ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Closiver Solution for Injection for Sheep (UK & IE)
Closamectin Solution for Injection for Sheep (AT, BE, CZ, IT, ES & SK)
Oestrocur Solutionfor Injection for Sheep (FR)
Closamectin FF Solution for Injection for Sheep (PT)

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0277/002/DC
Name, strength and pharmaceutical form	Closiver Solution for Injection for Sheep (UK & IE) Closamectin Solution for Injection for Sheep (AT, BE, CZ, IT, ES & SK) Oestrocur Solution for Injection for Sheep (FR) Closamectin FF Solution for Injection for Sheep (PT)
Applicant	Norbrook Laboratories Limited Station Works Camlough Road Newry Co Down, Northern Ireland BT35 6JP
Active substance(s)	Ivermectin Closantel (as closantel sodium dehydrate)
ATC Vetcode	QP54AA51
Target species	Sheep
Indication for use	For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to gastrointestinal roundworms, trematodes, lungworms, nasal bots and mites of sheep. <u>Gastrointestinal roundworms</u> *Ostertagia circumcincta* (including inhibited L4), *Ostertagia trifurcata* (adult and L4), *Haemonchus contortus* (including inhibited L4), *Trichostrongylus axei* (adult), *Trichostrongylus colubriformis* (adult and L4), *T. vitrinus* (adult) *Cooperia curticei* (adult and L4), *Oesophagostomum columbianum* (adult and L4), *O. venulosum* (adult) *Chabertia ovina* (adult and L4) *Nematodirus filicollis* (adult and L4), *Trichuris ovis* (adult). [L4 = fourth stage larave] <u>Lungworms</u>

	Dictyocaulus filaria (adult and 4th stage larvae) *Protostrongylus rufescens* (adult) Liver Fluke (Adults and 7 weeks immature) *Fasciola gigantica, Fasciola hepatica* Nasal Bots *Oestrus ovis* Mange Mites *Psoroptes ovis (Treatment require a second injection of an ivermectin-only product 7 days later. See sections 4.4 and 4.9)* Benzimidazole – resistant strains of *Haemonchus contortus* and *Ostertagia circumcincta* are also controlled.

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	Application in accordance with Article 13b of Directive 2001/82/EC, as amended by 2004/28/EC.
Date of completion of the original decentralised procedure	28 April 2010
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Austria Belgium Czech Republic France Ireland Italy Portugal Slovakia Spain

I. SCIENTIFIC OVERVIEW

Closiver Solution for Injection for Sheep is authorised for use in sheep for the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to gastrointestinal roundworms, trematodes, lungworms, nasal bots and mites of sheep. Specifically, the treatment is directed against the following: gastrointestinal roundworms, *Ostertagia circumcincta* (including inhibited L4[1]), *Ostertagia trifurcate* (adult and L4), *Haemonchus contortus (*including inhibited L4*), Trichstrongylus axei* (adult), *Trichostrongylus colubriformis* (adult and L4), *T. vitrinus* (adult) *Cooperia curticei* (adult and L4), *Oesophagostomum columbianum* (adult and L4), *O. venulosum* (adult) *Chabertia ovina* (adult and L4) *Nematodirus filicollis* (adult and L4), *Trichuris ovis* (adult).

Additionally, the product is to be used to treat lungworms, *Dictyocaulus filarial* (adult and 4th stage larvae) and *Protostrongylus fufescens* (adult), liver fluke (adults and 7 weeks immature), *Fasciola gigantica, Fasciola hepática.*

Closiver Solution for Injection for Sheep can also be used to treat Nasal Bots (*Oestrus ovis*), and mange mites (*Psoroptes ovis*).

Closiver Solution for Injection for Sheep may also be used in the control of resistant strains of *Haemonchus contortus* and *Ostertagia circumcincta*.

Closiver Solution for Injection for Sheep is an extension of the authorised product Closiver Solution for Injection to add a new target species, the food-producing species sheep.

