ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Closamectin Solution for Injection for Cattle and Sheep

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/0262/001/MR
Name, strength and pharmaceutical form	Closamectin Solution for Injection for Cattle and Sheep
Applicant	Norbrook Laboratories Limited
Active substances	Closantel and Ivermectin
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. <u>Gastrointestinal roundworms</u> *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. <u>Lungworms</u> *Dictyocaulus viviparus* (adult and 4th stage larvae) <u>Liver Fluke (trematodes)</u> *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* Closamectin Injection 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. Persistent activity in cattle When cattle have to graze on pasture contaminated with infective larvae of cattle nematodes, treatment with Closamectin Injection at the recommended dose rate of 200 g ivermectin per kg bodyweight and 5 mg closantel per kg bodyweight controls re-infection with: **Prolonged activity** *Dictyocaulus viviparus* Up to 21 days *Ostertagia ostertagi* Up to 21 days *Oesophagostomum radiatum* Up to 21 days *Cooperia* spp Up to 14 days *Trichostrongylus axei* Up to 14 days *Haemonchus placei* Up to 14 days **Sheep:** For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to gastrointestinal roundworms, trematodes, lungworms, nasal bots and mite of sheep. Gastrointestinal roundworms *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 larvae] <u>Lungworms</u> *Dictyocaulus filaria* (adult and 4th stage larvae) *Protostrongylus rufescens* (adult) <u>Liver Fluke (trematodes)</u> *Fasciola gigantica, Fasciola hepatica* Treatment of fluke at 12 weeks (mature) >95% efficacy. Treatment of fluke at 7 weeks (late immature) 100% efficacy. <u>Nasal Bots</u> *Oestrus ovis* <u>Mange Mites</u> *Psoroptes ovis (Treatment requires a second injection of an ivermectin-only containing product 7 days later. See section 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	Mutual recognition application in accordance with Article 13b of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	04 January 2008
Date product first authorised in the Reference Member State (MRP only)	28 July 2006
Concerned Member States for original procedure	Ireland

I. SCIENTIFIC OVERVIEW

Closamectin 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 product has been formed by a combination of two qualitatively and quantitatively identical products licensed for cattle and sheep by way of a Decentralised Extension variation procedure. Closamectin Injection is authorised for use in cattle and sheep for the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to gastrointestinal roundworms, lungworms, eyeworms, warbles, mites and lice. These parasites cause damage to animals leading to loss of condition, suffering and possibly death. For example:

- Lungworm cause inflammation and irritation to the lungs, leading to coughing, difficulty in breathing and in severe cases can lead to death.
- Roundworms live in the gut, causing damage to the gastro-intestinal tract which can result in diarrhoea and reduced nutrient intake and utilisation.
- Lice can cause extreme discomfort to cattle. The lice feed on the dead skin, hair and in some species, blood, causing severe itching. The animal will lose weight and become stressed, and in acute cases the lice can cause anaemia.
- Liver fluke cause damage to the liver and lungs and cause loss of production of meat and milk. In severe cases it can lead to death.

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.

II. QUALITY ASPECTS

A. Composition

The solvents are polyethylene glycol 200, glycerol formal and povidone K12. The product also contains sodium formaldehyde sulphoxylate, an anti-oxidant.

The product contains the active substances closantel and ivermectin. The product also contains the excipients povidone K12, sodium formaldehyde sulphoxylate, macrogol 200 and glycerol formal.

The product is a non-aqueous solution presented in amber glass vials in volumes of 100 ml, 250 ml and 500 ml. The vials are sealed with a pierceable rubber stopper, allowing removal of the required dose volume. The product does not contain an anti-microbial preservative, which is appropriate as it is non-aqueous. 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

The active substance is closantel presented as the dihydrate of the sodium salt and complies with the monograph in the European Pharmacopeia. The synthesis of closantel sodium is not enantioselective[2] and the resulting material is racemic[3]. Ivermectin complies with the requirements of the European Pharmacopoeia. The active substance specifications are considered adequate to control the quality of the material.

[1] SPC=Summary of Product Characteristics
[2] 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.
[3] A racemic mixture or *racemate* in chemistry is one that has equal amounts of left- and right-handed enantiomers of a chiral molecule.

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 for it. Glycerol formal is not described in a pharmacopoeia but an in-house raw material specification was provided.

The product is supplied in amber 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

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The specification that is applied to the finished product immediately after its manufacture controls appropriate parameters, including appearance, content of active substances, water content, particulate matter, syringeability and sterility. Data show the suitability of the analytical methods employed in testing.

