle cells. This induces an increase in the permeability of the cell membrane to chloride ions which hyperpolarize the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA). Mammals do not have glutamate-gated chloride channels, therefore a margin of safety for compounds of this class exist with respect to human exposure, enhanced by the fact that the macrocyclic lactones have a low affinity for other mammalian ligand-gated chloride channels, and that they do not readily cross the blood-brain barrier.
Pharmacokinetics
Bibliographical data was also provided showing that bioavailability of topically applied eprinomectin in cattle is about 30%, with most absorption occurring by about 10 days after treatment. Eprinomectin consists of the components B1a (≥ 90% availability) and B1b (≤ 10% availability) which differ by a methylene unit and is not extensively metabolized in cattle following topical administration. Metabolites amount to approximately 10% of the total residues in plasma, milk, edible tissues and faeces.
In specified biological matrices the metabolism profile is nearly identical, and does not change significantly with time after administration of eprinomectin. The ratio of the two drug components in the biological matrices is identical to that in the formulation demonstrating that the two eprinomectin components are metabolised at a near equal rate. Since the metabolism and the tissue distribution of the two components are quite similar, the pharmacokinetics of the two components would also be similar. Eprinomectin is strongly linked to plasma proteins (99%) and faeces are the major route of elimination.

In view of the data provided, it is considered appropriate that the proposed SPC is almost identical to that of the reference product.

Toxicological Studies
The applicant has provided bibliographical data which show:

Oral toxicity
No Observed Effect Level (NOEL) of 5mg/kg/day in rodents and 1mg/kg/day in dogs (Allen, *et al*, 1990, Bagdon, *et al*. 1993, Bagdon & Kloss. 1993 and EMEA/MRL/114/96-FINAL).

Dermal toxicity
Eprinomectin was shown to be safe following topical administration at 1, 3 and 5 times the therapeutic dose in cattle. (EMEA/MRL/114/96-FINAL). In tests on other species, the minor irritation that did occur was attributed to the formulation vehicle (Durand-Cavagna, 1994 & Kloss, *et al*. 1994).
Excipients

Substance:	**PoD:**	**Species:**	**Route:**	**Level:**
Isopropyl Alcohol	LD_{50} Data quoted from the Handbook of Pharmaceutical Excipients 5th Edition	Dog	Oral	4.8 g/kg
		Mouse	Oral	3.6 g/kg
			IP	4.48 g/kg
			IV	1.51 g/kg
		Rabbit	Oral	6.41 g/kg
			Skin	12.8 g/kg
		Rat	IP	2.74 g/kg
			IV	1.09 g/kg
			Oral	5.05 g/kg
Isopropyl myristate		Mouse	Oral	49.7 g/kg
		Rabbit	Skin	5 g/kg
Butylhydroxytoluene		Guinea pig	Oral	10.7 g/kg
		Mouse	IP	0.14 g/kg
			IV	0.18 g/kg
			Oral	0.65 g/kg
		Rat	Oral	0.89 g/kg
Propylene glycol dicaprylate/dicaprate		Mouse	Oral	22.0 g/kg
			IP	9.72 g/kg
			IV	6.63 g/kg
			SC	17.34 g/kg
		Rat	Oral	0.02 g/kg
			IP	6.66 g/kg
			IV	6.42 g/kg
			SC	22.5 g/kg
Denatonium benzoate		Rabbit	Oral	0.508 g/kg
			Skin	0.584 g/kg

User Safety
A user risk assessment was submitted, which identifies nearly all potential routes of exposure, as well as any hazards associated with such exposure. The user warnings, as presented on the SPC are as follows:

This product may be irritating to human skin and eyes and may cause hypersensitivity. Avoid skin and eye contact with the product during treatment and when handling recently treated animals. Users should wear rubber gloves, boots and a waterproof coat when applying the product. Should clothing become contaminated, remove as soon as possible and launder before re-use. If accidental skin contact occurs, wash the affected area immediately with soap and water. If accidental eye exposure occurs, flush eyes immediately with water.

