IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Closamectin 5 mg/ml/125 mg/ml Solution for Injection for Sheep

PRODUCT SUMMARY

EU Procedure Number	IE/V/0519/001 (formerly UK/V/0277/001)
Name, Strength, Pharmaceutical Form	Closamectin 5 mg/ml/125 mg/ml Solution for Injection for Sheep
Active Substances(s)	Ivermectin, closantel
Applicant	Norbrook Laboratories (Ireland) Limited, Rossmore Industrial Estate, Monaghan, Ireland
Legal Basis of Application	Fixed combination application (Article 13b of Directive No 2001/82/EC)
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. 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), *Trichurisovis* (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.
ATC Code	QP54AA51
Date of completion of the original decentralised procedure	06 February 2007 (UK)
Date product first authorised in the Reference Member State (MRP only)	25 April 2008 (IE)
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, France, Ireland, Italy, Portugal, Slovakia, Spain

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

Closamectin Solution for Injection for 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 Closamectin 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. 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.
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 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 at 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).
Closantel is presented as dihydrate of the sodium salt and complies with the monograph in the European Pharmacopoeia (Ph. Eur).

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 substances, have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions.
Stability data and in-use 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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

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 veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

III.B Residues documentation

Residue Studies

A GLP-compliant residues depletion study using the final formulation was conducted in sheep. The product was administered 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 listed in Table I of the Annex to Commission Regulation (EU) No 37/2010 for sheep as follows:

	Ivermectin	**Closantel**
Muscle	30 µg/kg	1500 µg/kg
Liver	100 µg/kg	1500 µg/kg
Kidney	30 µg/kg	5000 µg/kg
Fat	100 µg/kg	2000 µg/kg
Milk	-	45 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

Sheep

Meat and offal: 28 days.
Milk: Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

The two active substances in Closamectin 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 Cmax 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 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 sheep were assessed 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, were injection site reactions which resolved without treatment within 2-3 weeks and transitory pain at the time of injection.
It is considered that Closamectin Injection 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 Closamectin 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
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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.
This section 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.

Changes:

Summary of change (Application number)	**Approval date**
Deletion of target species – cattle (IE/V/0519/001/A/024)	