Veterinary Medicines Directorate

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

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

Date Created: November 2015

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	FleaCidal 67 mg Spot-on Solution for Small Dogs FleaCidal 134 mg Spot-on Solution for Medium Dogs FleaCidal 268 mg Spot-on Solution for Large Dogs FleaCidal 402 mg Spot-on Solution for Very Large Dogs
Applicant	Perrigo Pharma International D.A.C. Treasury Building Grand Canal Street Lower Dublin 2 Ireland
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	For the treatment of dogs against flea infestations (Ctenocephalides spp.) Insecticidal efficacy against new infestation with fleas persists for up to 6 weeks. Although the product does not consistently show an immediate acaricidal efficacy (several ticks may be present after 48 hours), it has a persistent acaricidal efficacy for up to 4 weeks against *Dermacentor variabilis* and up to 3 weeks against *Rhipicephalus sanguineus*.

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	Generic 'hybrid' applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

These were generic 'hybrid' applications, as bioequivalence to a reference product was not established via bioavailability studies. The reference product was Frontline Spot on Dog 10% w/v Spot on Solution, marketed in the UK since 1996.

The products are intended to treat dogs against flea infestations for up to six weeks. The product does not have immediate acaricidal activity, but has a persistent activity against ticks of up to four weeks against *Dermacentor variabilis* and up to three weeks against *Rhipicephalus sanguineus*. Although the product does not consistently show an immediate acaricidal efficacy (several ticks may be present after 48 hours), it has a persistent acaricidal efficacy for up to 4 weeks against *Dermacentor variabilis* and up to 3 weeks against *Rhipicephalus sanguineus*.

The products are produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any 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 products 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 CONSTIUENTS

II.A. Composition

The products contain fipronil at varying quantities depending on the size of the animal to be treated, (67 mg fipronil in 0.67ml, 134 mg in 1.34 ml, 268 mg in 2.68 ml or 402 mg in 4.02 ml). The excipients are butylhydroxyanisole (E 320), butylhydroxytoluene (E 321), and diethylene glycol monoethyl ether. One pipette of 0.67 ml is sufficient for the treatment of a dog with a body weight of 2 kg up to 10 kg corresponding to a recommended minimum dose of 6.7 mg fipronil/kg body weight. One pipette of 1.34 ml is sufficient for the treatment of a dog with a body weight of 10 kg up to 20 kg corresponding to a recommended minimum dose of 6.7 mg fipronil/kg body weight. One pipette of 2.68 ml is sufficient for the treatment of a dog with a body weight of 20 kg up to 40 kg corresponding to a recommended minimum dose of 6.7 mg fipronil/kg body weight. One pipette of 4.02 ml is sufficient for the treatment of a dog with a body weight of 40 kg up to 60 kg corresponding to a recommended minimum dose of 6.7 mg fipronil/kg body weight. For dogs over 60 kg: use two pipettes of 2.68 ml.

The container/closure system: The pipettes are made of:

- bottom foil: polyethylene terephthalate/polypropylene

- lidding foil: polyethylene terephthalate/aluminium

To protect the content of the pipettes from moisture and light the pipettes are individually packed in blister foils made of:

- cold-form foil for blister: polyvinyl chloride/(biaxially) oriented poly-amide/aluminium/polyvinyl chloride

- lidding foil for blister: polyethylene terephthalate/aluminium

Cartons contain 1, 2, 3 or 6 pipettes.

The choice of the formulation and the absence of preservative are justified. The products are an established pharmaceutical form and the development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the mixing of the excipients and active substance, filtering, filling into pipettes and packing into cartons.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is fipronil an established active substance which is not described in a Pharmacopoeia. Reference was made to two Active Substance Master Files. The active substance is manufactured in accordance with the principles 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 are monographed in the European Pharmacopoeia, with Certificates of Analysis presented for each.

