



**Veterinary  
Medicines  
Directorate**

**United Kingdom  
Veterinary Medicines Directorate  
Woodham Lane  
New Haw  
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Surrey KT15 3LS**

**DECENTRALISED PROCEDURE**

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY  
MEDICINAL PRODUCT**

**Fipronil Pyriproxifen Virbac 50 mg/60 mg Spot-on Solution for Cats  
Fipronil Pyriproxifen Virbac 100 mg/120 mg Spot-on Solution for Very  
Large Cats**

**Fipronil Pyriproxifen 50 mg/60 mg Spot-on Solution for Cats  
Fipronil Pyriproxifen 100 mg/120 mg Spot-on Solution for Very Large Cats**

**Effipro Comp 50 mg/60 mg Spot-on Solution for Cats  
Effipro Comp 100 mg/120 mg Spot-on Solution for Very Large Cats  
(DK, FI, NO, SE)**

**Date Created: February 2016**

**PuAR correct as of 21/01/2019 when RMS was transferred to FR.  
Please contact the RMS for future updates.**

## MODULE 1

### PRODUCT SUMMARY

EU Procedure number	UK/V/0543/005/DC UK/V/0543/006/DC
Name, strength and pharmaceutical form	Fipronil Pyriproxifen 50 mg/60 mg Spot-on Solution for Cats Fipronil Pyriproxifen 100 mg/120 mg Spot-on Solution for Very Large Cats
Applicant	Virbac 1ère avenue – 2065m – L.I.D. 06516 Carros France
Active substance(s)	Fipronil, pyriproxifen
ATC Vetcode	QP53AX65
Target species	Cats
Indication for use	<p>In cats, to be used against infestations with fleas alone or in association with ticks.</p> <p><u>Against fleas:</u>                      Treatment and prevention of infestations by fleas (<i>Ctenocephalides felis</i>). One treatment prevents further infestations for 5 weeks.                      Prevention of the multiplication of fleas by preventing flea eggs developing into adult fleas for 12 weeks after application.                      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.</p> <p><u>Against ticks:</u>                      Treatment of infestations by ticks (<i>Ixodes ricinus</i> and <i>Rhipicephalus turanicus</i>).                      One treatment provides persistent acaricidal efficacy for one week.                      If ticks are present at the time of application, not all ticks may be killed within 48 hours.</p>

## **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](http://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	22 July 2015
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden

#### I. SCIENTIFIC OVERVIEW

Fipronil Pyriproxifen for cats has been developed as a new 'fixed combination' application made in accordance with Article 13b of Directive 2001/82/EC as amended. The product has been developed to treat flea and tick infestations in cats. It is also indicated for use as part of a control programme to treat flea-allergic dermatitis. The product is contraindicated in rabbits, as adverse reactions and even death could occur.

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.<sup>1</sup> 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<sup>2</sup> 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.

<sup>1</sup> SPC – Summary of product Characteristics.

<sup>2</sup> Efficacy – The production of a desired or intended result.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### II.A. Composition

The product contains fipronil and pyriproxyfen as the active substances.

Cat weight	Pipette volume	Fipronil (mg)	Pyriproxyfen (mg)
1-6 kg	0.5 ml	50	60
>6-12 kg	1 ml	100	120

The excipients are butylhydroxyanisole (E320), butylhydroxytoluene (E321) and diethylene glycol monoethyl ether.

The container/closure system consists of transparent multi-layer plastic single-dose pipettes containing 1 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, 4, 24 and 60 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 an established pharmaceutical form and its 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 and certificates of analysis have been provided.

#### ***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 and assay of active substances and antioxidants, assay 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 is 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 (PHARMACOTOXICOLOGICAL)

#### 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% through the urine. Fipronil has several metabolites, of which the major one is a sulfone derivative, which also possesses insecticidal and acaricidal properties. Following dermal application of fipronil to dogs, 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<sub>50</sub><sup>3</sup> values were cited as 97 mg/kg (oral, rats) and 95 mg/kg (oral, mice). An LC<sub>50</sub><sup>4</sup> of 0.36 – 0.68 mg/l/4h was noted in rats following inhalation exposure. Dermal LD<sub>50</sub> 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<sup>5</sup> 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 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<sup>6</sup> 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 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 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 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

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<sup>3</sup> LD<sub>50</sub> – dose that will destroy half of a test population.

<sup>4</sup> LC<sub>50</sub> – concentration that will destroy half a target population.

