Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fleascreen 67 mg Spot-On Solution for Small Dogs
Fleascreen 134 mg Spot-On Solution for Medium Dogs
Fleascreen 268 mg Spot-On Solution for Large Dogs
Fleascreen 402 mg Spot-On Solution for Extra Large Dogs

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fleascreen 67 mg Spot-On Solution for Small Dogs Fleascreen 134 mg Spot-On Solution for Medium Dogs Fleascreen 268 mg Spot-On Solution for Large Dogs Fleascreen 402 mg Spot-On Solution for Extra Large Dogs
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Dermacentor* r*eticulatus*) infestations. For treatment of *Trichodectes canis* biting lice infestations on dogs. Most lice are killed within 2 days. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. The product has a persistent acaricidal efficacy for up to 3 weeks against *Ixodes ricinus* and up to 4 weeks against *Rhipicephalus sanguineus* and *Dermacentor reticulatus*. If ticks of some species (*Ixodes ricinus, Rhipicephalus sanguineus*) are present when the product is applied, all the ticks may not be killed within the first 48 hours.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic (hybrid) duplicate applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

These were generic (hybrid) duplicate applications, submitted in accordance with the above Directive and based on the reference product Frontline Spot on Dog 10% Spot on Solution, authorised in the UK since November 1996.

Data presented in this report are based on those reports created for subsequent products, RSPCA FleaAway Spot-On Solution for small, medium, large and extra large dogs respectively, authorised in the UK since June 2014.

The Fleascreen products are intended for the treatment of fleas (*Ctenocephalides* spp.), and tick (*Dermacentor reticulatus*) infestations in dogs. For the treatment of *Trichodectes canis* biting lice infestations on dogs. Most lice are killed within 2 days. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. The product has a persistent acaricidal efficacy for up to 3 weeks against *Ixodes ricinus* and up to 4 weeks against *Rhipicephalus sanguineus* and *Dermacentor reticulatus*. If ticks of some species (*Ixodes ricinus, Rhipicephalus sanguineus*) are present when the product is applied, all the ticks may not be killed within the first 48 hours.

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

II. QUALITY ASPECTS

A. Composition

The product contains 100mg/ml fipronil as the active substance and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), polysorbate 80, povidone K25 and dimethyl sulfoxide.

The container/closure system consists of white polypropylene pipette closed with either a polyethylene or polyoxymethylene cap. Pipettes are packed individually into a polyethylene terephthalate/aluminium/low density polyethylene triplex bag. Boxes contain 1, 3, 6, 10, 20 or 30 pipettes. Not all pack sizes may be marketed. The particulars of the containers and controls performed are provided and conform to the regulation.

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

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines. The manufacturing process consists of several solubilisation and mixing steps, followed by final fill into pipettes.

C. Control of Starting Materials

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

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.

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

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

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Tests include relevant general characteristics, identification, and quantitative determination and purity tests.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 3 years was deemed satisfactory. Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Data were available from batches were stored under real time (25^{o}C/60% RH), or accelerated conditions (40^{o}C/75% RH), for 36 months and 6 months respectively. The shelf-life as described in the SPC is appropriate.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 36 months.
Store in the original container in order to protect from light and moisture. The product should be maintained at room temperature (above 14°C) for approximately one hour prior to administration.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA complex, binding to the chloride channel and thereby blocking pre-and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarids.

Pharmacokinetics

Fipronil is mainly metabolised to its sulfone derivative (RM1602), which also possesses insecticidal and acaricidal properties. The concentration of fipronil on treated hair decreases with time.

Toxicological Studies

The applicant provided bibliographical data:-

- Single Dose Toxicity

Data were provided on the acute toxicity of fipronil. In studies, the LD_{50}[2] values were cited as 97 mg/kg (oral, rats), and 95 mg/kg (oral, mice). An LC_{50}[3] of 0.36-0.42 mg/l was noted in rats after one inhalation exposure. Dermal LD_{50} in rats, administered fipronil in distilled water, exceeded 2000 mg/kg, and when moistened with corn oil a dermal LD_{50} of 354 mg/kg was exhibited in rabbits. Adverse clinical signs were not seen in rats, but proved moderately hazardous in rabbits.