This product may be toxic after accidental ingestion. Avoid accidental ingestion of the product by hand to mouth contact. Do not smoke, eat or drink while handling the product. In the event of ingestion, wash out mouth with water and seek medical advice. Wash hands after use. This product is flammable. Keep away from sources of ignition. Inhalation of the product may cause irritation.
Use only in well ventilated areas or outdoors.

Ecotoxicity
An environmental risk assessment consisting of both Phase I and Phase II, performed as part of the recognised tiered approach, was submitted. Since the active substance in this product is an ectoparasiticide, it has been identified that the assessment goes into Phase II, as ectoparasiticides used on pasture animals automatically require that a Phase II assessment is carried out.
Animals will be treated on pasture, and residues of eprinomectin will reach the environment directly via excreta of treated animals. However, there are sufficient data to conclude that environmental exposure to the active substance will not unduly affect organisms dwelling in groundwater, or adversely affect the ecological state of the pasture itself. Eprinomectin is very toxic to dung fauna and aquatic organisms and may accumulate in sediments, however the warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation
Residue Studies
Residue depletion studies using the final formulation have been conducted in Friesian, Hereford and Limousin cattle. Samples of muscle, liver, kidney, peri-renal fat and muscle from the site of administration and milk were taken from animals at several time points. Results show that residues did not exceed the maximum residue limit (MRL) at any time point.

Bovine Tissues:
The analyte is extracted from the samples using acetonitrile as the solvent, concentrated under nitrogen, then put through an SPE cartridge, derivatised with trifluoroacetic anhydride, reconstituted in the mobile phase, and finally determined using HPLC with fluorescence detection.

Bovine Milk:
Eprinomectin is extracted from milk by a series of solvent extractions followed by sample concentration under nitrogen, derivitization with trifluoroacetic anhydride and reconstitution in mobile phase. Final determination is by HPLC with fluorescence detection.
These methods were fully validated.

Withdrawal Periods
Based on the data provided above, a withdrawal period of 10 days for meat and offal and zero hours for milk are justified.

IV. CLINICAL ASSESSMENT

The efficacy claims for this product are equivalent to those of the reference product.

The applicant has provided the results of a bioequivalence study, using the proposed product and the reference product Eprinex Pour-On Solution for Beef and Dairy Cattle. For the bioequivalence study, the 90% confidence interval for C_{max}[1] was contained entirely within the limits of 0.7 – 1.43. These limits were widened due to greater intra-individual variability and pre-defined in the protocol which has been judged satisfactory justification and in compliance with European guidance. For AUC[2], the lower limit was within 0.8 – 1.25, but the upper acceptance limit was breached. Therefore, bioequivalence between the test and reference product has not been adequately demonstrated in this study.

In order to demonstrate safety of the product in the absence of bioequivalence, the applicant submitted a target animal safety study. This is acceptable given the application has been made in accordance with Article 13(3) of Directive 2001/82/EC, where the applicant is required to provide the results of appropriate pre-clinical tests or clinical trials. The safety study adequately demonstrated tolerance in the target species at 1x, 3x and 5x the recommended dose, for a period in excess of the recommended use. Taking into account the results of both the bioequivalence and target animal safety studies, it can be concluded that the efficacy and target species safety requirements for the test product have been satisfied.

IV.A Pre-Clinical Studies
Tolerance in the Target Species of Animals
The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. An untreated group of animals was used as a control. All doses were administered topically on 3 occasions. A variety

of relevant parameters were analysed, and all data were tested by ANOVA. No adverse effects were seen following doses up to 5 times the recommended dose. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance
The current SPC for the reference product indicates that, to date, no resistance to eprinomectin has been reported within the EU. Nevertheless, it is recommended that use of the product should be based on local (regional, farm) epidemiological information on susceptibility of nematodes.

IV.B Clinical Studies
As this was a generic 'hybrid' application, no data were required for this section.
[1] C_{max} – Maximum concentration of the active substance.
[2] AUC – Area under the curve.

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