Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fipralone duo 67 mg/20 mg Spot-on Solution for Small Dogs
Fiprokil duo 67 mg/20 mg spot-on solution for small dogs (FR)

Fipralone duo 134 mg/40 mg Spot-on Solution for Medium Dogs
Fiprokil duo 134 mg/40 mg spot-on solution for medium dogs (FR)

Fipralone duo 268 mg/80 mg Spot-on Solution for Large Dogs
Fiprokil duo 268 mg/80 mg spot-on solution for large dogs (FR)

Fipralone duo 402 mg/120 mg Spot-on Solution for Very Large Dogs
Fiprokil duo 402 mg/120 mg spot-on solution for very large dogs (FR)

Date Created: September 2015

PuAR correct as of 22/01/2019 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0544/001-4/DC
Name, strength and pharmaceutical form	Fipralone duo 67 mg/20 mg Spot-on Solution for Small Dogs Fipralone duo 134 mg/40 mg Spot-on Solution for Medium Dogs Fipralone duo 268 mg/80 mg Spot-on Solution for Large Dogs Fipralone duo 402 mg/120 mg Spot-on Solution for Very Large Dogs
Applicant	Alfamed, 13ème rue - L.I.D, Carros Cedex, 06517, France
Active substance(s)	Fipronil Pyriproxyfen
ATC Vetcode	QP53AX65
Target species	Dogs
Indication for use	To be used against infestations with fleas alone or in association with ticks. <u>Against fleas:</u> Treatment and prevention of infestations by fleas *(Ctenocephalides felis).* One treatment prevents further infestations for 7 weeks. Prevention of the multiplication of fleas by preventing flea eggs developing into adult fleas for 12 weeks after application. <u>Against ticks:</u> Treatment of infestations by ticks (*Ixodes ricinus).* One treatment provides persistent acaricidal efficacy for 2 weeks against *Ixodes ricinus*, and for 4 weeks against *Dermacentor reticulatus* and *Rhipicephalus sanguineus*. If ticks of some species (*Dermacentor reticulatus*, *Rhipicephalus sanguineus*) are present at the time of application, not all ticks may be killed within 48 hours.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Fixed combination application in accordance with Article 13b of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	17th June 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	France, Italy, Netherlands, Spain

I. SCIENTIFIC OVERVIEW

This was a new 'fixed combination' application made in accordance with Article 13b of Directive 2001/82/EC as amended.

These products are spot-on solutions containing fipronil and pyriproxyfen in unit-dose pipettes with a range of strengths to treat dogs of increasing sizes. The products can be used against infestations with fleas alone or in association with ticks. The products are intended for: the treatment and prevention of infestations by fleas *(Ctenocephalides felis)* for 7 weeks, and *p*revention of the multiplication of fleas by preventing flea eggs developing into adult fleas for 12 weeks after application. Treatment of infestations by ticks (*Ixodes ricinus).* One treatment provides persistent acaricidal efficacy for 2 weeks against *Ixodes ricinus*, and for 4 weeks against *Dermacentor reticulatus* and *Rhipicephalus sanguineus*. If ticks are present when the product is applied, not all ticks may be killed within 48 hours.

The product is 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 product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is 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 product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains the following amounts of the active substances fipronil and pyriproxyfen respectively 67.0 mg / 20.1 mg; 134.0 mg / 40.2 mg; 268.0 mg / 80.4 mg and 402.0 mg / 120.6 mg.

Dog weight	Fipronil (mg)	Pyriproxyfen (mg)
2-10 kg	67.0	20.1
10-20 kg	134.0	40.2
20-40 kg	268.0	80.4
40-60 kg	402.0	120.6

The excipients are Butylhydroxyanisole (E320), Butylhydroxytoluene (E321) and Diethylene glycol monoethyl ether.

The container/closure system consists of a transparent multi-layer plastic single-dose pipettes containing 1.34 ml obtained by thermoforming a transparent bottom complex (polyacrylonitrile-methacrylate, polypropylene or polyethylene-ethylene vinyl alcohol-polyethylene), cyclic olefin copolymer, polypropylene) and closed by heat sealing with a lid complex (polyacrylonitrile-methacrylate or polyethylene-ethylene vinyl alcohol-polyethylene), aluminium, polyethylene-terephthalate).

The boxes contain individual pipette(s) placed in overblister(s) made from polypropylene, cyclic olefin copolymer, polypropylene and closed with lid made from polyethylene-terephthalate, aluminium, polypropylene.

Boxes of 1, 2, 3, 4 and 6 pipettes. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified. The products are established pharmaceutical forms and their 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 products have been presented in accordance with the relevant European guidelines. The manufacturing process consists of several dissolution and mixing steps, followed by final fill into pipettes.

II.C. Control of Starting Materials

The active substances fipronil and pyriproxyfen are established active substances and not described in the European Pharmacopoeia (Ph. Eur.). Data

on the active substance fipronil was supplied in the form of an Active Substance Master File (ASMF) from one manufacturer and suitable data were provided

from an alternative manufacturer. Data related to the active pyriproxyfen has been provided in the form of an ASMF. The active substances are manufactured in accordance with the principals of good manufacturing practice.