<sup>5</sup> NOAEL – No observed adverse effect limit

<sup>6</sup> NOEL – No observed effect limit.



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<sup>7</sup> developmental study, an oral maternal NOAEL of 100 mg/kg bodyweight per day was established in rats. Abortion or premature delivery was found at high doses and a developmental NOEL of 100 mg/kg/d was established. 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 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 413 mg/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

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<sup>7</sup> GLP - Good laboratory practice

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

Pyriproxyfen was considered to be non-irritating to skin based on a GLP-compliant skin irritation study where 500 mg of pyriproxyfen was applied to abraded skin of rabbits for 4 hours. No reactions were observed in 72 hours after the application. Skin irritation studies in rabbits show fipronil can cause slight skin irritation depending on the vehicle used.

#### Eye irritation

In an eye irritancy study conducted in rabbits, 100 mg of pyriproxyfen was found to cause mild, transient eye irritation that resolved within 48 hours. In eye irritation studies in rabbits, 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 were 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<sup>8</sup> 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 fipronil alone were lethal. The oral LD<sub>50</sub> 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<sub>50</sub> 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 female rabbits. The formulation was applied to the skin on a gauze

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<sup>8</sup> OECD – Organisation for Economic Cooperation and Development

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 cats 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. Cats were treated with a 0.5 ml pipette of the product applied topically. Cats 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. One hour post application levels of residual fipronil and pyriproxyfen were approximately 2.76% and 2.83% respectively. The presence of fipronil sulfone was negligible.

#### Haircoat distribution

Six cats received the recommended dose of the product. Hair samples were taken in three areas, (neck, shoulder, and dorsal), 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

Studies in rats have been conducted to establish the toxicity of fipronil sulfone. Doses above 100 mg/kg fipronil sulfone elicited neurotoxic behaviour 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 and mice administered fipronil desulfinyl were also conducted. The conclusion is that no fipronil metabolites present higher hazards than the parent compound fipronil is supported.

Pyriproxyfen metabolites studies conducted demonstrated an oral LD<sub>50</sub> 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. The main adverse events were central nervous system toxicity with seizures, sweating, nausea, vomiting and agitation. The adverse events were generally mild, transient and reversible, and were reported after massive oral intoxication. One patient died, however it was not clear if this was attributed to fipronil overdosing.

Pyriproxifen is not used in human medicinal products and no human cases of toxicity are reported.

### **User Safety**

A large series of studies were 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. The main routes of exposure have been identified as accidental spillage onto skin and through transfer of residues from treated animals. Appropriate warnings are included on the SPC and product literature. When the product is used as recommended unwanted exposure to the active substances is minimised.

- The product may cause neurotoxicity. The product may be harmful if swallowed.
- Avoid ingestion including hand-to-mouth contact. Avoid contact with skin and mouth.
- Do not smoke, drink or eat during application.
- Wash hands after use. In the event of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- In the case of accidental skin contact, flush with water.
- 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.
- Keep the pipettes in the original packaging until ready for use and dispose of used pipettes immediately.

### **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.

- 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 CLINICAL DOCUMENTATION

### *IV.1. 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. Excretion of fipronil is predominantly via the faeces, with a small amount eliminated via the urine.

In cats, it was seen that after a topical administration of pyriproxyfen, at an approximate dose of 10 mg/kg, the absolute bioavailability was of 25 % and peak of pyriproxyfen (plasmatic) was 24 ng/mL at 3-8 days post administration.

The excretion of fipronil is predominantly achieved via the faeces, with a smaller amount eliminated via the urine.

For pyriproxyfen, dispersal is seen in the major organs at low levels, with the concentration tending to remain high in fat deposits. Elimination is generally achieved via the faeces.

When administered dermally to cats, fipronil and pyriproxyfen are well distributed over the surface of the animal within 24 hours of 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 40 clinically eligible cats, 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. Cats receiving the placebo and 1 x dose received a total of 6 doses at monthly intervals, and cats receiving the 3x and 5x dose received a total of 3 doses at monthly 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. Several dose confirmation studies were provided. These included the following:

