ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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

Reference Member State

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Closiver 5 mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep (United Kingdom, Ireland)

Closamectin 5 mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep (Austria, Belgium, Czech Republic, Spain, Slovak Republic)

Closamectine 5mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep (France)

Closamectin FF 5mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep (Portugal)

Closivet 5 mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep (Italy)

PuAR correct as of 24/08/2018 when RMS was transferred to IE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0277/001/MR
Name, strength and pharmaceutical form	Closiver 5mg/ml/125 mg/ml Solution for Injection for Cattle and Sheep
Applicant	Norbrook Laboratories Ltd Station Works Newry Co. Down Northern Ireland
Active substances	Ivermectin Closantel (as closantel sodium dihydrate)
ATC Vetcode	QP54AA51
Target species	Cattle and sheep
Indication for use	**Cattle:** For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to gastrointestinal roundworms, lungworms, eyeworms, warbles, mites and lice of cattle. Gastrointestinal roundworms *Ostertagia ostertagi* (including inhibited larval stages), *Ostertagia lyrata* (adult), *Haemonchus placei* (adult and immature), *Trichostrongylus axei* (adult and immature), *Trichostrongylus colubriformis* (adult and immature), *Cooperia oncophora* (adult and immature), *Cooperia punctata* (adult and immature), *Cooperia pectinata* (adult and immature), *Oesophagostomum radiatum* (adult and immature), *Nematodirus helvetianus* (adult), *Nematodirus spathiger* (adult), *Strongyloides papillosus* (adult), *Bunostomum phlebotomum* (adult and immature), *Toxocara vitulorum* (adult), *Trichuris* spp. Lungworms *Dictyocaulus viviparus* (adult and 4th stage larvae)

	Liver Fluke (trematodes) *Fasciola gigantica, Fasciola hepatica* Treatment of fluke at 12 weeks (mature) >99% efficacy. Treatment of fluke from 7 weeks (late immature) >90% efficacy Eyeworms (adult) *Thelazia* spp Cattle grubs (parasitic stages) *Hypoderma bovis, Hypoderma lineatum* Lice *Linognathus vituli, Haematopinus eurysternus, Solenopotes capillatus* Mange Mites *Psoroptes ovis* (syn *P communis var bovis*), *Sarcoptes scabiei var bovis* The veterinary medicinal product may also be used as an aid in the control of the biting louse *Damalinia bovis* and the mange mite *Chorioptes bovis*, but complete elimination may not occur. **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. Gastrointestinal roundworms *Teladorsagia circumcincta* (including inhibited L4), *Teladorsagia 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]

	Lungworms *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 *Teladorsagia 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	Mutual recognition application in accordance with Article 13b of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	21 December 2007
Date product first authorised in the Reference Member State (MRP only)	06 February 2007
Concerned Member States for original procedure	First Use Austria, Belgium, Czech Republic, France, Ireland, Italy, Portugal, Slovak Republic, Spain Repeat Use (First Wave) Bulgaria, Croatia, Cyprus, Greece, Hungary, Romania

I. SCIENTIFIC OVERVIEW

Closiver Solution for Injection for Cattle and Sheep is an endectocide (it contains drugs that expel parasitic worms from the body and kill external parasites such as lice) and contains the active substances ivermectin and closantel. The application for a marketing authorisation was based on combining known active substances, so called fixed combination. The product should be administered by injection via the subcutaneous route into the neck at a dose of 200 µg ivermectin per kg body weight and 5 mg closantel per kg body weight. This equates to a dose of 1 ml Closiver Solution for Injection per 25 kg body weight of the animal.

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[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 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.

II. QUALITY ASPECTS

A. Composition

The product contains the active substances ivermectin and closantel. Excipients include povidone K12, sodium formaldehyde sulphoxylate, polyethylene glycol 200 and glycerol formal.

The container/closure system comprises 100 ml, 250 ml and 500 ml amber Type I glass multidose vials and aluminium caps complete with bromobutyl bungs and aluminium seals. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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.

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

The active substance is closantel presented as the dihydrate of the sodium salt and supporting data have been provided in the form of a European Drug Master File (EDMF)[2] to show compliance with the monograph in the European Pharmacopeia. The synthesis of closantel sodium is not enantioselective[3] and the resulting material is racemic[4]. The other active substance, ivermectin, is an established substance described in the European Veterinary Pharmacopoeia. The active substance specifications are considered adequate to control the quality of the material.