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. All excipients comply with their 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 this product.

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 product. The tests include those for appearance, density, water content, uniformity of dosage, identification of active substances and excipients, identification of impurities and microbial purity.

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.

II.F. Stability

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.

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 provided for batches stored under real time conditions (25°C/60% RH and 30°C/65% RH) for 36 months or accelerated conditions (40°C/75% RH) for 6 months. The data support a shelf-life of 3 years and pipettes in their over-blister should be stored in the carton to protect the products from light.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Do not store above 30°C.
Store in a dry place.
Keep the blister pack in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics
The active substances are fipronil and pyriproxyfen. Fipronil is a broad spectrum insecticide used in veterinary products to control fleas, ticks and other ectoparasites in cats and dogs. Fipronil is a blocker of the gamma-aminobutyric (GABA)-regulated chloride ion channel, which interferes with the passage of chloride ions across the membranes. This results in uncontrolled activity of the central nervous system and death of the insect. The active substance is more toxic to insects than mammals.

Pyriproxyfen is an insect growth regulator (IGR) that targets insect endocrine systems and mimics juvenile hormone activity. Pyriproxyfen sterilises adult fleas and inhibits the development of immature stages. The molecule prevents, by contact, the emergence of adult insects by blocking the development of eggs (ovicidal effect), larvae and pupae (larvicidal effect), which are subsequently eliminated. Following contact and/or ingestion by adult fleas, the molecule also acts by sterilising eggs during their maturation and before being laid.

Pharmacokinetics
Dermal application studies in rats show that levels of absorbed fipronil are very low, indicating that fipronil is poorly absorbed across rat skin *in vivo*. Another study in rats demonstrated that up to 75% of orally administered fipronil was excreted via the faeces and between 5-25% though the urine. Fipronil has several metabolites, of which the major one is a sulfone derivative, which also possesses insecticidal and acaricidal properties. Fipronil plasma concentrations peak between 3 to 7 days and the active metabolite peaks between 7 to 14 days. Concentrations of fipronil and fipronil sulfone are respectively quantifiable up to 42 and 70 days after administration.

Pyriproxyfen is not fully absorbed following oral administration. An oral distribution study in rats demonstrated a wide distribution with the highest content in fat. A sex absorption difference was noted in blood, with male distribution levels up to four times higher than in females. Another study in rats

demonstrated up to 54% of the dose is excreted in the faeces with the major metabolite being 4'-OH-pyriproxyfen.

Toxicological Studies

The active substances, fipronil and pyriproxyfen, are both found individually in authorised veterinary medicinal products. Data provided includes published literature in addition to specific studies using the final combination product.

- Single Dose Toxicity

Data were provided on the toxicity of fipronil. In studies the LD_{50}[3] values were cited as 97 mg/kg (oral, rats) and 95 mg/kg (oral, mice). An LC_{50}[4] of 0.36 – 0.68 mg/l/4h was noted in rats following inhalation exposure. Dermal LD_{50} exceeded 2000 mg/kg in rats. Following single doses of oral fipronil, signs of clinical toxicity including neurotoxicity were observed.

Data were provided on the toxicity of pyriproxyfen. In a number of studies, single doses of pyriproxyfen were administered orally to rats and mice. A decrease in spontaneous activity and a reduced bodyweight gain was observed. Rats treated orally at 1000 mg/kg showed no clinical signs. Following a dermal dose of pyriproxyfen, no clinical effects were observed in rats and mice.

- Repeated Dose Toxicity

A review of a large series of repeat dose studies was provided. NOAEL[5] were established for some of the studies. Of note were observations that neurotoxicity was observed in mice and rats, when increased doses of fipronil were administered via the oral route. Less toxicity was seen in studies in which the active substance was administered via the dermal route. In the target species, dogs, some neurotoxicity was also observed following increased administration of the active substance. NOAEL were established as being between 0.2 mg/kg/day and 0.3 mg/kg/day, with a NOEL[6] at 0.3 mg/kg/day. Administration of pyriproxyfen in various studies resulted in a NOEL of between 100 mg/kg per day and 300 mg/kg/day when the target species, dogs, were treated with an oral dose of up to 1000 mg/kg/day. Any warnings applicable to dose-related toxicity are cited in the SPCs.

- Reproductive Toxicity, including Teratogenicity:

During a two-generation reproductive study, parental toxicity of fipronil was equivalent to a NOAEL of 0.25 – 0.27 mg/kg per day, increased thyroid weights and decreased body weight were observed. A NOAEL for reproductive toxicity was 2.5 – 2.7 mg/kg bodyweight per day. Decreased litter size bodyweight and a decrease in the percentage of animals that mated were noted in offspring. A study in which a fipronil-based spot on product was applied topically noted that

[3] LD_{50} – dose that will destroy half of a test population.
[4] LC_{50} – concentration that will destroy half a target population.
[5] NOAEL – No observed adverse effect limit
[6] NOEL – No observed effect limit.