Study title	Impact of water showering on the effectiveness of a combined product against fleas ( <i>Ctenocephalides felis</i> ) on cats
Objectives	To identify any possible impact that water showering may have on the effectiveness of a combined product against fleas ( <i>Ctenocephalides felis</i> ) on artificially infested cats
Test site(s)	Single centre
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 12% (w/vol) pyriproxifen administered once at day 0 based on bodyweight range: 2.21 – 5.49 kg 0.5 ml per cat.
Control product/placebo	Negative control
Animals	28 cats, older than 6 months, 13 males 15 females, mixed breed mainly shorthair. Group 1 negative control, Group 2 treated with product day 0 Group 3 treated with product and showered two hours prior to treatment (day 0), and day 16 and day 30 post-administration. 4 cats with the lowest pre-treatment flea counts were excluded.
Outcomes/endpoints	Flea counts occurred on various days of assessment. This was performed by calculating the number of live fleas on each of the cats.
Randomisation	Randomised.
Blinding	Not blinded.
Method	The dose of the 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 one-way ANOVA and non-parametric analysis using the Mann-Whitney test. Criteria for adulticidal efficacy was assessed as being the termination of $\geq 95\%$ of fleas.
<b>RESULTS</b>	
Outcomes for endpoints	No treatment-related adverse events were observed. The three treatment products had clinically comparable immediate persistent efficacy against <i>C. felis</i> infestation. No interaction between the two active ingredients was evident.
<b>DISCUSSION</b>	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	Interaction efficacy study of a combined product against the further development of flea ( <i>C.felis</i> ) eggs collected from cats infested with gravid fleas
Objectives	To identify any possible interaction between 10% fipronil and 12% pyriproxifen and their impact on efficacy against the further development of flea eggs collected from cats experimentally infested with gravid fleas
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	IVP1 10% fipronil and 12% pyriproxifen IVP2 10 % fipronil IVP3 12% pyriproxifen
Control product/placebo	Negative control
Animals	46 cats >6 months, mixed breed and sex, bodyweight 2.03 – 6.60 kg.
Outcomes/endpoints	Flea emergence was checked on various days of assessment. This was performed by calculating the mean number of live fleas emerged on each of the cats 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 $\geq 95\%$ of fleas.
<b>RESULTS</b>	
Outcomes for endpoints	Mean percentage of emergence ranged from 15.1 to 37.7 in the control group. The results were significantly lower in groups 2, 3 and 4.
<b>DISCUSSION</b>	No adverse reactions were noted between the active substances, and suitable, statistically relevant efficacy of the combined product was confirmed.

Study title	Efficacy study of a combined product against the further development of flea eggs ( <i>C.felis</i> ) eggs collected from water showered cats infested with gravid fleas
Objectives	To identify any impact of water on the efficacy of a combined product against the further development of eggs from cats experimentally infested with <i>C.felis</i>
Test site(s)	Single centre
Compliance with	Good Clinical Practice (GCP)



Regulatory guidelines	
Test Product	A topical spot-on – 10% fipronil and 12% pyriproxyfen
Control product/placebo	Negative control
Animals	24 cats >6 months, mixed sex and breed
Outcomes/endpoints	Flea emergence was checked on various days of assessment. This was performed by calculating the mean number of live fleas emerged on each of the cats in the treated groups. Water treatment to the animals' coats was applied at certain time points.
Randomisation	Randomised.
Blinding	Blinded.
Method	The dose of the relevant product was applied directly onto the skin between the shoulder blades. Two groups received the combined product, (one showered, one not showered) and one group received no treatment (negative control group, showered). 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. Criteria for adulticidal efficacy was assessed as being the termination of $\geq 95\%$ of fleas.
RESULTS	
Outcomes for endpoints	Statistically relevant efficacy was noted for all treated animals.
DISCUSSION	No statistical difference was noted for showered versus the non-showered, treated group.

Study title	Evaluation of the efficacy and safety of a combined product against <i>I. ricinus</i> (ticks) in artificially infested cats under laboratory conditions
Objectives	To evaluate the safety and efficacy of a single treatment of a combined product against <i>I. ricinus</i> in artificially infested cats under laboratory conditions
Test site(s)	Single centre
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A topical spot-on – 10% fipronil and 12% pyriproxyfen administered once.
Control product/placebo	Negative control.
Animals	16 cats. Mixed sex and breed. 2.7 – 5.2 kg.
Outcomes/endpoints	If the product was $\geq 90\%$ in killing ticks, efficacy was assured.
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 tick counts were performed on pre-defined assessment days.
Statistical method	Statistical analysis was performed using appropriate software.
RESULTS	
Outcomes for endpoints	There was a statistically lower tick count for the treated group as compared to the untreated group.
DISCUSSION	Suitable efficacy was demonstrated against <i>I. ricinus</i> , and persisted for 1 week.

