United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Norofas Pour-On Solution for Cattle (UK)
Closamectin Pour-On Solution for Cattle (FR)

Updated: December 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0369/001/DC
Name, strength and pharmaceutical form	Norofas Pour-On Solution for Cattle
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry County Down BT35 6JP Northern Ireland
Active substance(s)	Ivermectin, Closantel (as closantel sodium)
ATC Vetcode	QP54AA51
Target species	Cattle
Indication for use	For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice of cattle. <u>Gastrointestinal roundworms (adults and fourth stage larvae)</u> *Ostertagia ostertagi* (including inhibited *O. ostertagi*), *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia* spp, *Oesophagostomum radiatum, Nematodirus helvetianus* (adult), *Strongyloides papillosus* (adult). <u>Lungworms (adult and fourth stage larvae)</u> *Dictyocaulus viviparus* <u>Trematodes (adult and late immatures)</u> *Fasciola gigantica* *Fasciola hepatica* Treatment of fluke at 12 weeks (mature). Treatment of fluke at 7 weeks (late immature).

	Eyeworms (adult) *Thelazia* spp Cattle grubs (parasitic stages) *Hypoderma bovis, Hypoderma lineatum* Lice *Linognathus vituli, Haematopinus eurysternus, Damalinia bovis* Mange Mites *Chorioptes bovis, Sarcoptes scabiei* var *bovis*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	20 April 2011
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	France

I. SCIENTIFIC OVERVIEW

Norofas Pour-On Solution for Cattle has been designed for use in cattle for the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice of cattle. Specifically, the treatment is directed against the following: gastrointestinal roundworms (adults and fourth stage larvae), *Ostertagia ostertagi*, (including inhibited *O. ostertagi*), *Haemonchus placei, Trichostrongylus axei, Trichostrongylus colubriformis, Cooperia* spp, *Oesophagostomum radiatum, Nematodirus helvetianus* (adult), and *Strongyloides papillosus* (adult).

Additionally, the product is to be used to treat lungworms, *Dictocaulus viviparus* (adult and fourth stage larvae), trematodes *Fasciola gigantica* and *Fasciola hepatica* (adult and late immature stages). Treatment of fluke at 7 weeks (late immature) and 12 weeks (mature).

Norofas Pour-On Solution for Cattle may also be used to treat adult eyeworms (*Thelazia* spp), parasitic stage cattle grubs, (*Hypoderma bovis* and *Hypoderma lineatum*), lice (*Linognathus vituli, Haematopinus eurysternus, Damalinia bovis*), and mange mites, (*Chorioptes bovis, Sarcoptes scabiei* var *bovis*).

This application for Norofas Pour-On Solution for Cattle was submitted in accordance with Article 12 (3) of Directive 2001/82/EC, as amended.

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, although care should be taken when using the product in the vicinity of particular breeds of dog, (refer to SPC[1]). The reactions observed are indicated in the SPC.

[1] Summary of Product Characteristics

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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains the active substances ivermectin 5 mg/ml and closantel (as closantel sodium) 200 mg/ml. The product also contains the excipients brilliant blue FCF (E133) dye, anhydrous ethanol, macrogol, cetearyl ethylhexanoate, isopropyl myristate, povidone, denatonium benzoate, trolamine and isopropyl alcohol.

The containers for the product are translucent 250 ml, 500 ml and 1L HDPE[2] containers with white HDPE caps and white 1L, 2.5L and 5L HDPE backpacks with white polypropylene screw 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, anti-microbial preservative efficacy data were provided to demonstrate the self-preserving properties of the product.

The product is 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 method of preparation involves a step-wise mixing and dissolution of the ingredients to produce a final product that is filled into bottles or backpacks.

C. Control of Starting Materials

The active substances, ivermectin and closantel, are established substances described in the European Veterinary Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

All excipients, with the exception of cetearyl ethylhexanoate and isopropyl myristate, are the subject of monographs in the European Pharmacopoeia.

[2] High density polyethylene

Compliance with the requirements of the pharmacopoeia is therefore applied as the specification for each of these ingredients. Cetearyl ethylhexanoate and isopropyl myristate comply with a detailed list of specifications. This is considered acceptable.

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 have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

An HPLC[3] method is used to detect quantities of ivermectin and closamectin and related substances. Analysis of three batches of final product demonstrated compliance with the specification.

G. Stability

Stability data on closantel were provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Ivermectin has an established retest period, and this is acceptable.