pregnancy rates in rats were reduced at higher doses of 280 mg/kg while hormonal changes were found at lower doses (70 mg/kg). Doses used in this

study are considered higher than those that may be expected to be applied topically with the new fixed combination. A maternal and developmental toxicity study in rats administered fipronil orally demonstrated a NOAEL of 0.9 mg/kg/d and a NOAEL of 0.05 mg/kg/d, respectively. A second maternal and developmental toxicity study in rats administered fipronil orally demonstrated a NOAEL of 4 mg/kg bodyweight per day and 20 mg/kg bodyweight per day respectively. Maternal effects were only observed in animals receiving high doses and included reduced body weight gain, increased water consumption and decreased food consumption. Another study showed no treatment-related effects on pregnancy rates or litter size and weights in rabbits administered fipronil. A NOAEL for developmental toxicity of 1 mg/kg bodyweight per day was observed.

In a two-generation study pyriproxyfen was administered in the diet of rats at various concentrations. Decreased bodyweight and food intake were observed, and increases in liver and kidney weights were found. No adverse effect on male or female reproductive parameters was observed. In a GLP[7] developmental study, a parental NOEL of 100 mg/kg bodyweight per day was established. Abortion or premature delivery was found at higher doses. A second study to determine the effects on dams, embryotoxicity/foetotoxicity and teratogenicity showed a NOEL of 300 mg/kg bodyweight per day for embryotoxicity/foetotoxicity and 1000 mg/kg bodyweight per day for teratogenicity. No significant treatment related effects were observed on postnatal growth and reproductive performance of offspring.

The studies indicate that fipronil is a non-teratogenic substance and does not cause reproductive toxicity and that pyriproxyfen is not teratogenic.

- Mutagenicity

Fipronil and pyriproxyfen are not regarded as mutagenic substances on the basis of the results of a battery of genotoxicity tests.

- Carcinogenicity (if necessary):

Fipronil has been shown to increase the incidence of thyroid tumours in rats, although this is regarded as a species specific effect and is not considered to be carcinogenic to humans.

A study in rats was conducted with pyriproxyfen in the diet at doses of 0, 120, 600 or 3000 ppm. Overall no carcinogenic effects were observed and a NOEL was established for males and females, at 27 mg/kg/day and 7 mg/kg/day respectively. A second study in mice was conducted with pyriproxyfen in the diet at doses of 0, 120, 600 or 3000 ppm. Liver, spleen and kidney weights were affected in mice treated at 3000 ppm and decreased survival rates were seen at

[7] GLP - Good laboratory practice

the highest dose. A NOEL for males and females was established at 16 mg/kg/day and 21 mg/kg/day respectively. In addition, a dose of up to 413mg/kg bodyweight per day and 530 mg/kg per day in females respectively is not associated with oncogenicity in mice.

Studies of Other Effects

Neurotoxicity
Clinical signs of toxicity were evaluated in rats following a single dose of fipronil administered orally at doses of 0, 0.5, 5 and 50 mg/kg bodyweight. Clinical signs of toxicity were only observed at the high dose. A NOAEL of 0.5 mg/kg bodyweight was established. A study in rats treated daily with a fipronil diet for 13 weeks led to the establishment of a NOAEL of 0.3 mg/kg per day. In a neurotoxicity study, fipronil was administered in capsules to dogs. Animals received doses of either 0 or 20 mg/kg bodyweight per day for a maximum of 14 days, with a 28 day recovery period. All treated animals displayed reversible neurotoxic signs which included hypoactivity, salivation, ataxia, convulsions, tremors, stiffened body, and muscle twitching. These clinical signs were not associated with histopathological observations. A NOAEL for neurotoxicity could not be established. No neurotoxicity studies were submitted for pyriproxyfen, but no evidence was seen that pyriproxyfen induces neurotoxic behaviour.

Skin irritation
A GLP-compliant skin irritation study was conducted using 500 mg of pyriproxyfen applied to abraded skin of rabbits for 4 hours. No reactions were observed in 72 hours after the application and pyriproxyfen was therefore considered to be non-irritating to the skin.

Eye irritation
An eye irritancy study was conducted in rabbits. 100 mg of pyriproxyfen was found to cause mild, transient eye irritation that resolved within 48 hours. IN eye irritation studies, fipronil was reported to be a slight or minor eye irritant.

Skin sensitisation
In a GLP-compliant skin sensitisation study, pyriproxyfen was applied to male guinea pigs in a Maximisation Test. No skin reactions where observed after treatment and it was concluded that pyriproxyfen was not a skin sensitiser.
Based on Buehler and Manusson-Kligman tests, it was concluded that fipronil did not exhibit a clear skin sensitisation potential.

Studies on final formulation
Acute oral toxicity of the final formulation
GLP and OECD[8] acute oral toxicities achieved with each active substance given alone or in combination within the formulation were investigated in rats. At 2000 mg/kg, no mortality occurred for pyriproxyfen but the combination product and

[8] OECD – Organisation for Economic Cooperation and Development

fipronil alone were lethal. The oral LD_{50} for the final formulation was calculated to be between 300 and 2000 mg/kg in rats.