- Repeated Dose Toxicity

A review of a series of repeat dose studies was provided, which established the basis of the user risk assessment (URA). NOEL[4] was established for some of the studies. A 13 week study in rats, administered fipronil in the diet, resulted in a NOEL of 0.33 mg/kg bodyweight. Alterations were observed in serum protein values, and increased liver and thyroid weights were additionally observed. In a 13 week oral study (gelatine capsules) in dogs, a NOEL of 0.5 mg/kg bodyweight was observed. The highest dose administered was 10 mg/kg, at which neurotoxicological effects were observed. Two further oral studies in dogs, conducted over a year, resulted in NOEL of 0.2 mg/kg (gelatine capsules), and 0.3 mg/kg (fipronil in the diet) respectively. In the first study, neurotoxicity was seen at doses higher than 2 mg/kg, and in the second study, at the next highest dose within the study, which was 1.0 mg/kg. A 21 day dermal study in rabbits established a NOEL of 5.0 mg/kg, with systemic effects resulting at the end of the study that were possibly related to treatment. No skin irritation was observed.

- Reproductive Toxicity, including Teratogenicity:

Suitable published studies were provided. During a two-generation study of reproductive toxicity, adverse reproductive effects were noted only at doses well above those which caused parental systemic toxicity. A further study in which 70, 140 or 280 mg/kg were administered to 2 rats was provided. Results indicated that fipronil at high doses caused adverse reproductive effects. No embryotoxic effects were noted in a study in which female rats were given up to

[2] LD_{50} – dose that will destroy half of a test population.
[3] LC50 –concentration that will destroy half a target population.
[4] NOEL – No observed effect limit.

20 mg/kg during gestation, and in a similar study in rabbits, no effects were noted at the highest dose of 1 mg/kg.

- Mutagenicity

Various studies were submitted which indicated that fipronil was not genotoxic.

- Carcinogenicity (if necessary):

Studies in rats indicated that at high levels, fipronil causes non-genotoxic thyroid changes. A NOAEL[5] for neurotoxic changes was established at 0.019 mg/kg. It was noted that rats are more sensitive than humans to thyroid changes.

- Studies of other effects

Fipronil was shown not to be a dermal irritant in 2 dermal studies in rabbits, and was seen to be only slightly irritant in 2 ocular studies in rabbits. In guinea-pigs, the active substance was not a sensitiser when tested by the Buehler method, but was a weak sensitiser under the Magnusson-Kligman method.

In a single-dose neurotoxicity study in rats, a NOAEL of 0.5 mg/kg was calculated at the high 5 mg/kg dose. Neurotoxic signs were also observed in a study in dogs receiving daily oral doses of 20 mg/kg. In a developmental neurotoxicity study in rats, a NOAEL of 0.9 mg/kg was noted.

Observations in Humans

The applicant provided bibliographical data. A 77 year old woman ingested a product containing 0.14 mg of fipronil, but did not exhibit toxic effects. A 50 year old man showed sign of fipronil toxicity following the spraying of fields whilst wearing no protective equipment. Symptoms consisted of headache, nausea, vertigo and weakness, and these resolved spontaneously over approximately 5 hours. A further report cited several people ingesting large but unknown amounts of fipronil for agricultural use. Vomiting, agitation and seizures were observed, but all recovered.

User Safety

The applicant provided a URA which was identical to the reference product, and with certain additions subsequently added, this was acceptable. The URA cites the active substance and the major metabolite, the photodegredation product, fipronil-desulfinyl. A further report was provided on the major excipient, dimethyl sulphoxide (DMSO), which is not present in the reference product. Suitable data were provided which determined the safety data provided within the SPC. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

[5] NOAEL – No observed adverse effect level.

- This product can cause mucous membrane and eye irritation. Therefore, contact between the product and the mouth or eyes should be avoided.
- In the case of accidental eye contact, immediately and thoroughly flush the eyes with water. If eye irritation persists seek medical advice and show the package leaflet or the label to the physician.
- Avoid contents coming into contact with the fingers. If this occurs, wash off immediately with soap and water.
- Wash hands after use.
- Do not smoke, drink or eat during application.
- People with a known hypersensitivity to fipronil or dimethyl sulfoxide or other excipients 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 should be treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children.
- Keep pipettes in the original packaging and dispose of used pipettes immediately.

