ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey
KT15 3LS
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Closiver 5 mg/ml + 200 mg Pour-On Solution for Cattle (UK)
Closamectin Vet 5mg/ml + 200mg/ml Pour-On Solution for Cattle (SE)
Closamectin 5mg/ml + 200mg/ml Pour-On Solution for Cattle

PuAR correct as of 12/03/19 when RMS was transferred to ES.
Please contact the RMS for future updates.

Updated: October 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0368/001/DC
Name, strength and pharmaceutical form	Closiver 5 mg/ml + 200 mg Pour-On Solution for Cattle
Applicant	Norbrook Laboratories Limited
Active substance(s)	Ivermectin, Closantel (as closantel sodium dehydrate)
ATC Vetcode	QP54AA51
Target species	Cattle
Indication for use	For the treatment of mixed trematode (fluke) and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice of cattle. Trematodes (adult and late immatures) *Fasciola gigantica* *Fasciola hepatica* Treatment of fluke at 12 weeks (mature) >95% efficacy. Treatment of fluke at 7 weeks (late immature) >95% efficacy. Gastrointestinal roundworms (adults and fourth stage larvae) *Ostertagia ostertagi* (including inhibited *O. ostertagi*), *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia* spp, *Oesophagostomum radiatum, Nematodirus helvetianus* (adult), *Strongyloides papillosus* (adult). Lungworms (adult and fourth stage larvae) *Dictyocaulus viviparus* Eyeworms (adult) *Thelazia* spp Cattle grubs (parasitic stages) *Hypoderma bovis, Hypoderma lineatum*

	Lice *Linognathus vituli, Haematopinus eurysternus, Damalinia bovis* Mange Mites *Chorioptes bovis, Sarcoptes scabiei* var *bovis*

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application submitted in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	23rd February 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Czech Republic, Denmark, Germany, Greece, Italy, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden

I. SCIENTIFIC OVERVIEW

This was a decentralised application for the authorisation of Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle. The application was submitted in accordance with Article 12 (3) of Directive 2001/82/EC, as amended. The product contains the active substances ivermectin and closantel (as closantel dosium dehydrate). The indication is for the treatment of mixed trematode and nematode or arthropod infestations due to roundworms, lungworms, eyeworms, warbles, mites and lice in cattle. Ivermectin is present in the product at 5 mg/ml, with closantel present at 200mg/ml. Specific pathogens targeted are Trematodes; *Fasciola gigantica* and *Fasciola hepatica*, for which treatment of cattle at both 7 or 12 weeks gives greater than 95% efficiency. Gastro-intestinal roundworms treated are *Ostertagia ostertagi*, *Haemonchus placei*, *Trichostrongylus axei*, *Trichostrongylus colubriformis*, *Cooperia* spp, *Oesophagostomum radiatum*, *Nematodirus helvetianus and Strongyloides papillosus.* Lungworms targeted are *Dictocaulus viviparous*, eyeworms; *Thelazia* spp, Cattle grubs; *Hyopderma bovis* and *Hyopderma lineatum*, lice; *Linognathus vituli, Haematopinus eurysternus, Damalinia bovis*and mange mites *Chorioptes bovis* and *Sarcoptes scabiei* var *bovis.* The dose rate for the product is 500 µg ivermectin per kg bodyweight and 20 mg closantel per kg bodyweight, (1 ml of product per 10 kg).

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. Any adverse reactions or contraindications which may occur are indicated in the SPC[1]. The

[1] SPC – Summary of Product Characteristics.

product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains ivermectin at 5 mg/ml and closantel (as closantel sodium hydrate) at 200mg/ml. The excipients are brilliant blue FCF (E133) dye, anhydrous ethanol, cetearyl ethylhexonate, isopropyl myristate, povidone K30, denatonium benzoate, trolamine, and isopropyl alcohol.

The closure/container system consists of translucent 250 mL, 500mL and 1L HDPE containers with integral squeeze measure pour system and white HDPE caps, or white 1L, 2.5L and 5L HDPE backpacks for use with a dosing gun delivery system and white polypropylene screw caps.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

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

Ethanol and isopropanol is mixed prior to the addition of closantel sodium and polyethylene glycol. povidone K30 is then added, followed by ivermectin, cetearyl ethylhexanoate and isopropanol myristate, deatonium benzoate and Brilliant Blue FCF. The mixture is pH adjusted, prior to adjustment to final batch volume with isopropanol and then filled into the appropriate packaging.