Acute dermal toxicity
An acute GLP and OECD dermal toxicity study was conducted and the test formulation was applied to the shaved skin of male and female rats at a single dose of 2000 mg/kg for 24 hours. Rats were observed daily for 15 days. Following necropsy no treatment-related signs of toxicity were observed. Focal crusts were noted in some animals but these were reversible. The dermal LD_{50} was determined to be in excess of 2000 mg/kg. Neither toxicity nor mortality was reported at 2000 mg/kg.

Skin irritation
A GLP and OECD skin irritation study was conducted with the final formulation applied to male rabbits. The formulation was applied to the skin on a gauze pad held in place for 4 hours. No skin reactions were observed and the final formulation was not classified as a skin irritant.

Eye irritation
A GLP and OECD compliant *in vivo* eye irritation study was carried out. Rabbits received 0.1 ml of the final formulation in the left eye. Mean scores for corneal opacity, iritis and redness of the conjunctivae were calculated. Reddening of the conjunctivae and sclera and discharge were observed but these were reversible. Based on the results, the final formulation was not classified as an eye irritant.

Skin sensitisation
A GLP and OECD skin sensitisation study was conducted in guinea pigs. The final formulation was topically applied under an occlusive dressing for 6 hours at weekly intervals for 3 weeks. 2 weeks after the final application a challenge formulation was applied. No skin reactions were observed and the final formulation was not classified as a skin sensitiser.

Wipe test
A GLP compliant wipe test study was conducted in dogs treated with the product at the recommended dose to determine the amount of residual fipronil (including its sulfone derivative) and pyriproxyfen that could be wiped off the application site. Dogs were treated with a 1.34 ml pipette of the product applied topically. Dogs were wiped at Day 0 and at pre-planned time points up to 84 days. A cotton glove was placed on the petting hand and the animal was stroked ten times from head to tail. Following wiping the cotton glove was assessed for fipronil, fipronil sulfone and pyriproxyfen. 1 hour post application levels of residual fipronil and pyriproxyfen were approximately 5% and 6.2% respectively. The presence of fipronil sulfone was negligible.

Haircoat distribution
Six dogs received the recommended dose of the product. Hair samples were taken in four areas, (neck, shoulder, back and thigh), at regular time points up to 84 days post-application. Fipronil, fipronil sulfone and pyriproxyfen were

measured at each time point. Fipronil and pyriproxyfen were detected for up to 84 days. Fipronil sulfone concentrations were significantly lower than that of fipronil and emergence of the metabolite in the fur was delayed.

Studies with metabolites
A study in rats has been conducted to establish the toxicity of fipronil sulfone. Doses above 100 mg/kg fipronil sulfone elicited neurotoxic behaviours and in some cases, death. Studies of fipronil sulfone in rabbits showed no signs of dermal irritation, but caused transient eye irritation. Fipronil sulfone did not elicit genotoxicity.
Studies in rats, mice and dogs administered fipronil desulfinyl were also conducted. The conclusion that no fipronil metabolites present higher hazards than the parent compound fipronil is supported.

Pyriproxyfen metabolites studies conducted demonstrated an oral LD_{50} higher than 2000 mg/kg and therefore, the conclusion that no pyriproxyfen metabolites present higher hazards than the parent compound pyriproxyfen is supported.

Observations in Humans

Eight recorded cases of human intoxication with fipronil were referenced in published data. Two cases resulted in central nervous system toxicity with seizures, sweating, nausea, vomiting and agitation. All other patients were asymptomatic within 12 hours of ingestion. One patient died, however it was not clear if this was attributed to fipronil overdosing.
Pyriproxyfen is not used in human medicinal products and no human cases of toxicity are reported.

User Safety

A large series of studies was provided that investigated all aspects of user safety, including dermal and oral toxicity tests. Tests were performed on the individual active substances, and also on the combination of the actives. Warnings have been included within the safety section of the SPC to state that when the product is used as recommended, unwanted exposure to the active substances is minimised.

Environmental Safety

The applicant provided a Phase I environmental risk assessment (ERA) in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product will be administered for individual treatment of companion animals only and the risk of environmental exposure is low. Warnings and precautions as listed in the product literature are adequate to ensure safety to the environment when the product is used as directed.

- Fipronil and pyriproxyfen may adversely affect aquatic organisms. Dogs should be prevented from accessing streams and rivers for 48-hours following treatment.
- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
- Do not contaminate ponds, waterways or ditches with the veterinary medicinal product or empty container as this may be dangerous for fish and other aquatic organisms.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant provided referenced pharmacodynamic and pharmacokinetic data. Additional pharmacodynamic data were provided in the form of six interaction studies, in order to establish the efficacy of the combined product. This was assured. A further study was conducted to analyse drug/drug interaction between the active substances. No adverse effects were noted.

Pharmacodynamics

In veterinary medicinal medicine, fipronil is a broad spectrum insecticide used as a spray or concentrated spot-on formulation to control flea, ticks and other ectoparasites on dogs and cats and to control Flea Allergy Dermatitis. Fipronil is a member of the phenylpyrazole family. Its mode of insecticidal action is interference with the passage of chloride ions through the gamma aminobutyric (GABA)-regulated chloride ion channel, which results in uncontrolled central nervous system activity and subsequent death of the insect.