Ecotoxicity

Warnings and precautions as listed on 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 products should be disposed of in accordance with local requirements.

- Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty container.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this was a 'hybrid' application, no further data were required for this section.

Tolerance in the Target Species of Animals

The applicant conducted a GLP[6]-compliant target animal safety study. A suitable number of young dogs received the product in a partially blinded, parallel grouped, randomised, and negatively controlled study. The animals were divided into groups, and received treatment which consisted of placebo, or the recommended dose, three times the recommended dose, or five times the recommended dose. No adverse reactions to the treatment were observed, in the different groups, or between male and female animals.

Resistance

Published data were provided to confirm that there is a low risk of resistance developing in the target parasites. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant provided data that had previously been assessed for the reference products. This was acceptable.

Dose confirmation studies:

Study 1

Study title	Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of a 10% fipronil product against ticks (*Rhipicephalus sanguineus* and *Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) on dogs under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (*Rhipicephalus sanguineus* and *Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) on dogs under laboratory conditions.

[6] GLP – Good Laboratory Practise.

Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 1.34 ml. (Dogs 10 - 20 kg).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v Spot-On Solution, at 1.34 ml. (Dogs 10 - 20 kg). Negative control group (no treatment).
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against cat fleas and ticks on dogs. Efficacy of the test product was compared to the negative control and reference product up to Day 30.
Randomisation	Randomised.
Blinding	Partially blinded.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog or approximately 50 of one of two tick species per dog), at various time points, and given treatment according to their respective groups. Tick and flea counts were performed on several occasions up to 30 days after treatment.
Statistical method	All tests were two-sided. Statistical analysis was performed using appropriate software. Level of significance was set at 5% ($p<0.05$). Primary calculations for efficacy were based on mean flea counts. Comparisons were made by ANOVA.
RESULTS	
Outcomes for endpoints	<u>Flea Counts</u> Where either product had been used, there was >95% efficacy against fleas on all assessment days. Both products therefore had 4 weeks persistent efficacy against fleas (*C. Felis*). No treatment-related adverse effects were noted. <u>Efficacy against *R. sanguineus*</u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>90%), demonstrating a 4 week persistent effectiveness against *R. sanguineus*. <u>Efficacy against *D. reticulatus*</u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment

	groups (>90%), demonstrating a 4 week persistent effectiveness against *D. reticulatus*.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 2

Study title	A study to determine the efficacy of a 10% fipronil product when compared to a comparator product and an untreated group against artificially induced infestations of ticks (*Ixodes ricinus*) on dogs under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (*Ixodes ricinus*) on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 1.34 ml. (Dogs 10 - 20 kg).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v Spot-On Solution, at 1.34 ml. (Dogs 10 - 20 kg). Negative control group (no treatment).
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against ticks on dogs. Efficacy of the test product was compared to the negative control and reference product up to Day 30.
Randomisation	Randomised.
Blinding	Partially blinded.
Method	After acclimatisation, animals were infested as appropriate (approximately 50 ticks per dog), at various time points, and given treatment according to their respective groups. Tick counts were performed on several occasions up to 30 days after treatment.
Statistical method	Statistical analysis was performed using appropriate software. Level of significance was set at 5% ($p<0.05$). Primary calculations for efficacy were based on mean tick count. Comparison was made by Mixed Model ANOVA.
RESULTS	
Outcomes for endpoints	Tick Counts There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. A 3 week persistent efficacy claim was accepted for *I. ricinus*.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 3

Study title	A controlled, randomised study to evaluate a single application of a 10% fipronil product for lice treatment, for *Trichodectes canis* on dogs naturally infested with lice under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against lice on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.67 ml/ (dogs weighing over 2 kg and up to 10 kg) and 0.34ml (dogs 10 – 20 kg).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v Spot-On Solution, at 0.67 ml/day (dogs weighing over 2 kg and up to 10 kg) and 0.34ml (dogs 10 – 20 kg). Negative control group (no treatment).
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against lice on dogs. Efficacy of the test product was compared to the negative control and reference product up to Day 35.
Randomisation	Randomised
Blinding	Colour coded groups.
Method	After acclimatisation, animals were infested with at least 10 lice, and given treatment according to their respective groups. Lice counts were performed on several occasions up to Day 35.
Statistical method	This was a block design study. The Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p<0.05$). Comparison was made by Mixed Model ANOVA.
RESULTS	
Outcomes for endpoints	Lice Counts Comparable efficacy was observed for both treatment groups on most days. No treatment-related adverse effects were noted.
DISCUSSION	The product was shown to be effective against the target parasite.