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 substances are closantel and ivermectin, established active substances described in the European Pharmacopoeia, (Ph. Eur.). The active substances are manufactured in accordance with the principles of good manufacturing practice (GMP). Suitable Certificates of Suitability were provided.

The active substance specifications areconsidered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Excipients described in the Ph. Eur are povidone K30, anhydrous ethanol, triethanolamine, isopropyl alcohol and polyethylene glycol. Denatonium benzoate complies with the appropriate USNF[2] monograph, Brilliant Blue FCF with the JP[3]. Cetearyl ethylhexanoate and isopropyl myristate comply with a provided specification.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data have been provided, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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. Analysis includes tests for: appearance, identity, related substances, water content, fill volume and microbial quality.

G. Stability

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

Finished product
Samples from three production-scale batches were stored horizontally to test the closure system, at 25°C/60%RH for 12 months, and at 40°C/75%RH for 6 months. A similar study was performed on sample batches at 25°C/60% RH for up to 24 months and at 40°C/75% RH for 6 months, in order to further test the stability of the product. Results were considered acceptable.

[2] USNF – United States National Formulary.
[3] JP – Japanese Pharmacopoeia.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale, 18 months.

Special precautions for storage:

- Do not store above 25°C.
- Store upright in original container.
- Protect from light.
- Discard unused material. Avoid introduction of contamination.
- Replace the cap securely after use.
- If stored at temperatures below 0° C, Closiver Pour-On Solution for Cattle may appear cloudy. Allowing to warm at room temperature will restore the normal appearance without affecting efficacy.
- Accidental spillage or ingestion could be detrimental or even fatal therefore care should be taken when handling and storing this product.

Flammable – keep away from heat, sparks, open flame or other sources of ignition.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant provided bibliographical data supporting the pharmacological and toxicological action of closantel and ivermectin, in addition to providing data from in-house pharmacokinetic studies. A comprehensive user risk assessment was also provided.

Pharmacodynamics

Ivermectin

Eight references were provided for ivermectin. From these data, it was observed that ivermectin activates glutamate-gated chloride ion channels within the parasite, and that avermectins in general interact stereoselectively with specific glutamate-gated chloride channels. These are distinct from GABA[4]-sensitive chloride channels. A subsequent influx of chloride ions into neurones is thought to cause death in the parasite. Another reference noted that the effects of avermectins vary depending on the species of parasite. Further data presented noted that in rat brain homogenates, GABA postsynaptic receptors may be increased by levels of avermectin, in the presence of a functioning chloride ion

[4] GABA – Gamma-aminobutyric acid.

channel. This effect may lead to the opening of chloride ion channels, a decrease in membrane resistance, and subsequent membrane hyperpolarisation, thus causing the avermectin blockade of transmission from interneuron to motorneuron in parasites.

Closantel

Nine references were provided for closantel. In one reference, it was stated that closantel belongs to the salicylanilides class of compounds, proton ionophores. It is assumed that these molecules act on the membrane of parasite mitochondria, uncoupling oxidative phosphorylation and preventing the creation of a proton gradient across the inner mitochondrial membrane. Data from a further reference cited that closantel acts as a hydrogen ionophore, culminating in the uncoupling of electron transport associated phosphorylation. In another reference, data were provided describing studies of metabolic disturbances caused in *Fasciola hepatica* by closantel, which were carried out *in vivo.* Studies were also reported in fluke recovered from treated sheep. In both studies, fluke exposed to closantel exhibited increased carbohydrate mobilisation, diminished ATP[5] synthesis, increased end-product formation, increased oxaloacetate/malate ratios and increased pyruvate concentration. Data were consistent with the premise that closantel acts as an uncoupler of oxidative phosphorylation.

Pharmacokinetics

Ivermectin

Nineteen references were supplied for ivermectin. Pharmacokinetic data demonstrated that ivermectin is excreted in the faeces (<2% detected in urine), in sheep rats and cattle. Metabolism is dependent on the formulation given, the route of administration, and the species. In healthy human volunteers, the half-life of ivermectin is 22±5 hours on administration of 200 µg//kg/ bodyweight.

