Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Libbox 67 mg Spot-on Solution for Small Dogs
Libbox 134 mg Spot-on Solution for Medium Dogs
Libbox 268 mg Spot-on Solution for Large Dogs
Libbox 402 Spot-on Solution for Very Large Dogs

Date Created: 19th September 2014

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0486/002/DC UK/V/0486/003/DC UK/V/0486/004/DC UK/V/0486/005/DC
Name, strength and pharmaceutical form	Libbox 67 mg Spot-on Solution for Small Dogs Libbox 134 mg Spot-on Solution for Medium Dogs Libbox 268 mg Spot-on Solution for Large Dogs Libbox 402 Spot-on Solution for Very Large Dogs
Applicant	Vetoquinol UK Ltd Vetoquinol House Great Slade Buckingham Industrial Estate Buckingham MK18 1PA
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dog
Indication for use	Treatment of flea (Ctenocephalides spp.) and biting/chewing lice (*Trichodectes canis)* infestations in dogs. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. Newly arriving fleas are killed within 48 hours of landing on the animal. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon. The product has not demonstrated an immediate acaricidal effect against ticks but has demonstrated persistent acaricidal efficacy for up to 4 weeks against *Rhipicephalus*

	sanguineus and Dermacentor reticulatus and up to 3 weeks against *Ixodes Ricinus.* If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17th July 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Italy, Belgium, Poland, Spain, France, The Netherlands

I. SCIENTIFIC OVERVIEW

Libbox spot-on solutions for dogs are cutaneous spot-on solutions for use in dogs that contain 100 mg/ml of fipronil. The products are generic hybrids, where bioequivalence cannot be established via bioavailability studies with a reference product. As such, suitable safety, pre-clinical and clinical studies were provided instead. The products are a spot-on with little or no trans-cutaneous absorption. The original reference products were Frontline Spot on for Dogs (available in the UK since 1996). The indications are for the treatment of flea (*Ctenocephalides spp*.) and biting / chewing lice (*Trichodectes canis*) infestations in dogs. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. Newly arriving fleas are killed within 48 hours of landing on the animal. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon. The product has not demonstrated an immediate acaricidal effect against ticks, but has demonstrated persistent acaricidal efficacy for up to 4 weeks against *Rhipicephalus sanguineus* and *Dermacentor riticulatus*, and up to 3 weeks against *Ixodes ricinus*. If ticks of these species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week.

The products are produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the products can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The products are safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy[2] of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The products contain 100 mg/ml fipronil as the active substance and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone (K17) and diethylene glycol monoethylether.

The container/closure system consists of pipettes made of a polyacrylonitrile / polypropylene - cyclic olefin copolymer - polypropylene / polypropylene thermoforming foil sealed with a polyacrilonitrile / aluminium / polyethylene terephthalate lid foil. Each pipette is included in an individual blister and placed in a cardboard box. Each cardboard box contains 1, 3, 6, 30, 36 or 50 pipettes. 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 products are an established pharmaceutical form and development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The products are 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. The manufacturing process consists of several solubilisation and mixing steps, followed by final fill into pipettes.

II.C. Control of Starting Materials

The active substance is fipronil, an established active substance not described in the European Pharmacopoeia (Ph. Eur.). The active substance is manufactured in accordance with the principles of good manufacturing practice. All excipients are monographed in the Ph. Eur.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

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

The excipients comply with the relevant Ph. Eur. monographs.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of these products.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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 products.

Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification. Tests include those for appearance, density, water content, uniformity of dosage, active substance identity, related substances and microbial quality.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 4 years and 2 years for each manufacturer of the active substance was deemed satisfactory. 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. Data were available from batches stored under real time (25°C/60% RH), or accelerated conditions (40°C/75% RH) for 36 months and 6 months respectively. A shelf-life of three years with no special storage conditions was accepted.

G. Other Information

Shelf life of the veterinary medicinal products as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: use immediately.
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics
Fipronil is a phenylpyrazole which blocks gamma-amino butyric acid (GABA) receptors which affect the passage of chloride ions across the cell membrane of the target species. Death is induced via uncontrolled nervous system activity. Fipronil also inhibits glutamate-activated chloride channels (GloCls) which are only found in invertebrates. There is very little effect from fipronil on mammalian cells.