Pyriproxyfen is an insect growth regulator (IGR) that targets insect endocrine systems and mimics juvenile hormone activity. Pyriproxyfen is passively absorbed by all stages of flea and interferes with the regulation of the moulting process during larval development, which blocks the development of eggs (ovicidal effect) and larvae and pupae (larvicidal effect), resulting in associated mortality.

Pharmacokinetics

Pharmacokinetics of the products were investigated in a study determining hair-coat distribution and plasma kinetics of both active substances and fipronil sulphone, the S-oxidation product of fipronil, which defines the predominant metabolic pathway of this active substance. In mammals, percutaneous absorption of fipronil occurs slowly through the dermal layers when added topically, with subsequent dispersal in low concentration to the major organs. The distribution of fipronil when administered to dogs means that the product spreads from the treatment site to cover the entire surface of the animal within 24 hours. The excretion of fipronil is predominantly achieved via the faeces, with a smaller amount eliminated via the urine.

For pyriproxyfen, the maximum concentration of a standard dose of fipronil in dogs is generally achieved within 4-5 hours, with absolute bioavailability achieved by 1-3 days post-administration. Dispersal is seen to the major organs at low levels, with the concentration tending to remain high in fat deposits. Elimination is generally achieved via the faeces.

The distribution of fipronil and pyriproxyfen when administered to dogs means that the product is well-distributed over the surface of the animal at 24 hours after treatment.

Tolerance in the Target Species

The applicant has provided a target animal safety study and has also presented the safety data from all the preclinical and clinical studies performed with the product. A GLP-compliant study was performed in 36 clinically eligible dogs, using a product containing 1x, 3x or 5x the expected therapeutic dose of the final product. The animals were dosed at monthly intervals. Placebo was used as a negative control. Dogs receiving the placebo and 1 x dose received a total of 6 doses at monthly intervals, and dogs receiving the 3x and 5x dose received a total of 3 doses at 3 weekly intervals.

Appropriate observations and clinical measurements were made at suitable time points. Results show that final formulation was well tolerated locally and systemically at all dose levels. 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

The bibliography references were provided in relation to the possible resistance of target organisms to fipronil and permethrin. The studies provide no evidence of established resistance to fipronil or permethrin in the target parasites. Due to the different modes of action of the two active substances, cross-resistance is unlikely. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted dose confirmation studies for the selected doses of fipronil and pyriproxyfen against fleas and ticks. The studies were performed with the final formulation using the recommended dose.

Dose confirmation studies:

No dose determination studies were required, because both active substances are of 'well-established use' within the field of veterinary medicine.

Study title	Interaction efficacy study of a proposed product containing fipronil and pyriproxyfen against fleas (*Ctenocephalides felis*) on dogs.
Objectives	To identify any possible interaction between the two active ingredients in the proposed spot-on formulation and their impact on the efficacy against experimental infestations with fleas (*Ctenocephalides felis*) on dogs.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 based on bodyweight range: 0.67 ml/ dog ≥2.1 to 10 kg 1.34 ml/dog ≥10.1 to 20 kg
Control product/placebo	Placebo (no control product)
Animals	32 dogs, four groups of 8 dogs in each (each group was administered either combination product, or fipronil, or pyriproxyfen, or no control product).
Outcomes/endpoints	Flea counts occurred on various days of assessment. This was performed by calculating the mean number of live fleas on each of the dogs in the treated groups.
Randomisation	Randomised
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points according to the dosing schedule animals were infested as appropriate and flea counts were also performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against fleas was calculated using Abbott's formula. Criteria for adulticidal efficacy was assessed as being the termination of ≥ 95% of fleas.
RESULTS	
Outcomes for endpoints	No treatment-related adverse events were observed. The three treatment products had clinically comparable immediate persistent efficacy against *C. felis* infestation. No interaction between the two active ingredients was evident.
DISCUSSION	The study demonstrated that all three treated groups

	had clinically comparable immediate and persistent efficacies with no statistical difference in arithmetic means. Efficacy of the proposed product at the recommended dose against the target parasite was at least 95% for fleas at each counting, and persistence of efficacy was >95% for five weeks. No interaction between test materials was seen

Study title	Efficacy study of a proposed product containing fipronil and pyriproxyfen against fleas (*Ctenocephalides felis*) on dogs water immersed and shampooed.
Objectives	To identify any possible impact that water immersing and/or shampooing may have on the efficacy of the proposed spot-on formulation against fleas (*Ctenocephalides felis*) on dogs.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 with 1.34 ml/ dog ≥10.1 to 20 kg
Control product/placebo	Placebo (no control product)
Animals	35 dogs, five groups of 7 dogs in each (One group had no treatment, the remaining four groups were administered the combination product). Group 1: No treatment, shampooed 16 and 44 days post treatment Group 2: shampooed 2 hours prior to treatment Group 3: shampooed 16 and 44 days post-treatment Group 4: water immersed 16 and 44 days post treatment Group 5: not shampooed / showered.
Outcomes/endpoints	Flea counts occurred on various days of assessment. This was performed by calculating the mean number of live fleas on each of the dogs in the treated groups.
Randomisation	Randomised.
Method	The test product was administered at one spot directly onto the skin between the shoulder blades. At various time points according to the dosing schedule animals were infested as appropriate and flea counts were also performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against fleas was calculated using Abbott's formula. Criteria for adulticidal efficacy was assessed as being the termination of ≥ 95% of fleas.
RESULTS	