In the absence of a European Pharmacopoeia monograph for macrogol 200 (polyethylene glycol), the monograph for macrogol 300 has been applied, with appropriately amended limits for viscosity and hydroxyl value. In the case of the anti-oxidant sodium formaldehyde sulphoxylate compliance with the monograph of the United States Pharmacopoeia has been accepted, as there is no European Pharmacopoeia monograph available. Glycerol formal is not

[2] European Drug Master File or EDMF is a confidential document prepared by a manufacturer and contains detailed information about a substance
[3] Enantiomers are stereoisomers that are nonsuperimposable complete mirror images of each other, much as one's left and right hands are "the same" but opposite.
[4] A racemic mixture or *racemate* in chemistry is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule.

described in a pharmacopoeia. An in-house raw material specification was provided. Suitable data were also provided for Povidone K12.

The product is supplied in glass vials with bromobutyl rubber bungs secured by aluminium sealing strips. The vials, rubber bungs and containers comply with the tests specified in the relevant monographs of the European Pharmacopoeia for components used on injectable products.

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

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

Stability data for the active substance closantel sodium dihydrate have been provided in the form of a drug master file. The material has been assessed when stored under long-term and accelerated test conditions in accordance with the pharmacopoeial monograph. On the basis of the findings a storage temperature and shelf life have been specified.

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.

A study has been conducted demonstrating that the product remains stable for 28 days after a dose has been removed from the vial. A 28 day in-use shelf life is therefore appropriate.

H. Genetically Modified Organisms

Not applicable.

I. Other Information

Shelf-life of the veterinary product as packaged for sales: 18 months.
Shelf-life after first opening of immediate packaging: 28 days.
Do not store above 25°C.
Protect from light.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided a number of references on the pharmacodynamics and pharmacokinetics of the individual active ingredients. The applicant has also provided the reports of two in-house studies on the pharmacokinetics of the combination product compared with commercial formulations containing each of the actives singly. The results of these studies demonstrated that there is no interaction between ivermectin and closantel in the formulation.

It was shown that ivermectin acts on glutamate-gated chloride ion channels. This results in the opening of chloride ion channels, a decrease in membrane resistance and membrane hyperpolarisation in the parasite leading to paralysis of the worm. Closantel is a proton ionophore and acts on the mitochondrial membrane of the parasite, uncoupling oxidative phosphorylation. Therefore, the two actives in the fixed combination have separate modes of activity.

The pharmacokinetic data demonstrated 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 200 µg ivermectin/kg body weight, the half-life of ivermectin was 22±5 hours. 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. In two studies it was demonstrated that use of ivermectin and closantel in the fixed combination does not modify the pharmacokinetics of either compound. There were no statistically significant differences in the profiles of ivermectin or closantel when investigated alone or in combination.

Toxicological Studies

Single and repeat dose toxicity

The applicant provided reports with respect to the single and repeat dose toxicity of the individual actives in the formulation. The applicant also addressed the

single dose toxicity of the combination product. The oral LD_{50} value for the combination product was greater than the tested dose of 2000 mg/kg of ivermectin 0.5 %/closantel 12.5 %. The pharmacokinetic and single dose toxicity data on the combination product do not indicate an interaction between the individual active components. This provided reassurance that there will not be a negative impact on the toxicity profile of the combination product.

Reproductive toxicity, Embryotoxicity/fetotoxicity

Neither ivermectin nor closantel had an adverse impact on reproductive parameters in rats, dogs and horses investigated. However, ivermectin was shown to be toxic to young dogs exposed via the milk and to produce cleft palate in dogs at doses close to the maternotoxic level. Closantel at doses of 40 mg/kg was shown to lead to a decrease in fertility in male rats but all other fertility parameters were comparable between control and treated rats.

Mutagenicity

In mutagenicity studies, ivermectin was negative in a number of *in vitro* bacterial and mammalian cell assays. The mutagenicity of closantel was also investigated in an *in vitro* bacterial assay and two *in vivo* assays. In these assays closantel gave negative results.

Carcinogenicity

Abamectin (a close analogue of ivermectin) was shown not to possess carcinogenic potential. Closantel was not carcinogenic in mice or rats although spermatic granulomas were observed in mice in one study.

Studies on metabolites impurities, other substances and formulation

The applicant has provided information with respect to immunotoxicity and neurotoxicity. Ivermectin was shown to have an immunostimulatory effect on T lymphocytes at subcutaneous doses of 0.2 and 20 mg/kg in mice and at doses of 1-4 mg/kg to be a developmental neurotoxicant, although the relevance of the test system was not defined. In goats overdosed with closantel (4-13 x the recommended dose of 7.5 mg/kg) effects on the retina were observed. However, these doses were significantly higher than those the user is likely to encounter.

Observations in Humans

A number of references relating to observations in humans were provided for both ivermectin and closantel. Any adverse reactions were generally mild and it is considered that the special precautions to be taken by the person administering the product on the SPC are appropriate to minimise exposure.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which addresses potential exposure routes to the operator. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. These are as follows:

Do not smoke, eat or drink while handling the product. Avoid direct contact of the product with the skin. In case of spillage onto the skin rinse immediately with fresh water. 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. In case of accidental self-injection, seek medical advice immediately and show the package leaflet to the physician.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that further assessment was required.