Stability data from a number of studies 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. From these data, a shelf life for the product of 12 months was established, with the product being stored at not greater than 25°C.

H. Genetically Modified Organisms

Not applicable.

[3] High performance liquid chromatography

J. Other Information

Cattle must not be treated with Norofas Pour-On Solution for Cattle within 28 days of slaughter for human consumption and the product is not to be used in cattle producing milk for human consumption. Do not use in non-lactating animals including pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition.

The shelf life of the product as packaged for sale is 1 year.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided bibliographical data which indicate that ivermectin uptake by parasites is mainly transcuticular. The varying effects of avermectins on various parasites are believed to be due to differences in membrane permeability to chloride ions. It is likely that parasiticidal action is mediated by interaction of avermectins with glutamate-gated ion channels in nematodes. Other studies implicate GABA postsynaptic receptors, resulting eventually in membrane hyperpolarisation.

Closantel belongs to a class of compounds called salicylanilides, or proton ionophores. It is supposed that these ionophores act on the membrane of parasite mitochondria and ultimately prevent production of a proton gradient across the inner mitochondrial membrane.

The applicant also provided bibliographical data which show that ivermectin is only partially metabolised in cattle. 1% to 2% is excreted in the urine and the remainder in the faeces. Approximately 60% of ivermectin from cattle is unaltered in the dung, the remainder being excreted as metabolites or degradation products. Closantel is poorly metabolised and excreted 90% unchanged in the urine and faeces.

Toxicological Studies

The applicant has provided bibliographical data which show that relevant toxicity issues have been addressed with regard to single and repeated dose toxicity, reproductive toxicity, mutagenicity, carcinogenicity, and other appropriate parameters.

Single Dose Toxicity

Ivermectin

According to published literature, the LD_{50} for ivermectin, when delivered orally to mice is approximately 25 mg/kg, and in the dog, the LD_{50} is approximately 80 mg/kg. Much higher LD_{50}s were observed following dermal administration.

Closantel

For closantel, an LD_{50} of between 331 mg/kg and 453 mg/kg has been seen in mice. This figure, (observed when closantel was given orally), was several times higher than the figure obtained by intramuscular delivery of closantel.

A study was performed by the applicant to check the toxicity of ivermectin and closantel when the two substances are administered together. In this study, ivermectin and closantel were co-administered to mice at 10 mg/kg bodyweight, and 250 mg/kg bodyweight, respectively. There was no mortality.

Repeated Dose Toxicity

For ivermectin, the NOEL[4] has been identified in a 90-day study as being 0.4 mg/kg/day in rats, and 0.5 mg/kg/day in dogs. For closantel, NOELs of 2.5 mg/kg/day in rats, and 2.5 mg/kg/day in dogs have been reported.

Reproductive Toxicity, including Teratogenicity

Reports of several studies on reproductive toxicity/teratogenicity were provided. For ivermectin, a 3-generation study in rats showed no effects on mating, fertility or pregnancy at doses up to 3.6 mg/kg/day. An increase in pup mortality was found to be due to the fact that ivermectin concentrates in milk. NOELs of 0.2, 5.0 and 1.5 mg/kg bodyweight for developmental toxicity were derived from studies in mice, rats and rabbits respectively. Another study in dogs noted that there were no adverse effects in pups, where the drug was used at levels which did not cause maternal toxicity.

Studies in rats for closantel indicated no adverse effects at doses up to 100 mg/kg in single-generation studies, but some effect was seen on male fertility in multi-generation studies, (NOEL 10 mg/kgbodyweight). No adverse effects on offspring were observed in developmental studies in rats and rabbits at doses up to 40 mg/kg/bodyweight.

Mutagenicity

Neither ivermectin nor closantel showed any mutagenic potential in a range of studies.

Carcinogenicity

[4] No Observed Effect Level

Data from rodent studies, one on abamectin, (a compound structurally related to ivermectin), and two on closantel were provided.

Studies showed that abamectin was not carcinogenic to mice when given orally at 2.0 mg/kg/day for 105 weeks, with a NOEL of 1.5mg/kg/day, nor was abamectin carcinogenic to rats when given at 8 mg/kg/day over a period of approximately two years.

For closantel, data were presented which showed that in mice, up to 80 mg/kg/day was tolerated for 18 months. In the same study, it was found that in rats, where closamectin was given orally at up to 40 mg/kg/day for 2 years, some haemopoietic tumours were seen at a dose rate of 10 mg/kg/day. This incidence was however, within the historical range. Spermatic granulomas were also observed. The NOEL for this study was 2.5 mg/kg/day.