Outcomes for endpoints	Shampooing at 16 and 44 days post treatment reduced the duration of persistent adulticidal efficacy against *C. felis.* Water immersion at 16 and 44 days post treatment had no effect on the duration of persistent efficacy.
DISCUSSION	The study demonstrated that shampooing dogs prior to treatment and monthly water immersion had no significant impact of the efficacy of the test product against *C. felis* up to two months post treatment. When the dog is shampooed at monthly intervals, the product remains effective against *C. felis* for up to 5 weeks post treatment.

Study title	Comparative efficacy study of a proposed product containing fipronil and pyriproxyfen against fleas (*Ctenocephalides felis*) on dogs.
Objectives	To compare the efficacy of the proposed product and an authorised product against fleas (*Ctenocephalides felis*) on dogs.
Test site(s)	Single centre
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 with 0.067 ml/kg.
Control product/placebo	Placebo (No control treatment).
Animals	24 dogs, 3 groups of 8 dogs in each. (The groups received either the combination product, or fipronil, or no control product).
Outcomes/endpoints	Flea counts occurred on various days of assessment. This was performed by calculating the mean number of live fleas on each of the dogs in the treated groups.
Randomisation	Randomised.
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points according to the dosing schedule animals were infested as appropriate and flea counts were also performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against fleas was calculated using Abbott's formula. Criteria for adulticidal efficacy was assessed as being the termination of ≥ 95% of fleas.
RESULTS	
Outcomes for endpoints	The two treatment products had clinically comparable immediate and persistent efficacy against *C. felis* infestation.
DISCUSSION	Clinically comparable immediate and persistent efficacies were recorded. Persistent adulticidal efficacy

	against *C. felis* for up to seven weeks was demonstrated.

Study title	Interaction efficacy study of a proposed product containing fipronil and pyriproxyfen against the further development of fleas (*Ctenocephalides felis*) on dogs.
Objectives	To identify any possible interaction between the two active ingredients in the proposed spot-on formulation and their impact on the efficacy against the further development of flea eggs in dogs experimentally infested with gravid fleas (*Ctenocephalides felis*).
Test site(s)	Single centre
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0, dosage dependent on bodyweight.
Control product/placebo	Placebo (No control treatment).
Animals	28 dogs, 4 groups of 7 dogs in each. (The groups received either the combination product, or fipronil, or pyriproxyfen, or no control product).
Outcomes/endpoints	Adult flea emergence counts were performed. This was done by determining the mean number of flea larvae that had developed to adult fleas.
Randomisation	Randomised.
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points according to the dosing schedule animals were infested as appropriate and adult flea emergence counts were also performed on pre-defined assessment days.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against flea emergence was calculated using Abbott's formula. Criteria adult flea emergence was assessed as being the inhibition of the emergence of ≥ 90% of adult fleas.
RESULTS	
Outcomes for endpoints	Efficacy for the prevention of further development of flea eggs to adult fleas was greater with the combination product and pyriproxyfen and these were similarly effective in preventing adult flea emergence. No interaction between the two active ingredients was evident.
DISCUSSION	The study demonstrated that no interaction was observed between the two active ingredients in the test product. Persistent efficacy against emergence of adult

	fleas above 90% was demonstrated for up to 12 weeks.

Study title	Evaluation of the efficacy and safety of a proposed product containing fipronil and pyriproxyfen against ticks (*Ixodes ricinus*) in experimentally infested dogs.
Objectives	To evaluate the efficacy and safety of a single treatment of the spot-on product against ticks (*Ixodes ricinus)* in artificially infested dogs.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 based on bodyweight range: 0.67 ml/ dog ≥2.1 to 10 kg 1.34 ml/dog ≥10.1 to 20 kg
Control product/placebo	Placebo (no control product)
Animals	14 purpose bred dogs.
Outcomes/endpoints	Tick counts occurred on various days of assessment. Calculations were based on female ticks only, as male *I. ricinus* do not attach to a host.
Randomisation	Randomised
Blinding	Blinded.
Method	Dogs were infected with unfed adult ticks (*I. ricinus)* at various time points according to the dosing schedule. Tick counts were conducted 48±2 post application / tick infestations.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against ticks was calculated using Abbott's formula.
RESULTS	
Outcomes for endpoints	Based on the appropriate arithmetic means, the test product was effective against *I. ricinus*. The efficacy of the proposed product was at least 90% at all-time points.
DISCUSSION	It was demonstrated that the proposed product provided immediate adulticidal efficacy against *I. ricinus* and a persistent acaricidal efficacy for two weeks after treatment administration.

