Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fleasolve 67 mg Spot-on Solution for Small Dogs Fleasolve 134 mg Spot-on Solution for Medium Dogs Fleasolve 268 mg Spot-on Solution for Large Dogs Fleasolve 402 mg Spot-on Solution for Very Large Dogs
Applicant	Alfamed 13'eme rue – L.I.D Carros Cedex 06517 France
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Dermacentor reticulatus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. The product has a persistent acaricidal efficacy for up to 4 weeks against ticks (*Rhipicephalus sanguineus, Ixodes ricinus, Dermacentor reticulatus*). If ticks of some species (*Rhipicephalus sanguineus* and *Ixodes ricinus*) are present when the product is applied, all ticks may not be killed within the first 48 hours but they may be killed within a week.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

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

I. SCIENTIFIC OVERVIEW

The products are spot-on solutions, developed as generics of Frontline Spot-On Dog. However, bioequivalence with the reference product could not be demonstrated by appropriate studies, and therefore the products were deemed to be generic hybrids, whereby it is necessary for clinical endpoints to be produced.

The products are applied topically to dogs (each solution contains 100 mg/ml fipronil), according to the following dosage regimen: 1 pipette of 0.67 ml (67 mg fipronil) for dogs weighing 2-10 kg, 1 pipette of 1.34 ml (134 mg fipronil) for dogs weighing 10-20 kg, 1 pipette of 2.68 ml (268 mg) fipronil for dogs weighing 20-40 kg and 1 pipette of 4.02 ml (402 mg fipronil) for dogs weighing over 40 kg. The indication for use in dogs is to treat and prevent infestations of flea (*Ctenocephalides* spp.) and tick (*Dermacentor reticulatus*). If ticks of some species (*Rhipicephalus sanguineus* and *Ixodes ricinus*) are present when the product is applied, all the ticks may not be killed within the first 48 hours but they may be killed within a week.

The product is also indicated to be used as part of a treatment strategy in Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon. The products are available in blister cards or boxes of 1, 2, 3, 4 or 6 pipettes, and are contraindicated in puppies less than 2 months old or weighing less than 2 kg, sick and convalescent animals as well as in other species, particularly rabbits.

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 fipronil as active substance and butylhydroxyanisole (E320), butylhydroxytoluene (E321), benzyl alcohol and diethylene glycol monoethyl ether as excipients.

The container/closure system consists of 0.67 ml, 1.34 ml, 2.68 ml or 4.02 ml solution contained in either thermoformed or polypropylene single dose pipettes, closed by aluminium heat sealing and packaged into boxes or blister cards of 1, 2, 3, 4 or 6 pipettes. 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 products are 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 product is 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 product is manufactured by mixing the active substance and excipients to produce the final solution which is then used to fill the pipettes by weight.

C. Control of Starting Materials

The active substance is fipronil, an established active substance not described in the European Pharmacopoeia (Ph. Eur). Data on the active substance was provided in the form of an in-house monograph. 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 comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

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 this product.

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. The tests include identification of active substance and excipients, identification of impurities, uniformity of dosage units and microbial purity. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance has 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. A retest period of 12 months is supported for the active substance, the shelf life of the product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale: 3 years.
- Store below 30ºC.
- Store in a dry place.
- Store in the original package.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Data were required for this section, as bioequivalence demonstrated by bioavailability was not demonstrated with a reference product.

III.A Safety Testing

Pharmacological Studies

Following topical application fipronil spreads over the surface of the skin and is stored in sebaceous glands. Fipronil is then slowly eliminated with hair and sebum. It is poorly absorbed through the skin.

Toxicological Studies

The applicant has submitted toxicological studies using fipronil. The studies looked at the effect of single dose and repeat dose toxicity, reproductive toxicity, genotoxicity and carcinogenicity.