Pharmacokinetics
An *in vivo* dermal adsorption study in rats demonstrated that the quantity of fipronil absorbed was less than 1% of the applied dose at all doses tested across a 24 hour period. In modified dermal adsorption studies single spot-on applications of different doses of fipronil applied to cats and dogs, it was concluded that there was a good distribution of fipronil in the hair between the site of application and the untreated area.

Fipronil is slightly absorbed through the skin after local dermal application to the dog. Low levels of fipronil may be detected in the plasma, with high variability between dogs. After application there is a good distribution of fipronil in the hair, presenting a good gradient of concentration between the application site and the peripheral area. The principal metabolite of fipronil is the sulfone derivative, fipronil sulfone which in addition to the active substance, also possess insecticidal and acaricidal properties. The concentration of fipronil on hair decreases with time.

Toxicological Studies

The applicant has provided bibliographical data:

Single dose toxicity
A series of single dose toxicity studies were conducted in rat, mouse and rabbit via the oral and dermal route. In the studies the LD_{50}[3] values were cited as 92 mg/kg (oral, rat) and 91 mg/kg (oral, mice). Dermal LD_{50} in rats exceeded 2000 mg/kg and in rabbits was cited as 354 mg/kg. Adverse clinical signs were generally noted within 24 hours of treatment.

[3] LD_{50} – dose that will destroy half the test population.

Repeated dose toxicity

A series of repeat dose studies was provided. NOAEL[4] were established for some of the studies. A 21 day dermal study in rabbits established a NOAEL of 5.0 mg/kg, with adverse systemic effects resulting at the end of the study. No skin irritation was noted. A 13 week study in rats, administered fipronil in the diet, resulted in a NOAEL of 0.33 mg/kg. Alterations were observed in blood chemistry and increased liver and thyroid weights were also observed. In a combined chronic toxicity and carcinogenicity 52 week study in rats, administered fipronil in the diet, a NOAEL of 0.019 mg/kg was observed. An increased incidence of clinical signs and alterations in clinical chemistry was noted. In a 13 week oral study (capsule) in dogs, a NOAEL of 0.5mg/kg was observed. The highest dose administered was 10 mg/kg. Clinical signs of neurotoxicity were noted.

Reproductive Toxicity

A two generation reproductive toxicity study was conducted in rats administered various concentrations of fipronil. Parental toxicity of fipronil was equivalent to 0.25 mg/kg per day and a NOAEL for reproductive toxicity was observed as being 2.5 mg/kg per day. Decreased litter size bodyweight was noted.

Embryotoxicity / foetotoxicity (including teratogenicity)

A development toxicity study was carried out in female rats administered fipronil. Maternal effects associated with treated occurred only in animals treated with 20 mg/kg. No treated related effects on foetuses were noted. The NOAEL for developmental toxicity was established at 20 mg/kg per day. In another developmental toxicity study in rabbits, a NOAEL for developmental toxicity was established as 1 mg/kg per day at the highest dose tested.

Mutagenicity

No studies indicated that fipronil produces mutagenic effects.

Carcinogenicity

Studies in rats indicated that at high levels, fipronil causes non genotoxic thyroid changes and is not considered to be carcinogenic to humans.

Studies of Other Effects

Neurotoxicity

Single dose neurotoxicity studies were conducted in rats. In one study rats were administered fipronil orally at various doses and neurobehavioural evaluations were made. Clinical signs were observed in the 50 mg/kg group and a NOAEL of 0.5 mg/kg was noted. In another study rats administered fipronil orally, no treatment related deaths or clinical signs of toxicity were noted and a NOAEL of 0.3 mg/kg bodyweight per day was established. Single dose toxicity studies were conducted in dogs. Dogs were administered fipronil orally at various dose rates. All treated animals displayed neurotoxic signs; however a NOAEL was not established.

[4] NOAEL – No observed adverse effect level.