Study title	Interaction efficacy study of a proposed product containing fipronil and pyriproxyfen against ticks (*Rhipicephalus sanguineus*) in dogs.
Objectives	To identify any possible interaction between the two active ingredients in the proposed spot-on formulation and their impact on the efficacy against experimental infestation with ticks (*Rhipicephalus sanguineus)* on

	dogs.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 based on bodyweight range: 0.67 ml/ dog ≥2.1 to 10 kg 1.34 ml/dog ≥10.1 to 20 kg
Control product/placebo	Placebo (no control product)
Animals	32 dogs, four groups of 8 dogs in each (each group was administered either the combination product, or fipronil or pyriproxyfen alone, or no control product).
Outcomes/endpoints	Tick counts occurred on various days of assessment by calculating the mean number of live ticks and the mean number of live and dead engorged ticks within each of the treated groups.
Randomisation	Randomised
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points, according to the dosing schedule, animals were infested as appropriate (50 ticks per dog) and tick counts were performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against ticks was calculated using Abbott's formula.
RESULTS	
Outcomes for endpoints	Based on the appropriate arithmetic means, the test product was effective against *R. sanguineus.* The efficacy of the proposed product was at least 90% at all-time points
DISCUSSION	The study has demonstrated that there was persistent adulticidal efficacy above 90% after treatment with the product for up to 30 days. None of the test materials demonstrated immediate efficacy. No interaction between the test materials was seen.

Study title	A dose confirmation study to determine the efficacy of a proposed product containing fipronil and pyriproxyfen against ticks (*Dermacentor reticulatus*) on dogs.
Objectives	To confirm the target dose effectiveness of the proposed spot-on formulation against ticks (*Dermacentor reticulatus)* on dogs.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)

Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0, dosage 1.34 ml/dog ≥10.1 to 20 kg
Control product/placebo	Placebo (no control product)
Animals	16 dogs, two groups of 8 dogs.
Outcomes/endpoints	Tick counts occurred on various days of assessment by calculating the mean number of live ticks and the mean number of live and dead engorged ticks within each of the treated groups.
Randomisation	Randomised
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points, according to the dosing schedule, animals were infested as appropriate (50 ticks per dog) and tick counts were performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against ticks was calculated using Abbott's formula.
RESULTS	
Outcomes for endpoints	Based on the appropriate arithmetic means, the test product was effective against *D. reticulatus.* The efficacy of the proposed product was at least 90% at all-time points.
DISCUSSION	It was demonstrated that the proposed product provided persistent adulticidal efficacy above 90% against *D. reticulatus.* for 30 days after treatment administration.

Study title	A dose confirmation efficacy study of a proposed product containing fipronil and pyriproxyfen against ticks (*Rhipicephalus sanguineus*) on artificially infested dogs.
Objectives	To confirm the efficacy of the proposed spot-on formulation against induced infestations of ticks (*Rhipicephalus sanguineus)* on dogs administered the proposed doses.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0 based on bodyweight range: 0.67 ml/ dog ≥2.1 to 10 kg 1.34 ml/dog ≥10.1 to 20 kg 2.68 ml/dog >20 to 30 kg
Control	Placebo (no control product)

product/placebo	
Animals	14 dogs, two groups of 7 dogs.
Outcomes/endpoints	Tick counts occurred on various days of assessment by calculating the mean number of live ticks in the control group and the mean number of live and dead engorged ticks within the treated group.
Randomisation	Randomised
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. At various time points, according to the dosing schedule, animals were infested as appropriate (50 ticks per dog) and tick counts were performed on various days of assessment.
Statistical method	Statistical analysis was performed using appropriate software. Efficacy against ticks was calculated using Abbott's formula.
RESULTS	
Outcomes for endpoints	Based on the appropriate arithmetic means, the test product was effective against *R. sanguineus.* The efficacy of the proposed product was at least 90% at all-time points.
DISCUSSION	It was demonstrated that the proposed product provided persistent adulticidal efficacy above 90% against *R. sanguineus* for 30 days after treatment administration.

Field Trials

Study title	Clinical field study to confirm the efficacy and safety of a proposed product containing fipronil and pyriproxyfen in dogs naturally infested by fleas.
Objectives	To confirm the efficacy and safety of a proposed product, a combination of fipronil and pyriproxyfen, after spot-on application on dogs naturally infested by fleas, within normal conditions of use in the field, and in comparison with a reference product, Frontline Combo.
Test site(s)	Multi-centre
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0, dosage dependent on bodyweight.
Control product	Frontline Combo – a topical spot-on containing 100 mg/ml fipronil and 90 mg/ml (S)-Methoprene.
Animals	193 dogs and 25 supplementary dogs were included in the study. Inclusion criteria: • At least 7 live fleas • At least 2kg bodyweight and 10 weeks old • A maximum of 4 dogs and 4 cats per household • Privately owned dog • Healthy or well controlled concurrent disease • Healthy application site(s), dry fur • Signed owner consent and agreement to attend all protocol stated visits Exclusion criteria: • Dogs that cannot be treated with the IVP or CVP for any reason (e.g. pregnancy or known hypersensitivity) • Primary or supplementary dog or environment treated with a flea product with ongoing efficacy as per label • Major surgery within 7 days prior to or during the study period • Expected introduction of a new dog/cat during the study period • Requirement for a concurrent treatment not permitted for use during the study • Expected to require a shampoo before visit 3 (28±3 days) Post inclusion removal criteria: • Owner request • Major surgery has to be carried out during the study period