Study title	Evaluation of the efficacy and safety of a combined product containing fipronil and pyriproxyfen against ticks ( <i>Ixodes ricinus</i> ) in experimentally infested cats.
Objectives	To evaluate the efficacy and safety of a single treatment of the spot-on product against ticks ( <i>Ixodes ricinus</i> ) in artificially infested cats.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A combined product containing 10% fipronil and 12 % pyriproxyfen
Control product/placebo	Negative control.
Animals	14 cats, mixed sex and breed, 2.4 – 6.6 kg.
Outcomes/endpoints	Tick counts occurred on various days of assessment. If the product was $\geq 90\%$ in killing ticks, efficacy was assured.
Randomisation	Randomised.
Blinding	Blinded.
Method	Cats were infected with unfed adult ticks ( <i>I. ricinus</i> ) at various time points according to the dosing schedule. Tick counts were conducted at a variety of time points.
Statistical method	Statistical analysis was performed using appropriate software.
RESULTS	
Outcomes for endpoints	There was a statistically lower tick count for the treated group as compared to the untreated group.
DISCUSSION	Suitable efficacy was demonstrated against <i>I. ricinus</i> .

Study title	Evaluation of the efficacy of a combined product containing fipronil and pyriproxyfen against ticks ( <i>R. turanicus</i> ) in experimentally infested cats.
Objectives	To evaluate the efficacy of a spot-on product against ticks ( <i>R. turanicus</i> ) in artificially infested cats.
Test site(s)	Single centre.

Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A combined product containing 10% fipronil and 12 % pyriproxyfen.
Control product/placebo	Negative control.
Animals	30 cats, 16 selected for study. Mixed sex and breed, ≥ 6 months, 2.18 – 4.17 kg.
Outcomes/endpoints	Tick counts occurred on various days of assessment. If the product was ≥ 90% in killing ticks, efficacy was assured.
Randomisation	Randomised.
Blinding	Blinded.
Method	Cats were infected with unfed adult ticks ( <i>R. turanicus</i> ) at various time points according to the dosing schedule. Tick counts were conducted at a variety of time points.
Statistical method	Statistical analysis was performed using appropriate software.
RESULTS	
Outcomes for endpoints	There was a statistically lower tick count for the treated group as compared to the untreated group.
DISCUSSION	Suitable efficacy was demonstrated against <i>R. turanicus</i> and persisted for 1 week.

Study title	Evaluation of the efficacy of a combined product containing fipronil and pyriproxyfen against ticks ( <i>R. turanicus</i> ) in experimentally infested cats.
Objectives	To evaluate the efficacy of a spot-on product against ticks ( <i>R. turanicus</i> ) in artificially infested cats.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	A combined product containing 10% fipronil and 12 % pyriproxyfen
Control product/placebo	Negative control.
Animals	25 cats, 16 selected for study. Mixed sex and breed, ≥ 6 months, 1.94 – 3.94 kg.
Outcomes/endpoints	Tick counts occurred on various days of assessment. If the product was ≥ 90% in killing ticks, efficacy was assured.
Randomisation	Randomised.
Blinding	Blinded.
Method	Cats were infected with adult ticks ( <i>R. turanicus</i> ) at various time points according to the dosing schedule. Tick counts were conducted at a variety of time points.
Statistical method	Statistical analysis was performed using appropriate software.

<b>RESULTS</b>	
Outcomes for endpoints	There was a statistically lower tick count for the treated group as compared to the untreated group.
<b>DISCUSSION</b>	Suitable efficacy was demonstrated against <i>R. turanicus</i> .

### **Field Trials**

Study title	Clinical field study to confirm the efficacy and safety of a proposed product containing fipronil and pyriproxyfen in cats 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 cats 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 12% pyriproxyfen
Control product	Frontline Combo for Cats – a topical spot-on containing 100 mg/ml fipronil and 120 mg/ml (S)-Methoprene.
Animals	<p>180 cats, (124 used in study) mixed sex and breed, privately owned, mean age 5 years.</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• At least 7 live fleas</li> <li>• At least 1.5 bodyweight and 10 weeks old</li> <li>• A maximum of 4 dogs and 4 cats per household</li> <li>• Privately owned cat</li> <li>• Healthy or well controlled concurrent disease</li> <li>• Healthy application site(s), dry fur</li> <li>• Signed owner consent and agreement to attend all protocol stated visits</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Cats that cannot be treated with the IVP or CVP for any reason (e.g. pregnancy or known hypersensitivity)</li> <li>• Primary or supplementary cat <u>or</u> environment treated with a flea product with ongoing efficacy as per label</li> <li>• Major surgery within 7 days prior to or during the study period</li> <li>• Expected introduction of a new dog/cat during the study period</li> <li>• Requirement for a concurrent treatment not permitted for use during the study</li> <li>• Expected to require a shampoo before visit 3 (28±3 days)</li> </ul> <p>Post inclusion removal criteria:</p> <ul style="list-style-type: none"> <li>• Owner request</li> </ul>