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 slight reactions observed are indicated in the SPC[2]. 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 substances ivermectin and closantel (as closantel sodium dihydrate). The product also contains the excipients sodium formaldehyde sulphoxylate (as an antioxidant), povidone K12, macrogol 200 and glycerol formal.

[1] L4 - Fourth stage larvae
[2] SPC - Summary of Product Characteristics

The product is a clear amber solution presented in type 1 multidose vials in volumes of 100 ml, 250 ml and 500 ml, closed with a bromobutyl bung and aluminium overseal. The particulars of the containers and controls performed are provided and conform to the current guidelines.

The choice of formulation is justified.

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.

C. Control of Starting Materials

Ivermectin utilised in this product complies with the monograph in the European Pharmacopoeia (Ph. Eur) and conforms to a satisfactory Certificate of Suitability (CEP).

Closantel is presented as dihydrate of the sodium salt and complies with the monograph in the European Pharmacopoeia (Ph. Eur) and conforms to a satisfactory Certificate of Suitability (CEP).

As this is an extension application, the applicant has not provided any new additional data. 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.

G. Stability

The applicant has not provided any new data. This is considered acceptable.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

A shelf life of 18 months and an in-use shelf life of 28 days is justified, subject to the following storage warnings:

- Do not store above 25°C.
- Protect from light.
- Discard unused material.

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[3] 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.

[3] Gamma-aminobutyric acid

The applicant also provided bibliographical data which show that ivermectin is mainly excreted in the faeces (<2 % detected in the urine) in cattle, sheep and rats. The metabolism of ivermectin is dependent upon the formulation administered, the species and the route of administration. In healthy human volunteers dosed with 200µg ivermectin/kg body weight, the half-life of ivermectin is 22±5 hours. The excreted drug was detected in the faeces but no drug was detected in the urine. Closantel was shown to persist for a longer period, with a half-life of 15.9-23 days in sheep. Closantel is highly bound to plasma proteins in all species investigated.

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.

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

A study was performed to check the acute oral toxicity of the combination of ivermectin and closantel following single oral administration. In this study, ivermectin and closantel were co-administered to mice at 5 mg/kg, and 125 mg/kg bodyweight, respectively. There was no mortality.

Repeated Dose Toxicity:

For ivermectin, a 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 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 multigeneration study in rats showed no effects on mating, fertility or pregnancy at doses up to 3.6 mg/kg/bodyweight/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. Another study in dogs noted

[4] No Observed Effect Level

that there were no adverse effects in pups, where the drug was used at levels which did not cause maternal toxicity.

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

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 1.5 mg/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 was tolerated for 18 months. In the same study, it was found that in rats, where closantal 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 immunogenicity, 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 safety assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. The use of Closiver Solution for Injection for Sheep is not expected to present an undue hazard to the user. The product literature and SPC contain the following safety warnings:

- Do not smoke, eat or drink while handling the product.
- Direct contact of the product with the skin should be kept to a minimum.
- Wash hands after use.
- Take care to avoid self-injection.
- Inadvertent self-injection may result in local irritation and/or pain at the injection site

Ecotoxicity

The applicant provided a Phase II environmental risk assessment in compliance with the relevant guidelines.

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

The applicant submitted two GLP-compliant residue depletion studies to investigate residue depletion following administration of the ivermectin/closantel product and in addition following repeat ivermectin only treatment.

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

The product was administered topically in a single dose at a rate of 200 µg ivermectin and 5 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	-		1500
Liver	100		1500
Kidney	30		5000
Fat	100		2000

Withdrawal Periods

The following withdrawal period is acceptable based on the results of the residue depletion study report submitted by the applicant.

Meat and offal: 28 days

Milk: Not permitted for use in animals producing milk for human consumption, including pregnant animals intended to produce milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

The two active substances in Closiver Solution for Injection for Sheep, ivermectin and closantel, both have well-established uses in veterinary medicine. The applicant provided a review of published literature on the pharmacodynamics and pharmacokinetics of the individual active substances, supplemented with reports of two studies on the pharmacokinetics of the combination product compared to already authorised formulations of the individual substances. The studies showed that there is no interaction between ivermectin and closantel in the combination product.