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. 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. Tests on the finished product include those for appearance, identification and appropriate assay of fipronil, identification of related substances, water content, identity and assay of the excipients and uniformity of the dosage units.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Data were provided from three pilot batches, using the proposed packaging. The active substance was stored under VICH[3] conditions at 25°C/60% RH , (30°C/65% RH, not analysed as no effects related to accelerated storage conditions seen), and 40°C/75% RH. No adverse changes were noted for the active substance a retest period of 24

[3] VICH – International Cooperation on harmonisation of technical requirements for Registration of Veterinary Medicinal Products.

months was supported. Samples of all finished product sizes were stored 40°C/75% RH. Analysis was performed in accordance with the given specifications for the products. Data supported the proposed shelf life for the product; thirty months.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: thirty months.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

These were generic 'hybrid' applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data were provided. Fipronil acts by inhibiting the GABA[4] complex, blocking the chloride channels of the nervous system of the target parasite only. The host animal is not adversely affected when the product is used as directed. Following topical application of the products, fipronil spreads throughout the skin of the host animal, with dermal absorption considered to be low.

Toxicological Studies

The applicant provided bibliographical data:

- Single Dose Toxicity

Historical, acute toxicity studies were provided from laboratory species which demonstrated a variety of LD_{50}[5] data. Clinical signs noted at toxic levels included piloerection, diarrhoea, hunched posture, waddling gait, lethargy, decreased respiration, ptosis, convulsion and prostration. The SPC provides data on the acceptable dose regimen.

- Repeated Dose Toxicity

From a variety of studies, a NOEAL of 5 mg/kg bw was established in rats for fipronil exposure, (0.5% in carboxymethylcellulose), when administered dermally for fifteen days. Signs of toxicity were noted at 10 mg/kg/bw/day. Adverse reactions included reduced food intake, weight gain and hyperactivity).

[4] GABA – Gamma – aminobutyric acid.
[5] LD50 – The quantified level at which only half of a population survives treatment.

In laboratory animals, commonly observed adverse reactions observed were effects on the thyroid gland, liver and central nervous system. Significant results for rats included an observed NOAEL of 0.019 mg/bw in a two year carcinogenicity study, and 0.3 mg/kg/day for systemic toxicity and neurotoxicity.

- Reproductive Toxicity, including Teratogenicity:

In one study, toxicity was observed in F1 and F2 rat litters. Parental systemic toxicity (NOAEL) was noted as being 0.25 mg/kg/bw/day, and the NOAEL for reproductive toxicity was 2.5 mg/kg/bw/day. Severe adverse reactions were further noted in F1 and F2 litters at 26 mg/kg/bw/day, with postnatal survival in the F2 litters reduced, and ovarian weights decreased in F0 females. Fertility issues were also observed within the F1 parental generation. In a similar study, a NOAEL for maternal toxicity was established as being 4 mg/kg/bw/day, with a NOEL[6] of 20 mg/kg/bw/day for developmental toxicity. The SPCs carry suitable warnings with regard to dose, with regard to relevant study data.

- Mutagenicity

All data submitted suggested that fipronil was not genotoxic.

- Carcinogenicity

A study in rats showed that fipronil is carcinogenic to this species at 13/17 mg/kg/bw/day due to an increase in thyroid tumours. However, this was attributed to continuous stimulation of the thyroid gland due to increased levels of thyroid stimulating hormone. The overall NOAEL was established as being 0.019 mg/kg/bw/day, based on neurotoxicity.

Studies of Other Effects

The applicant provided data additional studies which observed neurotoxicity and sensitisation, and/or eye and skin irritation. As noted, there is some evidence of neurotoxicity in laboratory animals when the dosage is above that tolerated by individual species. In suitable studies, fipronil was shown to be a mild dermal and eye irritant, but is not considered to be a skin sensitiser (rabbits). The SPCs carry suitable warnings to ensure the product is used correctly.