The Phase II assessment was carried out for closantel and ivermectin. For both ivermectin and closantel the following factors were considered: effects on terrestrial and aquatic organisms, and risk to surface water and groundwater from exposure to the active substances. The risks were considered acceptable and warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

EXTREMELY DANGEROUS TO FISH AND AQUATIC LIFE. Do not contaminate surface waters or ditches with the product or used container. Any unused product or waste materials should be disposed of in accordance with national requirements.

III.B Residues documentation

Residue Studies

The applicant provided a study report for a residue depletion study in cattle that allowed the determination of an appropriate meat withdrawal period to ensure consumer safety. Groups of cattle were administered Ivermectin/Closantel Injection at the recommended dose (200 μg/kg ivermectin and 5 mg/kg closantel) subcutaneously on a single occasion. The volumes injected ranged from 10.2 ml to 20.0ml, with a maximum injection volume of 10 ml into each individual injection site. The groups comprised cattle with bodyweights ranging from 305-499 kg four days prior to administration of the product. One group of animals was sacrificed at each of the time-points, 14, 21, 28 and 35 days and samples of muscle, liver, kidney, fat and injection site were removed.

Samples were stored at below -20°C for at least 3 days before being sent for analysis. The analytical methods used to measure residue levels of ivermectin and closantel in bovine tissues were fully validated. The meat withdrawal period of 49 days was considered acceptable.

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 of 28 days.

MRLs

Both ivermectin and closantel are entered into Annex I of Council Regulation 2477/90 with the following MRLs:

Ivermectin:

Tissue	**MRL**	
	Cattle	**Sheep**
Liver	100 µg/kg	100 µg/kg
Fat	40 µg/kg	100 µg/kg
Kidney	30 µg/kg	30 µg/kg

Closantel:

Tissue	**MRL**	
	Cattle	**Sheep**
Muscle	1000 µg/kg	1500 µg/kg
Liver	1000 µg/kg	1500 µg/kg
Kidney	3000 µg/kg	5000 µg/kg
Fat	3000 µg/kg	2000 µg/kg

The proposed meat withdrawal periods are acceptable based on the results of the residue depletion study report submitted by the company.

Withdrawal Periods

Cattle
Meat and offal: 49 days
Not permitted for use in cattle producing milk for human consumption.

Do not use in non-lactating dairy cows including pregnant heifers which are intended to produce milk for human consumption within 60 days of expected parturition.
Do not use any closantel-containing products during the 49 day withdrawal period.

Sheep
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)

IV.A Pre-Clinical Studies

Pharmacology

The two active substances in Closiver Injection, ivermectin and closantel, both have well-established uses in veterinary medicine. The company 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 test formulation 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 test formulation and the pioneer single active substance products containing either ivermectin or closantel. 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 article 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 company submitted the report of a study to investigate whether the product was well-tolerated in cattle. In this study, cattle received a single dose of the product at the proposed dose rate, 1 ml per 25 kg. Tests were also carried out using twice the proposed dose rate, administered on two successive days. The dose volumes were divided so that the maximum per injection site was 10 ml. For the cattle receiving two administrations, one was given in each side of the neck.

A similar study was conducted in sheep. Sheep received a single subcutaneous injection of the product at the proposed dose rate of 1 ml per 25 kg bodyweight. In addition, tests using twice the proposed dose rate were performed in which the product was administered on three consecutive days. The dose volumes were divided so 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 cattle were assessed for up to 35 days, and the sheep for up to 28 days, after the 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, in both species, 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 Injection is well tolerated in cattle and 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 Injection, 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

Clinical studies were provided relating to the activity of the product against three key species (*Fasciola hepatica, Ostertagia ostertagi and Cooperia oncophora)* including a dose-limiting nematode species and liver fluke. The first formulation tested in the dose-determination study contained the same concentration of ivermectin as the single substance products and a similar concentration of closantel to the reference product. However, results showed that, whilst the ivermectin component produced the expected degree of efficacy against the nematode species tested, the closantel content was clearly inadequate against liver flukes. The closantel concentration in the formulation was subsequently doubled and the further two clinical studies indicated acceptable rates of efficacy against all three parasites tested, including liver fluke. The variable rate of efficacy against Cooperia species is not unexpected as it reflects the findings in other studies reported in published literature.

A further clinical study was also submitted. This evaluated the efficacy of Closiver Injection against naturally acquired infections of *F. hepatica* and gastrointestinal nematodes in cattle. Efficacy was measured by both faecal egg counts and by total worm counts following slaughter of representative samples from treated and untreated control groups. The findings indicated acceptable levels of efficacy.

Dose determination and dose confirmation studies in sheep 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.

It is considered that there are sufficient data to support the application. Sufficient warnings and contraindications have been included in the SPC.

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)