Study 4

Study title	Water immersion stability study of a topically applied 10% fipronil product against cat flea (*Ctenocephalides felis*) on dogs under laboratory conditions
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil (with water immersion), against fleas on dogs under laboratory conditions. Weekly immersion
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.34ml (dogs 10 – 20 kg). With and without immersion of animal in water.
Control product/placebo	Negative control group (no treatment), water immersion performed.
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against fleas on dogs, with and without water immersion. Efficacy of the test product was compared to the negative control and reference product up to Day 65.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested with approximately 100 fleas per animal, at various time points, and then treated according to their respective groups. Flea counts were performed on several occasions up to Day 65.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p<0.05$). Comparative analysis was performed using ANOVA.
RESULTS	
Outcomes for endpoints	Flea Counts Comparable efficacy was observed for both treatment groups (>95%), demonstrating a persistent effectiveness against *C. felis* up to 7 weeks for dogs not immersed in water. For the animals receiving water immersion, this period was reduced by 2 weeks. No treatment-related adverse effects were noted.
DISCUSSION	The product was shown to be effective against the target parasite.

Study 5

Study title	Study to determine the persistent efficacy of a single application of a flea treatment against artificially induced infestations of fleas (*Ctenocephalides felis*) on dogs
Objectives	To evaluate the persistent efficacy of a single application of a flea treatment against artificially induced infestations of fleas (*Ctenocephalides felis*) on dogs
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 1.34 ml (dogs 10 – 20 kg).
Control product/placebo	Negative control group (no treatment). Control product, Frontline Spot On Dog 10% w/v Spot-On Solution, at 1.34 ml/dog (dogs weighing over 10 kg – 20 kg).
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the persistent efficacy of a generic spot-on formulation against fleas on dogs. Efficacy of the test product was compared to the negative control and reference product up to Day 56.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested with approximately 100 fleas per animal, at various time points, and then treated according to their respective groups. Flea counts were performed on several occasions up to Day 56.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p<0.05$).
RESULTS	
Outcomes for endpoints	Flea Counts Comparable efficacy was observed for both treatment groups (>95%), demonstrating a persistent effectiveness against *C .felis* for up to 8 weeks. No treatment-related adverse effects were noted.
DISCUSSION	The product was shown to be effective against the target parasite.

Study 6

Study title	Study to determine the persistent efficacy of a single application of a flea treatment against artificially induced infestations of fleas (*Ctenocephalides felis*) on dogs that have been immersed in water weekly
Objectives	To evaluate the persistent efficacy of a single application of a flea treatment against artificially induced infestations of fleas (*Ctenocephalides felis*) on dogs. Weekly immersion in water.
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On Solution for Dogs (10% fipronil), synonymous with the product to be authorised. Product delivered at 1.34ml (dogs 10 – 20 kg).
Control product/placebo	Negative control group (no treatment), water immersion also performed.
Animals	Healthy adult and sub adult dog, 8 animals each group.
Outcomes/endpoints	Determine the persistent efficacy of a generic spot-on formulation against fleas on dogs, with water immersion. Efficacy of the test product was compared to the negative control up to Day 51.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested with approximately 100 fleas per animal, at various time points, and then treated according to their respective groups. Flea counts were performed on several occasions up to Day 51.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p<0.05$).
RESULTS	
Outcomes for endpoints	Flea Counts Comparable efficacy was observed for both treatment groups (>95%), demonstrating a persistent effectiveness against *C. felis* up to 7 weeks for dogs immersed weekly in water. No treatment-related adverse effects were noted.
DISCUSSION	The product was shown to be effective against the target parasite.

The studies conducted supported the claims in the authorised SPC, in compliance with the requirements laid out in the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats EMEA/CVMP/EWP/005/2000-Rev.2 June2008.

Field Trials

Field studies were not required for these applications.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the 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)