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

Active substances

A retest interval of 3 years for Ivermectin has been authorised when stored in the prescribed packaging.

The supplier of closantel sodium dihydrate presented data on its stability, assessing material 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.

Finished Product

The dossier contains stability data on batches of the product filled into containers of the smallest and largest container sizes. Tests were undertaken at different

temperatures, for which some containers were stored inverted. Among other parameters, determinations were made of the active substances, related substances, and appearance and syringeability of the product. It has been agreed that the product has a shelf life of 18 months and should be stored at temperatures not exceeding 25°C and protected from light.

In-Use

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

J. Other Information

The supporting data submitted by the company demonstrate that the product is suitably formulated and quality-controlled. A shelf life of 18 months 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

Toxicological Studies

The company provided a review of published literature in relation to single and repeat dose toxicity of the individual active substances, closantel and ivermectin. In addition the company provided data from studies on the single dose toxicity of the combination product in cattle.

Published single dose studies of ivermectin showed that subcutaneous injection at a dose rate of 6.0 mg/kg body weight in cattle did not elicit any signs of toxicity.

Another published study on rats showed that there was no significant sex related differences in toxicity of ivermectin.

A published study on the acute toxicity resulting from single dosing with closantel solution in rats and mice showed that the effects in the lethal dose range were hypotonia (reduced muscle strength), ataxia (unsteady motion of the limbs), diarrhoea and shortness of breath. Another published study showed clinical signs of toxicity in sheep and cattle following the single administration of closantel solution to be anorexia, laboured breathing, general weakness and decreased vision. The lethal dose for sheep and cattle derived from this study was greater than 40mg/kg body weight.

A study was conducted to assess the toxicity of the combination of ivermectin and closantel in mice. The acute oral median lethal dose (LD_{50}) of the test material in female albino mice was estimated as being greater than 2000 mg ivermectin 0.5 %/closantel 12.5 %/kg body weight.

User Safety

The use of Closamectin Injection 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

Ivermectin is extremely dangerous to fish and aquatic life. Therefore advice for users is:

Do not contaminate surface waters or ditches with product or used containers. Containers and any residual contents should be disposed of safely.

No environmental assessment was required for this particular product because the effects of the active ingredients in the environment following their administration to cattle are already known. Appropriate disposal advice is required for all veterinary medicines. For Closamectin Injection this is:

Dispose of any unused product and empty containers in accordance with guidance from your local waste regulation authority.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

The proposed meat withdrawal period of 49 days in cattle and 28 days in sheep is acceptable based on the results of the residue depletion study report submitted by the company.

Withdrawal Periods

Cattle

Meat and offal: 49 days.

Milk: Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

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 first lambing in ewes intended to produce milk for human consumption.

IV CLINICAL ASSESSMENT (EFFICACY)

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
Endectocides can be used in animals to control internal and external parasites. One active substance Ivermectin is an endectocide; it acts by inhibiting nerve impulses. Ivermectin binds selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarisation of the nerve or muscle cell, resulting in paralysis and death of the parasite. Mammals do not have glutamate-gated ion channels so the Ivermectin will not affect them in the same way as it does the invertebrate parasites.

The other active substance closantel is a parasiticide with flukicide activity and efficacy against other helminths (e.g. roundworms) and arthropods. Closantel is a salicylanilide and acts by uncoupling oxidative phosphorylation.

Pharmacokinetics
Following administration by subcutaneous injection ivermectin is only partially metabolised. In cattle, about 1-2% is excreted as unaltered dung; the remainder is excreted as metabolites or degradation products. In sheep 90% of the dose will be eliminated via the faeces and less than 2% is excreted in the urine, ivermectin will also be excreted by the mammary gland. Salicylanilides are poorly metabolised and are excreted mainly unchanged. About 90% of closantel is excreted unchanged in the faeces and urine in cattle whilst in sheep closantel has a long elimination half life and distribution to the tissues is poor.

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. In the study, sheep received a single dose of the product at the proposed dose rate, 1 ml per 25 kg bodyweight. Again tests were carried out using twice the proposed dose rate and administered on three consecutive days. The dose volumes were divided so that the maximum per injection site was 5 ml. For the sheep receiving three doses, one was given in the region of the right chest, the second in the region of the left chest and the third into the region of the right neck.

The cattle were assessed for up to 35 days and sheep 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 Closamectin 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 Closamectin Solution for 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

The company provided a review of published literature on the individual active substances and in addition provided reports on a number of 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 cattle and sheep were subsequently injected once with Closamectin Solution for Injection 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 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)