Observations in Humans

Information was provided describing the toxic effects of fipronil in humans. Adverse reactions include vomiting, headache, nausea, vertigo and weakness. In humans, any toxic response to fipronil is usually reversible. The SPC carries suitable user warnings.

[6] NOEL – No observed effect limit.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Suitable assessment was used to calculate the potential exposure to fipronil for adults and children. Particular attention was paid to ensuring that the SPC warns against the petting of animals prior the product drying.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The products are not expected to pose undue risk to the user or those in contact with treated animals when used as directed:

- This veterinary medicinal product can cause mucous membrane and eye irritation. Therefore avoid contact of the product with mouth and eyes.
- Should the veterinary medicinal product come into contact with the eyes, rinse thoroughly at once with water. If the eye irritation persists, seek medical help at once and show the package insert or label to the doctor.
- Avoid contact with the skin. Should the product come into contact with the skin, wash immediately with soap and water. Wash hands after use.
- Do not eat, drink or smoke during application.
- People with known hypersensitivity (allergy) to fipronil or one of the other ingredients (see 6.1) should avoid contact with the veterinary medicinal product.
- Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry.
- It is therefore recommended that animals are not treated during the day but during the early evening and that recently treated animals should not be allowed to sleep with owners, especially children.
- Keep stored pipettes in original packaging until ready for use. In order to prevent children getting access to used pipettes, dispose of used pipettes immediately.

Environmental Safety

The environmental assessment was in accordance with VICH and CVMP guidelines.

Phase I Environmental Risk Assessment (ERA)

The product will only be used in non-food animals, and as a result environmental exposure will be low. Suitable warnings are included in the SPC. A Phase II ERA was not required:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements. Fipronil may be harmful to aquatic organisms.

- Do not contaminate ponds, waterways or ditches with the product or empty container.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Fipronil belongs to the phenyl pyrazole family of anthelmintics, acting by inhibiting the GABA complex, blocking the chloride channels within the nervous system of the target parasite.

Pharmacokinetics

No additional data were required for this section. Section 5.2 of the SPC reflects appropriate data agreed for similar products.

Tolerance in the Target Species

No additional data were required for this section. The tolerance data are the same as those of the reference product. Suitable warnings appear in the SPC.

Resistance

A comprehensive literature review performed by the applicant showed that there was no current concern with regard to occurrences of resistance to the active substance when the products are used as specified in the SPC. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant provided a dose determination study, two dose confirmation studies and two studies on the efficacy of the product after the animal is washed.

Dose determination studies

The quantity of active substance used for the first study, (an *in vitro* bioassay), was the same as that of for the reference product. Tick species included in the study were *Rhipicephalus sanguineus, Ixodes ricinus* and *Dermacentor variabilis*. The fipronil formulation used in this study was not identical to the final formulation, being a crystalline powder in ethanol. A pre-study was performed on

female *R. sanguineus* ticks (strain I), and evaluated a suitable dose range to identify the least sensitive tick species, where the highest EC_{50}[7] leads to a 50% mortality of parasites. Doses provided to the parasites in a sealed environment ranged up to 1000 µg fipronil/ml, for 96 hours. Data were seen as significant up to 24 hours.

A second pre-study was a titration study in which female *R. sanguineus* (strains I and II), *I. ricinus* and *D. variabilis* were included. Fipronil was present at between 62.5 µg fipronil/ml and 750 µg fipronil/ml. Ten ticks per concentration were tested.

From these data, it was observed that *D. variabilis* and *R. sanguineus* were the least susceptible to the fipronil treatment, with EC_{50} values of 353 µg fipronil/ml and 129-245 µg fipronil/ml respectively. For *I. ricinus*, the EC_{50} was 93 µg fipronil/ml.