The applicant concluded that via the dermal route of administration fipronil is not acutely toxic to rats (LD_{50} of >2000 mg/kg bodyweight) and is only slightly toxic to rabbits. Oral repeat dose studies were conducted and a NOEL[2] of 0.07 mg/kg bodyweight per day was established following oral administration to rats for 90 days. Similar studies were conducted in dogs over a period of 1 year and the NOEL was established as 0.3 mg/kg bodyweight per day. These repeat dose studies of fipronil also showed evidence of neurotoxicity.

Mutagenic and teratogenic studies were also submitted. In these studies, fipronil tested negative and no evidence has been seen that would suggest fipronil could cause birth defects. In addition, fipronil is not carcinogenic and has no genotoxic potential.

Other Studies

The applicant has provided additional studies using the final formulation of the product. Studies were conducted to investigate if the product can cause skin and eye irritation. These studies were conducted on rabbits using single dose topical application and a guinea pig skin sensitisation study was also summarised. It was observed that the formula has a low acute toxicity and does not sensitise skin, however fipronil is a moderate eye irritant.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which describes the possible routes of exposure and the risk posed by oral, dermal and ocular contact with fipronil. Dermal exposure through

[2] NOEL – No observable effect limit

petting the animal is deemed to be likely whilst oral ingestion through spillage of the product or hand to mouth transfer is low risk. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

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

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the products are unlikely to pose a risk to the environment when used as directed. The following warning is listed on the product literature to ensure safety to the environment:

- Fipronil may adversely affect aquatic organisms. Dogs should not be allowed to swim in water courses for 2 days after application.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
As this is a generic application submitted according to Article 13 (3) of Directive 2001/82/EC as amended, and the pharmacodynamic properties are considered the same as for the reference product no additional data are required.

Pharmacokinetics

As this is a generic application submitted according to Article 13 (3) of Directive 2001/82/EC as amended, and the pharmacokinetic properties are considered the same as for the reference product no additional data are required.

Tolerance in the Target Species of Animals

The applicant has provided a target animal tolerance study using multiples of the recommended dose in the target species. A group receiving no treatment were included as a control. Doses were applied topically to the skin between the shoulder blades, at 1, 3 or 5 times the recommended dose and administered three times over a period of two and a half months.

Parameters evaluated included bodyweight, food consumption, clinical signs and blood samples were taken pre and post treatment to observe any effects on haematology, biochemistry and specific hormones, thyroxine and TSH. At the end of the procedure pathology investigated any effects on the organs, including weight, if there were any macroscopic lesions and histological differences. No adverse effects were seen following doses up to 5 times the recommended dose and the studies demonstrate local and systemic tolerance to the product.

Data from the clinical trials have also been provided which show that no adverse reactions have been linked to use of the product. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

As these were applications for a ‘generic antiparasitic product’ as submitted under Article 13 (3) of Directive 2001/82/EC as amended, the potential for resistance was considered to be the same as that of the reference products, and no further data were required.

IV.B Clinical Studies

Laboratory Trials

The applicant provided appropriate information on dose determination studies.

Dose determination studies:

A number of dose confirmation studies were presented:

Study 1

Study title	Comparative study on the efficacy of a generic fipronil spot-on formulation and Frontline Spot On Dog 10% w/v Spot-On Solution[3] against fleas (*Ctenocephalides felis*) on dogs.

[3] Cited as Frontline Top Spot in the trials.

Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against fleas (*Ctenocephalides felis*) on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v topical solution, at 0.67 ml or 1.34 ml. (Depending on dog size). Negative control group (no treatment).
Animals	Healthy dogs, 8 animals each group.
Outcomes/endpoints	Determine the 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 upon weekly infestation of fleas, up to Day 90.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog), at various time points, and given treatment according to their respective groups. Flea counts were performed on several occasions 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 95% for the appropriate time spans.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 2

Study title	Comparative study on the efficacy of a generic fipronil spot-on formulation and Frontline Spot On Dog 10% w/v Spot-On Solution against ticks (*Rhipicephalus sanguineus*) on dogs.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (*Rhipicephalus sanguineus*) on dogs under laboratory conditions.

Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v topical solution, at 0.67 ml or 1.34 ml. (Depending on dog size). Negative control group (no treatment).
Animals	Healthy dogs, 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 upon weekly infestation of fleas, up to Day 37.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. 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 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 90% for the appropriate time spans.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 3

Study title	Comparative study on the efficacy of a single application of a generic fipronil spot-on formulation and Frontline Spot On Dog 10% w/v Spot-On Solution against ticks (*Dermacentor reticulatus*) on dogs.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against fleas (*Dermacentor reticulatus*) on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)

Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v topical solution, at 0.67 ml or 1.34 ml. (Depending on dog size). Negative control group (no treatment).
Animals	Healthy dogs, 6 animals each group.
Outcomes/endpoints	Determine the 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 upon weekly infestation of fleas, up to Day 65.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog), at various time points, and given treatment according to their respective groups. Flea counts were performed on several occasions 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 95% for the appropriate time spans.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 4

Study title	Comparative study on the efficacy of a single application of a generic fipronil spot-on formulation and Frontline Spot On Dog 10% w/v Spot-On Solution against fleas (*Ixodes ricinus*) on dogs.
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 centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).

Control product/placebo	Control product, Frontline Spot On Dog 10% w/v topical solution, at 0.67 ml or 1.34 ml. (Depending on dog size). Negative control group (no treatment).
Animals	Healthy dogs, 6 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 upon weekly infestation of fleas, up to Day 37.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. 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 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 90% for the appropriate time spans.
DISCUSSION	The product was shown to be suitably effective against the target parasites. The SPC clarifies the efficacy of the product.

Study 5

Study title	The effect of shampooing on the efficacy of a generic fipronil spot-on formulation (104.07) against flea (*Ctenocephalides felis*) on dogs.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against fleas (*Ctenocephalides felis*) on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).
Control product/placebo	No additional positive control product. Negative control group (no treatment).
Animals	Healthy dogs, 8 animals each group.

Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against fleas on dogs. Efficacy of the test product was compared to the negative control upon weekly infestation of fleas, up to Day 65.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog), at various time points, and given treatment according to their respective groups. Flea counts were performed on several occasions 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 95% for the appropriate time spans.
DISCUSSION	The product was shown to be effective against the target parasites. No effect on the product was observed after repeated shampooing with 3% chlorhexidine, on weekly infestation of fleas, with shampooing occurring within an hour of application.

Study 6

Study title	'The effect of weekly water immersions on the efficacy of a generic fipronil spot-on formulation (104.07) against flea (*Ctenocephalides felis*) on dogs
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against fleas (*Ctenocephalides felis*) on dogs under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Formulation 104.7 (10% fipronil), synonymous with the product to be authorised. Product delivered at either 0.67 ml or 1.34 ml. (Depending on size of dog).
Control product/placebo	Control product, Frontline Spot On Dog 10% w/v topical solution, at 0.67 ml or 1.34 ml. (Depending on dog size). Negative control group (no treatment).
Animals	Healthy dogs, 8 animals each group.
Outcomes/endpoints	Determine the 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 upon weekly infestation of fleas, up to Day 65.
Randomisation	Randomised.
Blinding	Blinded.
Method	This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog), at various time points, and given treatment according to their respective groups. Flea counts were performed on several occasions 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	The product was seen to be effective, and no adverse events were observed during the study
Outcomes for endpoints	After 48 hours, the therapeutic efficacies of the products were comparable. Efficacy was demonstrated as being more then 95% for the appropriate time spans.
DISCUSSION	The product was shown to be effective against the target parasites, in dogs immersed on a weekly basis in water. The SPC carries appropriate efficacy information.

Field Trials

As these were generic 'hybrid' applications according to Article 13 (3) of Directive 2001/82/EC as amended, there was no requirement for data in this section.

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)