Closantel

Nine references were submitted for closantel. The active substance was demonstrated to persist in sheep with a half-life of 15.9-23.0 days. Closantel binds highly to plasma proteins in all species reported. In two GLP[6] compliant studies, it was demonstrated by the applicant that use of ivermectin and closantel in fixed combination does not alter the pharmacokinetics of either active substance. No significant statistical differences occurred in the profiles of both active substances when investigated individually or combined.

[5] ATP – Adenosine triphosphate.
[6] GLP – Good Laboratory Practise.

Toxicological Studies

The applicant provided bibliographical data.

Single and Repeated Dose Toxicity

A large number of references provided data on the toxicity of ivermectin and closantel in different species. Satisfactory reports were presented with regard to the individual activities of the proposed formulation, and the single dose toxicity of the combination product was also addressed. The oral LD_{50}[7] value for the combination product was greater than the tested dose of 2000 mg/kg of ivermectin 0.5% and closantel 12.5%. No interaction was indicated between the two active substances when used in combination. Thus it was established that there would be no negative impact on the toxicity profile of the combination product.

Reproductive Toxicity,Teratogenicity, Mutagenicity and Carcinogenicity

A large number of references provided data for ivermectin and closantel in different species. Neither active substance was shown to have an adverse effect on reproductive parameters, although evidence was seen of adverse effects in young dogs at doses close to the maternotoxic level. A dose of 40 mg/kg was demonstrated to lead to a decrease in fertility in male rats, in addition to the presence of spermatic granulomas. In mutagenicity studies, both active substances were negative in all assays. Abamectin, an analogue of ivermectin, was shown to possess clastogenic activity at 3 µg/kg in mice, resulting in spermhead abnormalities. Closantel was demonstrated not to be carcinogenic in rats or mice, however some spermatic granulomas were seen in one mouse study.

Other Studies

The applicant provided bibliographical data.

Immunotoxicity

Ivermectin

In repeat dose studies in rats, rhesus monkey and dogs, there was no evidence of an increase in number of infections or immunosuppression after treatment with ivermectin. In a second study, male mice were inoculated with antigen, one day after subcutaneous administration of ivermectin, (0.2 mg/kg or 20 mg/kg). The administration of ivermectin was seen to increase an immune response in some populations of T-lymphocytes,[8] but not others.

[7] LD_{50} – Median Lethal Dose.
[8] T-lymphocytes - Thyroid-derived lymphocytes.

Neurotoxicity

Ivermectin

In the first study, there was some evidence seen of ivermectin being a neurotoxicant in rats, at doses ranging from 1 to 4 mg/kg. In a second study, data were provided examining the effects of peri-natal ivermectin exposure on the behavioural development of rats. Some differences were seen between treated animals and negative controls for the following parameters: rearing, grooming and defaecation.

Closantel

A report was presented of an inadvertent overdose in young goats, at a dose 4-13 times that recommended. Blindness, either transient or permanent was observed in many of the animals.

Observations in Humans

The applicant has provided bibliographical data. In general, side effects seen due to the use of ivermectin were fever, headaches, light-headedness, myalgia, oedema, and sore throat or cough. Side effects were more pronounced where larger doses, (i.e.100-200 µg/kg) where used, due to a greater amount of parasite infectivity.

With closantel, a common complaint during one study was the bitterness of the taste of the active substance. Following subcutaneous administration, common side-effects seen were tachycardia, sweating, a metallic taste in the mouth, stress, excitation, induction of defaecation and micturition, reddening of the skin and anxiety. All physiological parameters remained normal. Other side effects noted were diarrhoea, drowsiness and blurred vision. Loss of eyesight was reported in another study, where closantel was administered in error. Sight was restored after cessation of treatment, although eye pain continued.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline. Likely means of exposure for the user are via the oral, dermal and ocular routes. Potential hazards from the two active ingredients in this product have been cited by the applicant. It was noted however that many of the side effects mentioned arose from the death of the target parasite, (ivermectin studies), or incorrect administration (closantel).

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- This product may be irritating to human skin and eyes or cause hypersensitivity. Avoid skin and/or eye contact with the product during treatment, when handling recently treated animals or when cleaning the used equipment. Operators should wear nitrile rubber gloves and boots

with a waterproof coat when applying the product. Protective clothing should be washed after use. If accidental skin contact occurs, wash the affected area immediately with soap and water. If accidental eye exposure occurs, flush the eyes immediately with water and get medical attention.