Two dose confirmation studies were provided, one using *Ctenocephalides felis* and *D. variablilis,* and another using *C. felis* and *R. sanguineus.*

Dose confirmation studies:

Study title	Dose confirmation study to evaluate efficacy and safety of a topically applied spot-on formulation of fipronil against ticks (*D. variabilis*) and fleas (*C. felis*) on dogs, including duration of efficacy.
Objectives	To evaluate efficacy and safety of a topically applied spot-on formulation of fipronil against ticks (*D. variabilis*) and fleas (*C. felis*) on dogs, including duration of efficacy.
Test site(s)	Single-centre, third country.
Test Product	Proposed product, 0.67 mg fipronil/kg/bw. Single dose. Minimum recommended dose of reference product.
Control product/placebo	Negative control.
Animals	16 dogs mixed breed (mainly mongrel), 5 males 11 females, (8 per group) mixed age. 4.4 kg – 21 kg bw. Hair length 13.5 – 36.5 mm. Healthy de-wormed, tick free. Two dogs (original animal total 18), with lowest pre-treatment flea counts excluded. Acclimatised for seven days, more than four months old. Not clinically pregnant. Not treated with acaricide/insecticide or an anti-infammatory product for 60 days prior to day 0.
Outcomes/endpoints	Primary outcomes: Comparison of the number of live ticks or fleas collected from both groups at various time points.
Randomisation	Randomised.

[7] EC_{50} – Effective concentration leading to 50% mortality.

Blinding	Parallel group, randomised, unicentre, blinded.
Method	Approximately 100 laboratory bred strains of mixed sex *C. felis* and were placed on pre-treated animals at days -6, -2, 7, 14, 21, 28, 35, 42, 49 and 56. Counts were performed two days after infestation. Ticks (*D. variabilis,* laboratory bred) were placed on animals on days -2, 7, 14, 21, 28, 35, and 42 with a minimum of 50 ticks of evenly balanced sex ratio. Counts were performed usually two days later.
Statistical method	**Efficacy against ticks:** Efficacy (%) = 100 x (Gm_c– Gm_t) / Gm_c, where: Gm_c= geometric mean ticks (category 1-3) in the negative control group (Group 1) at a specific time point, and Gm_t = geometric mean ticks (category 1-3; immediate efficacy) or (category 1-3 and 6; persistent efficacy) in the treatment group (Group 2) at a specific time point. **Efficacy against fleas:** Efficacy (%) = 100 x (m_c– m_t) / m_c, where: m_c= geometric mean of live fleas in the negative control group (Group 1) at a specific time point, and m_t = geometric mean live fleas in the treatment group (Group 2) at a specific time point. **Descriptive statistics**: arithmetic mean, minimum, maximum, standard deviation, CV%, geometric mean and median were calculated and tabulated for the various assessment days. **Group comparison:** Groups were compared using ANOVA with a treatment effect after a logarithmic transformation on the tick (count +1) data. Level of significance of formal tests set at 5%, all tests two-sided. **Efficacy criteria:** The IVP was regarded effective when adulticidal efficacy was ≥90% for ticks and ≥95% for fleas compared to untreated controls. The persistent period of protection against ticks and fleas was taken as the number of weeks post-treatment during which efficacy was ≥90% for ticks and ≥95% for fleas.
RESULTS	
Outcomes for endpoints	All sixteen animals completed the trial. The arithmetic mean was used to form final conclusions. Efficacy was seen to be variable for ticks, as two dogs were found to have live, attached, but not engorged ticks 48 hours after treatment with the proposed product. The product was seen to provide persistent efficacy against fleas.
DISCUSSION	Immediate and persistent efficacy was demonstrated for fleas (99.8% at day two, above 95% at day 44). Immediate efficacy was not demonstrated for ticks,