Photodegradation products

Two photometabolites of fipronil have been identified however only fipronil desulfinyl is of toxicological concern. In two studies in mice administered fipronil desulfinyl in the diet for 28 days and 90 days, clinical signs of neurotoxicity were observed with a NOAEL of 0.49 mg/kg bodyweight per day and 0.08 mg/kg bodyweight per day respectively. Similar studies conducted in rats and a NOAEL of 0.23 mg/kg bodyweight per day was established in a 28 day study and a NOAEL of 0.029 mg/kg bodyweight per day. Dogs administered various doses of fipronil desulfinyl in the diet for 90 days showed evidence of possible clinical toxicity with a NOAEL of 0.29 mg/kg bodyweight per day. Oral developmental toxicity studies in rats demonstrated developmental toxicity based on incomplete formation or reduced ossification of bones. A NOAEL for maternal and development toxicity was established 1 mg/kg bodyweight per day. Single dose neurotoxicity studies in rats administered various doses of fipronil desulfinyl showed decreased bodyweight gains and food consumption, a NOAEL of 2 mg/kg was noted. A 104 week carcinogenicity study in rats, administered fipronil desulfinyl demonstrated, no evidence of carcinogenicity and a NOAEL of 0.025 mg/kg per day was established.

Skin sensitisation

A skin sensitisation study was conducted to evaluate the potential of the formulated product to cause delayed hypersensitivity in guinea pigs. The study was conducted in two steps – the induction phase, by intradermal and cutaneous routes, followed by a cutaneous challenge test. No mortality or adverse systemic clinical signs were observed during the study. The proposed formulation did not induce delayed hypersensitivity in guinea pigs.

Eye irritation

An eye irritation study was performed in rabbits. One eye was treated with the formulated product and the other eye served as a control. Mean values of scores were calculated for chemosis, redness of the conjunctiva, iris lesions and corneal opacity. Under the conditions of the study the formulated product was moderately irritant but not classed as an eye irritant.

Skin irritation

A skin irritation study was conducted to evaluate the potential of the formulated product to induce skin irritation following single topical administration in rabbits. Mean values of the scores for erythema and oedema were noted. Under the conditions of the study the formulated product was not classified as a skin irritant.

Observations in Humans

A study provided reported 7 cases of poisoning with fipronil and one death. Of the 7 reported cases of poisoning only two suffered seizures. Symptoms included sweating, nausea, vomiting and agitation. All patients were symptomatic within 12 hours of ingestion. In another case, a person with dermal and inhalation exposure to fipronil was reported suffering from headache, vertigo and weakness. All symptoms resolved after 5 hours.

User Safety

A user risk assessment was provided in compliance with the relevant guideline and the likely routes of exposure have been identified as dermal and through accidental ingestions. Warning and precautions listed on the product literature are adequate to ensure safety to users of the product.

- This product can cause mucous membrane and eye irritation. Therefore, contact of the product with mouth eyes should be avoided.
- In case of accidental eye contact, rinse immediately with plenty of water. If the irritation persists, seek medical advice and show the container or the package leaflet to the physician.
- Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. Wash hands after use.
- Do not smoke, drink or eat during application.
- Operators with a known hypersensitivity to fipronil or any excipient should avoid contact with the product.
- Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children.

Environmental Safety

A short introduction indicating that the assessment was in accordance with VICH and CVMP guidelines was included.

Phase I:
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required. As the product is an ectoparasiticide and toxic to aquatic life, further assessment to assess the risk was required. Exposure of the product to the environment may occur via transfer of the animals coat to the terrestrial or aquatic environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

- Fipronil may adversely affect aquatic organisms. Dogs should not be allowed to swim in watercourses for 2 days after application.
- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.
- Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

A critical summary was provided and the pharmacodynamic effects of the active substance were found to be similar to the reference product. Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA complex, binding to the chloride channels and blocking pre- and post-synaptic transfer of chloride ions across the target parasite cell membrane. This results in uncontrolled activity of the central nervous system and death of the insect. Fipronil also inhibits glutamate-activated chloride ions (GloCls) which are only found in invertebrates. There is very little effect from fipronil on mammalian cells.