In an additional study, data were presented on mice and rats which established that in general, no adverse effects were seen in doses up to 40 mg/kg/day over 24 months in rats, and 80 mg/kg/day over 18 months in mice. No differences were noted between treated groups and controls, except for a slight increase in mortality in mice.

Other Studies

The applicant provided bibliographical data for ivermectin on immunotoxicity, neurotoxicity, and the behavioural development of rats, and for closantel, neurotoxicity and physiological development in goat kids.

Details of two immunotoxicity studies were provided for ivermectin. No evidence was found of immunotoxic effects in repeat dose studies in rats, dogs and rhesus monkeys. In a second study, an immunostimulatory effect observed was a T-lymphocyte-macrophage-dependent antibody response in mice to sheep red blood cells. With regard to neurotoxicity and behavioural development in rats, published reports noted that ivermectin given during gestation at 1, 2 or 4 mg/kg from days 6-20 caused a variety of anomalies. Delayed eye opening was seen in pups at the 2 mg/kg dose, and the cliff avoidance reflex was altered in all treated groups. 2 mg/kg of ivermectin also altered the surface righting reflex, the development of locomotion, and turning ability. Swimming ability was also affected.

Closantel caused blindness in goat kids at very high doses. It was observed that there was an apparent reduction in the number of ganglionic neurones in the retina.

Observations in Humans

Ivermectin and closantel have been used in human medicine, and the applicant provided several published reports of the administration of both substances to humans. In the case of ivermectin, side effects were minimal, including sore throat, fever and headache. More serious effects in one study included pruritis,

skin oedema, arthralgia and severe headache. In the case of closantel, side effects included nausea and vomiting following oral dosing, and tachycardia, sweating, micturition and defecation, reddening of the skin, nervousness, stress and a sense of anguish, on subcutaneous administration.

User Safety

The applicant has provided a user risk assessment in compliance with the relevant guideline which describes potential exposure routes for the operator. The most likely routes of exposure have been identified as oral, dermal and ocular. It is known from the single dose toxicity studies that dermal toxicity is comparatively low.

The following warnings and precautions as listed on the product literature and SPC are adequate to ensure safety to users of the product:

- This product may be irritating to human skin and eyes and users should be careful not to accidentally splash it on themselves or others.
- Wear 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 accidental eye exposure occurs, flush the eyes immediately with water and get medical attention.
- Do not smoke or eat whilst handling the product. Wash hands after use. Use only in well ventilated areas or outdoors.

Ecotoxicity

This product required a Phase II environmental risk assessment. The predicted no effect concentration (PNEC) values derived from several studies were acceptable and in accordance with VICH guidelines.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The product literature highlights the fact that the product is extremely dangerous to fish and aquatic life, and that care must be taken not to contaminate surface waters or ditches with the product or used container.

III.B Residues documentation

Residue Studies

A GLP-compliant residues depletion study using the final formulation was conducted in cattle.

The product was administered topically in a single dose at a rate of 500 µg ivermectin and 20 mg closantel/kg/bodyweight to animals which were slaughtered at various time points.

Samples of edible tissues were taken from animals at several time points, and results showed that residues depleted to below the maximum residue limit (MRL) in all tissues before the end of the withdrawal period.

The analytical method was HPLC, and quantification was derived from measurement of a sample peak in comparison with a previously spiked sample. The method was fully validated. Residues of each active ingredient were below the MRLs for the relevant tissues in all samples collected before the authorised withdrawal period.

MRLs

	Ivermectin		**Closantel**
	MRL (µg/kg)		MRL (µg/kg)
Muscle	-		1000
Liver	100		1000
Kidney	30		3000
Fat	100		3000

Withdrawal Periods

The data provided support the agreed meat withdrawal period of 28 days.

The product is not to be used in cattle producing milk for human consumption during the dry period. Do not use during the second half of pregnancy in heifers which are intended to produce milk for human consumption. Due to the significant likelihood of cross-contamination of non-treated animals with this product due to grooming (licking), all animals in a group should be treated at the same time and treated animals should be kept separately from non-treated animals throughout the withdrawal period. Non-compliance with this recommendation may lead to residues violations in non-treated animals.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant provided bibliographical information which gave an overview of the action of ivermectin and closantel. Ivermectin has a variety of effects in different species of parasite, the principal one being to cause flaccid paralysis leading to death, via its effect on the nervous system. Ivermectin binds with high affinity to glutamate-gated chloride channels within the invertebrate muscles and nerves. Closantel is thought to exert its toxic effects via the selective uncoupling of oxidative phosphorylation in parasite mitochondria. However, it may also have an effect on the tegument of the parasite.