	(83.8% on day 2, which is below the threshold for efficacy which was stated in the EMEA Tick and Flea Guideline 2007, but a residual protection period of four weeks was accepted (+90%).
Study title	Dose confirmation study to evaluate efficacy and safety of a topically applied spot-on formulation of fipronil against ticks (*R. sanguineus*) and fleas (*C. felis*) on dogs
Objectives	To evaluate efficacy and safety of a fipronil spot-on formulation of fipronil against ticks (*D. variabilis*) and fleas (*C. felis*) on dogs, at a dose of 6.7 mg/kg/bw.
Test site(s)	Single-centre, EU.
Test Product	Proposed product, 0.67 mg fipronil/kg/bw. Single dose. Minimum recommended dose of reference product.
Control product/placebo	Untreated negative control.
Animals	16 dogs (beagle), 8 male 8 female, (8 per group). Acclimatised for seven days, 4.5 – 5.5 months old. Bodyweight 5.9 – 11.2 kg. Not clinically pregnant. Not treated with acaricide/insecticide or an anti-infammatory product for 60 days prior to day 0. No animals bathed during pre-conditioning phase.
Outcomes/endpoints	Primary outcomes: Comparison of the number of live ticks or fleas collected from both groups at various time points.
Randomisation	Randomised.
Blinding	Parallel group, randomised, unicentre, blocked and blinded.
Method	Approximately 100 laboratory bred strains of *C. felis* (mixed sex) were placed on pre-treated animals at days -5, -2, 7, 14, 21, 28, 35, 42 and 49. Counts were performed two days after infestation. Ticks were placed on animals on days -2, 7, 14, 21, and 28, with a minimum of 50 ticks of evenly balanced sex ratio. Counts were performed usually two days later.
Statistical method	**Efficacy against ticks and fleas:** Efficacy (%) = 100 x ($m_{control}$– $m_{treated}$) / $m_{control}$, where: $m_{control}$= mean number of live ticks or viable fleas in the untreated control group (Group 2) at day x, and $m_{treated}$ = mean number of live ticks (category 1-3; immediate efficacy) or live and killed (category 1-3 and 6; persistent efficacy) or viable fleas in the treatment group (Group 1). **Descriptive statistics**: arithmetic and geometric mean, standard deviation, sample size, median, minimum, and maximum.

	Group comparison: Groups were compared for superiority of treated animals compared to untreated animals on days +2, +9, +16, +23 and +30 for ticks, and on days +9, +16, +23, +30, +37, +44, and +51 for fleas using a generalised Wilcoxon test combining all time points according to the Wei-Lachin procedure. **Efficacy criteria:** The IVP was regarded effective when adulticidal efficacy was ≥ 90% for ticks and ≥ 95% for fleas compared to untreated controls. The persistent period of protection against ticks and fleas was taken as the number of weeks post-treatment during which efficacy was ≥ 90% for ticks and ≥ 95% for fleas.
RESULTS	
Outcomes for endpoints	All sixteen animals completed the trial. The arithmetic mean was used to form final conclusions. Efficacy was seen to be variable for ticks, as some dogs were found to have live, attached, but not engorged ticks 48 hours after treatment with the proposed product. The product was seen to provide persistent efficacy against fleas.
DISCUSSION	Immediate efficacy was not demonstrated for ticks, (*R. sanguineus* 87.8%), which is below the threshold for efficacy which was stated in the EMEA Tick and Flea Guideline 2007, but a residual protection period of three weeks was accepted (+90%). Immediate and persistent efficacy of six weeks against fleas (day 44 90%, *C. felis*) was supported by the data.

Water Immersion and shampoo challenge studies

Two studies were submitted which examined the effect of shampooing prior to treatment and weekly immersion post-treatment on the efficacy of the products.

Study 1

This was a randomised, unicentre, parallel grouped, controlled and blinded, Good Clinical Practise (GCP) study. The study objective was to note the effect of shampooing prior to treatment for fleas (*C.felis*).