Pharmacodynamics

With regard to pharmacodynamics, the applicant has relied entirely on published data. The information provided on each active substance is considered satisfactory and supports information in section 5.1 of the SPC. Although no pharmacodynamic studies were conducted with the combination, the applicant has discussed the possibility of interaction between the active substances following administration adequately. Significant interaction between ivermectin and closantel appears very unlikely in view of the quite different modes and sites of action of these active substances and no evidence of any deleterious effects were observed in the various studies conducted with the test product.

Pharmacokinetics

For pharmacokinetics the applicant referred to the published literature on the individual active substances. Supportive studies were also provided. One of the studies was conducted with the final formulation containing both active substances and variants of it in which one or other of the active substances was excluded. This was adequate to demonstrate possible interference between the active substances. The results indicated small differences in plasma levels of the relevant active substances between the formulations, but these were generally small and not statistically significant. Consequently there was no evidence that combining ivermectin and closantel in the formulation resulted in any significant interference with the bioavailability of either active substance. The second study was supportive of this.

The second pharmacokinetic study made comparisons between the final formulation containing both active substances and the pioneer single active substance products containing either ivermectin, namely Ivomec Classic Injection or closantel, namely Flukiver 5 Injection. With regard to the latter substance, both the test and reference products produced very similar blood profiles of closantel. The test product can be considered as bioequivalent to Flukiver 5 Injection. In the case of ivermectin, whilst the AUC values were similar for the test formulation and Ivomec Classic Injection, the C_{max} values indicated a more rapid uptake from the test than from the pioneer product. However, when sampling times are taken into consideration it was concluded that both products would have a similar persistent effect. In view of this, it is noted that claims for persistent activity are identical to those approved for pioneer ivermectin product Ivomec Classic Injection.

Tolerance in the Target Species of Animals

The applicant submitted the report of a study conducted in sheep following the subcutaneous administration of ivermectin/closantel injection. The study was conducted in accordance with the principles of GLP. In this study, a suitable number of sheep received a single dose of the product at the proposed dose rate, 1 ml per 25 kg bodyweight i.e. 200 µg ivermectin and 5.0 mg closantel per kg bodyweight. Tests were also carried out using twice the proposed dose rate, administered on three consecutive days. The dose volumes were divided so that the maximum dose per injection site was 5 ml. For the animals receiving

three administrations, one was given in the region of the right chest, the second in the region of left chest and third into the region of the right neck. The animals were assessed for up to 28 days after final administration. This assessment involved clinical examination, measurement of heart rate and body temperature; blood samples were collected at intervals for blood cell count, testing of clotting ability and analysis of various enzymes and other blood components. In addition the injection sites were examined and all animals were observed for any abnormal behaviour.

The only adverse effects observed were injection site reactions which resolved without treatment within 2-3 weeks and transitory pain at the time of injection.

It is considered that Closiver Solution for Injection for sheep is well tolerated in sheep.

Treatment for overdose is symptomatic as there is no antidote. Signs of overdose can include loss of appetite, decreased vision, loose faeces and increased frequency of defecation.

Resistance

The introduction of the product Closiver Solution for Injection for Sheep, a combination of the active substances ivermectin and closantel, is unlikely to have any significant influence on resistance patterns compared to the use of the active substances separately.

IV.B Clinical Studies

The applicant provided a review of published literature on the individual active substances and in addition provided reports on various clinical studies conducted with the combination product. Dose determination and dose confirmation studies were carried out in accordance with EU guidelines on Good Clinical Practice. The animals involved in the studies, except the control animals, were infected with a number of parasitic larvae and all sheep were subsequently injected once with the test formulation subcutaneously in the neck region. The animals were observed daily for evidence of adverse reactions or illness. The studies established the efficacy of the product.

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 risk benefit 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)