Pharmacokinetics

Bibliographical information was provided with regard to the pharmacokinetics of ivermectin and closantel. Avermectins in general are lipophilic and have low water solubility. Pharmacokinetic behaviour varies depending on the route of administration, with significant distribution seen in the liver and in fat tissue. Closantel is a high molecular weight compound, and is also lipophilic in nature. There is a low volume of distribution of this drug and poor tissue distribution, 99.9% being bound to plasma proteins. Closantel has low renal and metabolic clearance, with 90% of the total drug being eliminated unchanged in the bile. In addition to the bibliographical information, the applicant submitted a pharmacokinetic study which investigated the plasma levels of closantel and ivermectin following topical application of the proposed product at the recommended dose rate of 20 mg closantel per kg and 500 µg ivermectin per kg.

Tolerance in the Target Species of Animals

The applicant has conducted two studies in the target animal using multiples of the recommended dose, with a placebo used as a control. All doses were administered topically to the animals. A suitable number of cattle were used in the first study, and doses of product used were zero, single dose, and twice or three times the recommended dose. A second, repeat single dose study was performed on a suitable number of cattle. Both studies showed that the product has a satisfactory local and systemic safety in cattle.

Resistance

Bibliographic information was provided on resistance to ivermectin and closantel. Some resistance to ivermectin in helminths has been seen when the drug has been used on sheep and goats, and less commonly in cattle. No resistance in arthropods has so far been reported in any species. Some resistance to closantel has been reported in *Haemonchus contortus.* Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Studies

The applicant conducted a series of dose-determination and dose-confirmation studies, and provided clinical bibliographical data which show that Norofas Pour-On Solution for Cattle is safe for use in cattle. There is no well established dose for topical application of closantel in cattle, therefore two dose-determination studies were performed as described below. There is a well established dose for topical ivermectin in cattle, which is 500 µg/kg, and the closantel dose-determination studies doubled as dose-confirmation studies to support this dose of ivermectin against *O. ostertagi* and *C. oncophora* at 500 µg/kg.

All studies were carried out in accordance with Good Clinical Practice and VICH guidelines.

The first dose-determination study aimed to determine the most appropriate dose rate for Norofas Pour-On Solution for Cattle in terms of the closantel component.

A suitable number of young cattle were infected orally with *Fasciola hepatica*, and subsequently with *Ostertagia ostertagi* and *Cooperia oncophora.* The cattle were then given an appropriate dose of a Norofas Pour-On Solution for Cattle equivalent, Ivermectin/Closantel Pour-On, with varying amounts of closantel. There were no adverse reactions and the drug was efficacious in treating the infections. 20 mg closantel/kg/bodyweight combined with 500ug ivermectin/kg/bodyweight gave the best results.

The second dose-determination study included a dose higher than 20 mg/kg. A suitable number of young cattle were dosed with Norofas Pour-On Solution for Cattle before being challenged with *F.hepatica*. The cattle were blood tested prior to slaughter for ivermectin B_1 and closantel concentration. This study supported the use of closantel at 20 mg/kg body weight.

A series of further studies were conducted to confirm the efficacy of the proposed dose of ivermectin and closantel against the variety of parasites at which Norofas Pour-On Solution for Cattle is targeted.

Field Studies

In this study, Norofas Pour-On Solution for Cattle was used against naturally acquired infections of *F. hepatica,* followed by subsequent acquired infections of gastrointestinal nematode species *C. oncophora, O. ostertagi* and *N. helvetianus,* in cattle.

The study was carried out in accordance with GCP[5] and with reference to VICH guidelines. This was a negatively controlled, parallel trial, conducted in cattle of

[5] Good Clinical Practice

a variety of ages. Faecal samples were taken and tested from all cattle prior to treatment, where appropriate, with Norofas Pour-On Solution for Cattle. Doses of 500 µg/kg ivermectin and 20 mg/kg closantel were administered. A proportion of the cattle were allowed to graze on pasture known to be infected with gastrointestinal nematode larvae and fluke metacercariae, and then faecal egg counts were taken prior to slaughter, from all cattle.

The study showed that Norofas Pour-On Solution for Cattle is effective in treating a wide variety of parasites.

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.

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)