67 mg, 134 mg, 268 mg and 402 mg products were used on appropriately-sized animals (14, mongrel, mixed sex. 12 selected, 6 per group). Shampooing was performed prior to treatment, and animals assessed forty-eight hours after treatment against fleas. Two groups of dogs were assessed. Group 1 consisted of untreated negative controls. Group 2 animals were treated with the appropriate dose of product. Both groups were shampooed. Hair length ranged

from 10.25 mm to 29.50 mm, with animals aged eight weeks or older. The dogs were appropriately acclimatised, deemed not pregnant, 2 kg or heavier, and had not been exposed to acaricidal or insecticidal treatment for twelve weeks prior to day 0. The two dogs exhibiting lowest flea count were excluded from the trial.

100 laboratory strain *C.felis* fleas were placed on animals on days -7 and 0, (after shampooing, and immediately prior to treatment). Flea counts were performed on days -5 and 2. The primary endpoint was the comparison of flea

numbers on treated and untreated dogs collected on day 2. Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) were calculated and tabulated for flea counts on the various assessment days.

Efficacy against adult fleas was calculated according to the following formula:
Efficacy (%) = 100 x (m_c – m_t) / m_c where: m_c = geometric mean of live fleas on the negative control group (Group 1) and m_t = geometric mean of live fleas on the treated group (Group 2).
(Efficacy calculations based on arithmetic means were also reported on.)

The IVP was regarded effective if the immediate adulticidal efficacy against fleas was ≥95%. Group comparison: this was performed using an ANOVA with a treatment effect after a logarithmic transformation on the flea (count +1) data. Level of significance set at 5%, all tests were two sided.

The study showed that efficacy against fleas was established within 48 hours after administration of the IVP, even if animals were shampooed within 1 to 2 hours prior to treatment, with an insecticidal efficacy based on arithmetic mean adult flea counts on day +2 of 95.8%.

Study 2

This was a randomised, unicentre, parallel grouped, controlled and partially blinded, Good Clinical Practise (GCP) study. The study objective was to note the effect of shampooing prior to treatment, followed by weekly immersion in water, following treatment for fleas (*C.felis*).

67 mg, 134 mg, 268 mg and 402 mg products were used on appropriately-sized animals (26, mongrel, mixed sex. 24 selected). Shampooing was performed prior to treatment, and animals assessed forty-eight hours after treatment against fleas. Two groups of dogs were assessed. Group 1 consisted of untreated negative controls. Group 2 animals were treated with the appropriate dose of the reference product, and group 3 were treated with an appropriate dose of the proposed product. All groups were shampooed. Hair length ranged from 10.5 mm to 51.5 mm, with animals aged eight weeks or older. The dogs were appropriately acclimatised, deemed not pregnant, 2 kg or heavier, and had not

been exposed to acaricidal or insecticidal treatment for twelve weeks prior to day 0. The two dogs exhibiting lowest flea count were excluded from the trial.

100 laboratory strain (*C.felis*) fleas were placed on animals on days -7 and 0, (after shampooing, and immediately prior to treatment), 7, 14, 21, 28, 35, 42 and

49. Flea counts were performed on days -5 and 2. The primary endpoint was the comparison of flea numbers on treated and untreated dogs at a variety of time points. Descriptive statistics (mean, minimum, maximum, standard deviation, CV%, geometric mean and median) were calculated and tabulated for flea counts on the various assessment days.

Efficacy against adult fleas was calculated according to the following formula:
Efficacy (%) = 100 x (m_c – m_t) / m_c where: m_c = geometric mean of live fleas on the negative control group (Group 1) and m_t = geometric mean of live fleas on the treated group (Groups 2 and 3).
(Efficacy calculations based on arithmetic means were also reported on.)

A linear interpolation of the arithmetic mean flea counts was done to determine the persistent predicted efficacy. The efficacy thresholds of 95% reduction in fleas were applied. Group comparison: this was performed using an ANOVA with a treatment effect after a logarithmic transformation on the flea (count +1) data. Level of significance set at 5%, all tests were two sided.

Results showed the influence of shampooing 2 hours prior to administration of the IVP and weekly bathing on the persistent insecticidal efficacy. It was agreed that insecticidal efficacy against new infestation with fleas persisting for up to 6 weeks was acceptable.

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)