	• An adverse event occurs and interferes with the study objectives • within a multi-dog household, if a primary or supplementary dog was not treated with the IVP or CVP • if a cat in the same household was not treated with the appropriate commercial veterinary spot-on product on day 0+1 and/or 28±3 days • the dog receives any forbidden concomitant treatment • an environmental ectoparasiticide was applied in the household • any other event occurred that could invalidate the data.
Outcomes/endpoints	Efficacy: percent reduction of live flea count. Safety: occurrence of serious adverse events (SAEs) and adverse events (AEs) and local tolerance at application site.
Randomisation	Randomised.
Blinding	Blinded.
Method	Each dog was assigned to one of the treatment groups according to the randomisation plan. At the first visit each dog (primary and supplementary) received a single treatment. Each primary dog was then examined every two weeks for 56 weeks. At each visit live flea counts) were completed and a physical exam was carried out.
Statistical method	The primary efficacy variable was the percent reduction of the live flea counts.' This was assessed in two ways: one with a 97.5% confidence interval and the other using a 95% confidence interval of the difference between the test product and the positive control. The non-inferiority margin was defined as 5%.
RESULTS	
Outcomes for endpoints	Data were considered sufficient to support the claims within the SPC.
Adverse events	Some adverse events were noted. All reported adverse events were classified as unrelated to treatment administration.
DISCUSSION	The test product has been demonstrated to be safe and efficacious in the treatment of flea infestation in dogs. Data were considered sufficient to support the claims within the SPC.

Study title	Clinical field study to confirm the efficacy and safety of a proposed product containing fipronil and pyriproxyfen in dogs naturally infested by ticks.
Objectives	To confirm the efficacy and safety of a proposed

	product, a combination of fipronil and pyriproxyfen, after spot-on application on dogs naturally infested by ticks, within normal conditions of use in the field, and in comparison with a reference product, Frontline Combo.
Test site(s)	Multi-centre
Test Product	A topical spot-on – 10% fipronil and 3% pyriproxyfen administered once at day 0, dosage dependent on bodyweight.
Control product	Frontline Combo – a topical spot-on containing 100 mg/ml fipronil and 90 mg/ml (S)-Methoprene.
Animals	190 privately owned dogs were included in the study. A large diversity of both pure breeds and mixed breeds was included in the study. A total of 128 dogs were treated with the proposed product and 62 with Frontline Combo. Inclusion criteria: • At least 3 live and attached ticks • At least 2kg bodyweight and 10 weeks old • A maximum of 3 dogs per household • Privately owned dog • Healthy or well controlled concurrent disease • Healthy application site(s), dry fur • Signed owner consent and agreement to attend all protocol stated visits Exclusion criteria: • Known to be pregnant or lactating • Intended for breeding during the 4-week period of study follow-up • Treatment of dog or environment treated with a parasiticide product with ongoing tick efficacy as per label • Major surgery within 7 days prior to or during the study period • Severe chronic disease • Requirement for a concurrent treatment not permitted for use during the study • Requirement for a shampoo during the study • Known hypersensitivity and/or adverse event to a spot-on or to one of the ingredients of the test products. Post inclusion removal criteria: • Owner request • Major surgery has to be carried out during the study period • An adverse event occurs and interferes with the study objectives • the dog receives any forbidden concomitant

	treatment • any other event occurred that could invalidate the data.
Outcomes/endpoints	Efficacy: percent reduction of live tick count. Safety: occurrence of serious adverse events (SAEs) and adverse events (AEs) and local tolerance at application site.
Randomisation	Randomised.
Blinding	Blinded.
Method	At the first visit each dog received a single treatment on Day 0 according to the randomisation plan. Each dog was examined weekly for four weeks. At each examination attached ticks were counted and sent to be identified and a physical examination was carried out.
Statistical method	The primary efficacy variable was the percent reduction of the live tick counts compared to the day 0 count. This was assessed using 95% confidence intervals between the test product and the positive control. The non-inferiority margin was set at 10%.
RESULTS	
Participant flow	One dog was excluded from the ITT population due to not presenting to the study visits except day 0. From the PP population an additional 32 dogs were excluded.
Outcomes for endpoints	Data were considered sufficient to support the claims within the SPC.
Adverse events	Some adverse events were noted. All but one reported adverse events were classified as unrelated to treatment administration. The other event reported gastrointestinal disturbances, possibly related to treatment administration, but this is not a recognised adverse reaction for either of the active substances and was therefore unlikely to be related to administration of the test product.
DISCUSSION	The test product has been demonstrated to be safe and efficacious in the treatment of tick infestation in dogs. Data were considered sufficient to support the claims within the SPC.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

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)