Pharmacokinetics

The pharmacokinetics of the active substance were discussed in a literature review to characterise adsorption, distribution, metabolism and elimination of the active substance. After local dermal application of fipronil to a dog, the product is slightly absorbed through the skin. Low levels of fipronil may be detected in the plasma, with a high variability between dogs. After application there is a good distribution of fipronil in the hair and concentrations of fipronil on hair decrease over time.

Tolerance in the Target Species

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. A GLP[5] compliant study was conducted in dogs. A suitable number of dogs (32 young dogs) were divided into groups and treated using a spot-on product containing 1x, 3x or 5x the maximum recommended dose of the final product. A placebo was used as the negative control. This was a two phase, randomised, blinded controlled study. Appropriate observations and clinical measurements were made at suitable time points. No adverse events were recorded in any group and few differences were noted between groups for any of the measurements taken. These data, along with pooled data from submitted studies contributed to the safety warnings as described in the SPC. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

A review of published data was submitted in support of resistance. The potential for development of resistance to these products is similar to that of the reference product. Suitable guidance with regards to administration is provided in the SPC.

[5] GLP – Good Laboratory Practice.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted four dose confirmation studies conducted on dogs.

Dose confirmation studies:

Study title	A study to determine the efficacy of a single application of a tick and flea treatment when compared to a control group against artificially induced infestations of *Ixodes ricinus* and *Ctenocephalides felis* on dogs.
Objectives	To determine the efficacy of a single topical application of fipronil compared to a control group against artificially induced infestations of *Ixodes ricinus* and *Ctenocephalides felis* on beagles.
Test site(s)	Laboratory environment. Single centre. EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Proposed fipronil spot-on solution. Product delivered at 1.34 ml. (Dogs 10-20 kg)
Control product/placebo	Negative Control product, sodium chloride solution 0.9% w/v
Animals	16 dogs, 8 of each sex, weighing 10.1-18.3 kg. Dogs were divided into two groups.
Outcomes/endpoints	Tick and flea counts occurred in various days of assessment. Efficacy of the test product was compared to control product
Randomisation	Randomised.
Blinding	Blinded
Method	After acclimatisation, dogs were divided into two groups. At various time points according to the study schedule, animals were infested with *Ixodes ricinus* and *Ctenocephalides felis*, approximately 100 fleas and 50 ticks. On Day 0 dogs in Group1 were treated with 1.34 ml of the negative control product and Group 2 were treated with 1.34 ml of the proposed fipronil spot-on product. Flea and tick counts were performed up to Day 72 of the study.
Statistical method	Statistical analysis was performed using Abbotts Formula. Efficacy against fleas was defined as at least a 95% reduction in geometric means of live fleas in the treated Group 2 compared to control Group1. Efficacy against ticks was defined as at least 90% reduction in geometric means of all live and killed, engorged ticks in the treated Group 2 compared to control Group 1. Flea and tick counts between groups were also compared

	using ANOVA.
RESULTS	
Outcomes for endpoints	Cosmetic effects were observed in both groups. Two adverse events were recorded during the study, but neither was deemed to be linked to treatment. A single topical administration to dogs of the product was well tolerated and demonstrated efficacy against *C. felis* infestations from Day 2 to Day 72 inclusive (10 weeks) and a significant treatment effect against *I. ricinus* infestations was observed at all times up to Day 23.
DISCUSSION	The study concluded that a single topical administration of the proposed product was well tolerated and demonstrated efficacy against artificial *C. felis* infestations from Day 2 to Day 75. A statistically significant treatment effect against artificial *I. ricinus* infestation was observed at all times up to 23 days. A claim for an 8 week immediate and persistent efficacy against *C. felis* and a 3 week persistent efficacy *I. ricinus* was supported. The SPC carries the appropriate indication.