	<ul style="list-style-type: none"> <li>Major surgery has to be carried out during the study period</li> <li>An adverse event occurs and interferes with the study objectives</li> <li>within a multi-cat household, if a primary or supplementary cat was not treated with the IVP or CVP</li> <li>The cat receives any forbidden concomitant treatment</li> <li>An environmental ectoparasiticide was applied in the household</li> <li>Any other event occurred that could invalidate the data.</li> </ul>
Outcomes/endpoints	<p>Efficacy: Primary endpoint was the percentage reduction of live fleas counted at days 14 and 28.</p> <p>Safety: occurrence of serious adverse events (SAEs) and adverse events (AEs) and local tolerance at application site.</p>
Randomisation	Randomised.
Blinding	Blinded.
Method	Each cat was assigned to one of the treatment groups according to the randomisation plan. At the first visit each cat (primary and supplementary) received a single treatment. Each primary cat was then examined at appropriate time points. 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%.
<b>RESULTS</b>	
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.
<b>DISCUSSION</b>	The test product has been demonstrated to be safe and efficacious in the treatment of flea infestation in cats. 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 pyriproxifen in cats naturally infested by ticks
Objectives	To confirm the efficacy and safety of a proposed product, a combination of fipronil and pyriproxifen, after spot-on application on cats 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 12% pyriproxifen
Control product	Frontline Combo for Cats – a topical spot-on containing 100 mg/ml fipronil and 120 mg/ml (S)-Methoprene.
Animals	<p>180 cats, (179 used in study) mixed sex and breed, privately owned, mean age 4.9 years. Some cats + 6.0 kg, (2 pipettes administered).</p> <p>Inclusion criteria:</p> <ul style="list-style-type: none"> <li>• At least 3 live ticks</li> <li>• At least 1.5 bodyweight and 10 weeks old</li> <li>• Not living with more than 3 cats</li> <li>• Privately owned cat</li> <li>• Healthy or well controlled concurrent disease</li> <li>• Healthy application site(s), dry fur</li> <li>• Signed owner consent and agreement to attend all protocol stated visits</li> </ul> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> <li>• Cats that cannot be treated with the IVP or CVP for any reason (e.g. pregnancy or known hypersensitivity)</li> <li>• Primary or supplementary cat <u>or</u> environment treated with a flea product with ongoing efficacy as per label</li> <li>• Major surgery within 7 days prior to or during the study period</li> <li>• Expected introduction of a new dog/cat during the study period</li> <li>• Requirement for a concurrent treatment not permitted for use during the study</li> <li>• Expected to require a shampoo</li> </ul> <p>Post inclusion removal criteria:</p> <ul style="list-style-type: none"> <li>• Owner request</li> <li>• Major surgery has to be carried out during the study period</li> <li>• An adverse event occurs and interferes with the study objectives</li> <li>• The cat receives any forbidden concomitant treatment</li> <li>• Any other event occurred that could invalidate the data.</li> </ul>
Outcomes/endpoints	<p>Efficacy: Primary endpoint was the percentage reduction of live ticks counted at appropriate time points.</p> <p>Safety: occurrence of serious adverse events (SAEs) and adverse events (AEs) and local tolerance at</p>

	application site.
Randomisation	Randomised.
Blinding	Blinded.
Method	Each cat was assigned to one of the treatment groups according to the randomisation plan. At the first visit each cat (primary and supplementary) received a single treatment. Each primary cat was then examined at appropriate time points. At each visit live tick counts were completed and a physical exam was carried out.
Statistical method	The primary efficacy variable was the percent reduction of the live tick 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%.
<b>RESULTS</b>	
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.
<b>DISCUSSION</b>	The test product has been demonstrated to be safe and efficacious in the treatment of flea infestation in cats. 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](http://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](http://www.gov.uk/check-animal-medicine-licensed)