- This product may be toxic after accidental ingestion. Avoid ingestion by hand-to-mouth contact. Do not eat, drink or smoke whilst handling the product. If accidental ingestion occurs, get medical attention and show the package leaflet to the physician. Wash hands after use.

- This product is flammable. Keep away from sources of ignition. Use only in well ventilated areas or outdoors.

Ecotoxicity

The applicant provided Phase II risk assessments for both ivermectin and closantel, as used on pasture animals. The assessment concluded that a potential risk of ivermectin to aquatic organisms and dung insects cannot be excluded. Warnings regarding the toxicity of the product to aquatic organisms and dung insects are therefore required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Ivermectin

A reference was provided of a study in cattle, in which a pour-on treatment of ivermectin at 500 µg/kg was given. Approximately 4% of the administered dose was excreted within seven days of treatment, with the majority of the active substance being found in the faeces. The majority of ivermectin remained at the application site on the animal. Further data were provided on the environmental impact of the use of ivermectin, all data were acceptable. All PNEC[9] calculated were within acceptable parameters.

Closantel

Reference data were provided on the effects of closantel. Results were provided from a study in which the metabolism and fate of closantel used on cattle and sheep was analysed. A 5% injectable solution was administered at 5 mg/kg, and an oral dose was given at 10 mg/kg. The majority of the active substance was eliminated in the faeces over an eight week period, with 43% of the oral dose and 10% of the intramuscular dose being excreted within 48 hours of administration. Supporting studies received so far were acceptable. A bioaccumulation study is in preparation. All PNEC calculated were within acceptable parameters.

[9] PNEC – Predicted No Effect Concentration.

The following conclusions were drawn with regard to environmental risk:-

The product as given to pasture animals provides PEC_{soil} [10] values of below 100 µg/kg showing that the risks to plant life and soil micro-organisms are acceptable. All risk parameters were proven acceptable for this application.

III.B Residues documentation

Data were provided in the form of a study and associated MRL[11] table.

Residue Studies

Results of a tissue residues study of ivermectiin and closantel in cattle at various timepoints after administration were provided. This GLP-compliant study analysed the use of a single administration of an ivermectin/closantel product, at a dose of 500 µg/kg ivermectin and 20 mg/kg closantel. A suitable number of animals were treated and then necropsied at a variety of timepoints post-treatment. Samples of liver, kidney, muscle, fat, and muscle underlying the injection point were analysed. The analytical methods used were HPLC-based[12]. Data contributed to the drawing up of an appropriate withdrawal period, and an appropriate MRL table.

MRLs

Pharmacologically active substance	Marker Residue	Animal Species	MRLs (µg/kg)	Target Tissues	Other Provisions
Ivermectin	22,23 Dihydro-avermectin B1A	All mammalian food-producing species	100 µg/kg 100 µg/kg 30 µg/kg	Fat Liver Kidney	Not for use in animals producing milk for human consumption
Closantel	Closantel	Bovine	1000 µg/kg 1000 µg/kg 3000 µg/kg 3000 µg/kg	Muscle Liver Kidney Fat	

Withdrawal Periods

Based on the data provided above, a withdrawal period of 28 days for meat and offal in cattle is justified. The product is not to be used in cattle producing milk for human consumption, and is not to be used in pregnant animals intended to produce milk for human consumption.

[10] PEC_{soil} - Predicted Environmental Concentration for soil.
[11] MRL – Maximum Residues Limit.
[12] HPLC – High Performance Liquid Chromatography.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant provided bibliographical data reviewing the chemistry and mode of action of avermectins and closantel. It is noted that interactions between the two active substances are not relevant, as the two active substances target different parasite species.

Pharmacodynamics

A study was cited analysing the plasma levels of ivermectin and/or closantel in cattle following the subcutaneous administration of various formulations of ivermectin/closantel injection. A suitable number of target animals were allocated into three groups post-acclimatisation, prior to injection with the test product at 200 µg/kg ivermectin and 5.0 mg/kg closantel.

Blood samples were taken for both active substances at various timepoints and analysed using a validated HPLC method. The results ascertained that no interference was seen between the active substances.