Study title	A study to determine the efficacy of a single application of a tick and flea treatment when compared to Frontline Spot on Dog and a control against artificially induced infestations of *Rhipicephalus sanguineus* and *Ctenocephalides felis* on dogs
Objectives	To determine the efficacy of a single topical application of fipronil compared to Frontline Spot on Dog and a control against artificially induced infestations of *Rhipicephalus sanguineus* and *Ctenocephalides felis* on dogs.
Test site(s)	Single centre. EU country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Proposed fipronil spot-on solution. Product delivered at 1.34 ml. (Dogs 10-20 kg)
Control product/placebo	Control product – Frontline spot-on Dog. Product delivered at 1.34 ml. Negative control product - sodium chloride solution 0.9% w/v
Animals	18 dogs, 10 male and 8 female, weighing 12.8-19.8 kg. Dogs were divided into three groups.
Outcomes/endpoints	Tick and flea counts occurred in various days of assessment. Efficacy of the test product was compared to control products.
Randomisation	Randomised.
Blinding	Blinded

Method	After acclimatisation, dogs were divided into three groups. At various time points according to the study schedule, animals were infested with *Rhipicephalus sanguineus* and *Ctenocephalides felis*, approximately 100 fleas and 50 ticks. On Day 0 dogs in Group 1 were treated with 1.34 ml of the negative control product and dogs in Group 2 and 3 received Frontline and the proposed fipronil spot-on solution respectively. Flea and tick counts were performed up to Day 93 of the study.
Statistical method	Statistical analysis was performed using Abbott's Formula. Efficacy against fleas was defined as at least a 95% reduction in geometric means of live fleas in the treated Group 2 or 3 compared to control Group 1. Efficacy against ticks was defined as at least 90% reduction in geometric means of all live and killed, engorged ticks in the treated Group 2 or 3 compared to control Group 1. Flea and tick counts between groups were also compared using ANOVA.
RESULTS	
Outcomes for endpoints	Cosmetic effects were observed in all groups. One adverse event was recorded during the study, but was deemed to be linked to treatment. A single topical administration to dogs of the proposed product was well tolerated and demonstrated efficacy against *C. felis* infestations from Day 2 to Day 72 inclusive (10 weeks) and a significant treatment effect against *R. sanguineus* infestations was observed from Day 9 to Day 30.
DISCUSSION	The study concluded that following a single topical administration, the proposed fipronil spot-on product was well-tolerated and had demonstrated efficacy against artificial *C. felis* infestations from Day 2 to Day 93 and against *R. sanguineus* infestation from Day 9 to Day 30. The reference product was effective against *R. sanguineus* from Day 2 to Day 30 but there were no significant differences between the efficacy of the reference product or the fipronil spot-on against either ectoparasite. The SPC carries the appropriate indication.

Study title	A study to determine the efficacy of a single application of a tick and flea treatment when compared to a control group against artificially induced infestations of *Dermacentor reticulatus* on dogs
Objectives	To determine the efficacy of a single topical application of fipronil compared to a control group against artificially induced infestations of *Dermacentor reticulatus* on dogs.
Test site(s)	Laboratory environment. Single centre. EU country.

Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Proposed fipronil spot-on solution. Product delivered at 1.34 ml. (Dogs 10-20 kg)
Control product/placebo	Negative control product, sodium chloride solution 0.9% w/v
Animals	16 dogs, 8 of each sex, weighing 10.8-18.3 kg. Dogs were divided into two groups.
Outcomes/endpoints	Tick and flea counts occurred in various days of assessment. Efficacy of the test product was compared to control product
Randomisation	Randomised.
Blinding	Blinded
Method	After acclimatisation, dogs were divided into two groups. At various time points according to the study schedule, animals were infested with *Dermacentor reticulatus*, approximately 50 ticks. On Day 0 dogs in Group 1 were treated with 1.34 ml of the negative control product and Group 2 were treated with the proposed fipronil spot-on product. Tick counts were performed up to Day 58 of the study.
Statistical method	Statistical analysis was performed using Abbott's Formula. Efficacy against ticks was defined as at least 90% reduction in geometric means of all live and killed, engorged ticks in the treated Group 2 compared to control Group 1. Tick counts between groups were also compared using ANOVA.
RESULTS	
Outcomes for endpoints	Efficacy was defined as at least a 90% reduction in geometric means of all live and killed, engorged in the treated Group 2 compared to control Group 1
DISCUSSION	No adverse events were recorded during the study. The study concluded that a single topical administration of the proposed product was well tolerated and demonstrated efficacy against artificial *D. reticulatus* infestations from Day 9 to Day 51. The SPC carries the appropriate indication.

Study title	A study to determine the efficacy of fipronil against *Dermacentor reticulates* infestation in dogs compared to the reference product Frontline Spot-on.
Objectives	To determine the efficacy of a single topical application of fipronil compared to a negative and positive control groups against artificially induced infestations of *Dermacentor reticulatus* on dogs.
Test site(s)	Uni-centre. EU country.
Compliance with	Good Clinical Practice (GCP)

Regulatory guidelines	
Test Product	Proposed fipronil spot-on solution. Product delivered at 1.34 ml. (Dogs 10-20 kg)
Control product/placebo	Control product – Frontline spot-on Dog. Product delivered at 1.34 ml. Negative control product - sodium chloride solution 0.9% w/v
Animals	24 dogs, weighing 10 -20 kg. Dogs were divided into three groups.
Outcomes/endpoints	Tick counts occurred in various days of assessment. Efficacy of the test product was compared to control product
Randomisation	Randomised.
Blinding	Blinded
Method	After acclimatisation, dogs were divided into three groups. At various time points according to the study schedule, animals were infested with *Dermacentor reticulatus*, approximately 50 ticks. On Day 0 dogs in Group 1 were treated with 1.34 ml of the negative control product and Group 2 and Group 3 were treated with the proposed fipronil spot-on product. Tick counts were performed > Day 30 of the study.
Statistical method	Primary efficacy calculations were based on geometric means. Percentage efficacy for each treated group and day against ticks were also calculated.
RESULTS	
Outcomes for endpoints	Efficacy was declared at >90% reduction compared to the saline treated control group.
DISCUSSION	Fipronil spot-on efficacy rates were similar to those obtained in the Frontline spot-on group. Persistent effectiveness for the fipronil spot-on group remained >90% up to 4 weeks post treatment. The efficacy of the product persisted in *D. reticulatus* infestations in dogs for up to 4 weeks. The SPC carries the appropriate indication.

Study title	A study to determine the efficacy of a proposed product containing fipronil against a natural infestation of *Trichodectes canis* following a single topical administration at the recommended dose to mixed breed dogs.
Objectives	To determine the efficacy of a single topical application of a proposed product containing fipronil compared to a control group against natural infestations of *Trichodectes canis* on mixed breed dogs
Test site(s)	Single site. EU country.
Compliance with	Good Clinical Practice (GCP)

Regulatory guidelines	
Test Product	Proposed fipronil spot-on solution. Product delivered at 1.34 ml or 2.68 ml depending on bodyweight of dog.
Control product/placebo	Negative control product - sodium chloride solution 0.9% w/v
Animals	16 dogs, weighing 10.4 – 20.5 kg. Dogs were divided into two groups.
Outcomes/endpoints	Lice counts occurred in various days of assessment. Efficacy of the test product was compared to control product
Randomisation	Randomised.
Blinding	Unblinded
Method	After acclimatisation, dogs were divided into three groups. At various time points according to the study schedule, animals were infested with *Dermacentor reticulatus*, approximately 50 ticks. On Day 0 dogs in Group 1 were treated with 1.34 ml / 2.68 ml of the negative control product and Group 2 were treated with the proposed fipronil spot-on product. Lice counts were performed up to Day 28 of the study.
Statistical method	Statistical analysis was performed using Abbott's Formula. Efficacy against lice was defined as at least 95% reduction in geometric means of all lice counted in the treated Group 2 compared to control Group 1. Lice counts between groups were also compared using ANOVA.
RESULTS	
Outcomes for endpoints	Efficacy was declared at >95% reduction compared to the saline treated control group.
DISCUSSION	The study concluded that following a single topical administration to dogs, the proposed fipronil spot-on product was well tolerated and had demonstrated efficacy in treating *T. canis* infestations within 7 days of the product application and controlling lice infestations for up to 28 days. The SPC carries the appropriate indication.

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 of the product(s) is favourable

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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)