Pharmacokinetics

Results of a study were provided in which analysis of plasma levels of closantel, and subsequently of ivermectin were performed in the target species, followed by the topical administration of Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle. This was a GLP-compliant, parallel design study using a suitable number of animals. After an acclimatisation period, all animals received the test product, Ivermectin Closantel Pour-On, administered to the midline of the back at 500 µg/kg and 20 mgkg closantel on one occasion. Blood samples were taken at various timepoints, and analysed using a validated HPLC method. Results demonstrated that the product was adequately absorbed through the skin.

Tolerance in the Target Species of Animals

The applicant conducted two target species safety studies in cattle in order to evaluate the safety of the product following administration of the final formulation of Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle.

The first study was a GLP-compliant, parallel, single-phase, randomised study using a suitable number of cattle divided into four groups after a suitable acclimatisation period. The product used was Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle. Group A received 500 µg/kg ivermectin and 20 mg/kg closantel at the recommended dose. Group B received 1000 µg/kg ivermectin and 40 mg closantel/kg at two times the recommended dose. Group C received 1500 µg/kg ivermectin and 60 mg/kg closantel at three times the recommended dose. Group D were negative controls and received a placebo at 1 ml/kg. All treatments were given on a single occasion. The treatments were

administered by topical application along the midline of the back. It was concluded that the product was well-tolerated at up to three times the recommended dose.

In a second study, the repeated dosing of the target animal following the topical application of Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle. This was a parallel, single-phase, randomised study in a suitable number of animals divided into two groups after a period of acclimatisation. Group A received 500 µg/kg ivermectin and 20 mg/kg closantel on two occasions, 24 hours apart. The product was administered at the recommended dose. Group B, (negative control group), received a placebo on two occasions, 24 hours apart. The formulation was deemed to be well-tolerated in the target species.

Resistance

The bibliographic information provided suggests that the combined use of ivermectin and closantel would not have any additional impact on the development of resistance when used in the target species. The product should only be used where mixed infections are seen, and should not over-used prophylactically, which would promote resistance.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant provided dose determination and confirmation studies and provided bibliographical data.

In an initial GLP-compliant study, the appropriate dose rate for the product was determined using late immature infections of *F. hepatica*, adult *C. Oncophora* and adult *O. ostertagi* in cattle. The aim of the study was the determination of the correct dose in terms of the closantel component. A suitable number of cattle were infected with the test parasites, followed by administration of the product in which closantel doses were 5 mg/kg, 10 mg/kg or 20 mg/kg. The dose of ivermectin remained constant at 500 µg/kg. Results showed that the optimum dose for closantel was 20 mg/kg.

A second pair of studies analysed the dose determination for the product for the treatment of late immature infections of *F. Hepatica* in cattle. Over the two studies, doses ranged from a 0.25 dose to a 1.50 x the recommended dose. The dose-rate of 20 mg/kg for closantel was confirmed, the dose-rate of 500 µg/kg was already established.

Further dose confirmation studies established the product as suitable for use with all parasite target species cited.

Field Trials

A field study was conducted which analysed the efficacy of Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle against naturally acquired infections of *F. Hepatica* and gastro-intestinal nematodes in cattle. The study was a GLP compliant, negatively controlled, parallel trial. A suitable number of cattle were divided into two groups, with one group acting as negative controls. Animals were treated with Closiver 5 mg/ml + 200 mg/ml Pour-On Solution for Cattle, after initial eradication of any current infestation, and subsequent grazing on infected herbage. Faecal worm counts were conducted at various timepoints. The efficacy of the product was established.

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 Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

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.

•	25 September 2014	Change of QPPV and update to the DDPS.
•	05 September 2014	Change to the distributor address.
•	21 November 2013	Change to update the withdrawal periods on the SPC and product literature following an EU Directive.
•	14 December 2012	Updated Ph. Eur. Certificate of Suitability from an already approved manufacturer of an active substance, submission of a new Ph. Eur. Certificate of Suitability from a new manufacturer of an active substance, updated Ph. Eur. Certificate of suitability from an already approved manufacturer of an active substance.
•	08 November 2012	Variation to add a 500 ml HDPE single neck dispensing bottle, to add additional target animals safety warnings and dosing guide to the SPC, change of shelf-life from 1 year to 18 months.
•	28 September 2012	Addition of safety warnings to SPC and labelling.