Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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MUTUAL RECOGNITION

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Vetflea 67 mg Spot-On Solution for Small Dogs
Vetflea 134 mg Spot-On Solution for Medium Dogs
Vetflea 268 mg Spot-On Solution for Large Dogs
Vetflea 402 mg Spot-On Solution for Very Large Dogs

PuAR correct as of 17/09/2018 when RMS was transferred to HU.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0397/002/DC UK/V/0397/003/DC UK/V/0397/004/DC UK/V/0397/005/DC
Name, strength and pharmaceutical form	Vetflea 67 mg Spot-On Solution for Small Dogs Vetflea 134 mg Spot-On Solution for Medium Dogs Vetflea 268 mg Spot-On Solution for Large Dogs Vetflea 402 mg Spot-On Solution for Very Large Dogs
Applicant	ALFAMED 13ème Rue – L.I.D. 06517 CARROS CEDEX FRANCE
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indications 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 the ticks may not be killed within the first 48 hours but they may be killed within a week. 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.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	'Hybrid' applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended by Directive 2004/28/BC.
Date of completion of the original Decentralised Procedure	21 March 2012.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Hungary, Romania.

I. SCIENTIFIC OVERVIEW

These applications were submitted using the Decentralised Procedure, in accordance with Article 13 (3) as amended, as 'hybrid' applications, where bioequivalence could not be demonstrated via bioavailability studies, but was demonstrated by clinical equivalence. The reference product was Frontline Spot On Dog 10% w/v Spot-On Solution, first authorised in the UK in 1996. The products are spot-on solutions intended for use in dogs, for the treatment of flea and tick infestations caused by *Ctenocephalides* spp. and the tick species *Dermacentor reticulatus, Rhipicephalus sanguineus* and *Ixodes ricinus.*

Insecticidal activity may be seen against new infestations of adult fleas, persistent for up to 8 weeks. There is persistent activity of up to 4 weeks against the specified tick species, however if *Rhipicephalus sanguineus* and *Ixodes ricinus* are already present prior to treatment, all ticks may not be killed within the first 48 hours, but will be killed within a week. The products are presented in a range of pack sizes.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species, the slight reactions observed are indicated in the SPC[1]. The products are safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPCs. The efficacy of the products was demonstrated according to the claims made in the SPCs. 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 products consist of the active substance fipronil at 67 mg, 134 mg, 268 mg or 402 mg per pipette, prepared to manufacturer's specification, and the excipients butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethylene glycol monoethyl ether, all of which are monographed in the European Pharmacopoeia. The packaging consists of pipettes of varying colours, one colour for each presentation, delivering a different amount of solution for each product: 0.67 ml, 1.34 ml, 2.68 ml or 4.02 ml. The internal layers in contact with the product are made of polyacrylonitrile-methacrylate or polyethylene-ethylene vinyl alcohol-polyethylene. The white or transparent external complex is composed of polypropylene/ cyclic olefine copolymer/ polypropylene. Pipettes are presented in 1, 2, 3, 4, 6, 8, 12, 24, 30, 60, 90 or 150; not all presentations may be marketed. The particulars of the containers and controls performed are provided and conform to the regulation. 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 products have been presented in accordance with the relevant European guidelines. The method of preparation is essentially a mixing process: two excipients are added to a vessel and mixed, followed by the active substance and then the remainder of the excipients.

C. Control of Starting Materials

Fipronil is an established active substance described in the European Pharmacopoeia. 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.

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

There are no intermediate products.

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 performed include those for appearance, clarity of solution, colour, density, uniformity of dosage units, relevant HPLC[2] testing and microbiological analyses.

G. Stability

Stability data on the active substances and the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Three batches of active substance were analysed under a variety of storage conditions, with satisfactory data being presented in order to support the proposed retest period. Storage data on the finished product supported the shelf-life as defined in the SPC.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

The product has a shelf-life as packaged for sale: 3 years.

[2] HPLC – High Performance Liquid Chromatography.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

These applications were submitted in accordance with Article 13 (3) of Directive 2001/82/EC, and therefore the results of relevant data were required.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline, suitable warnings are cited in the SPC:-

- 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. of the SPC) 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 Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Not applicable.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is was a generic 'hybrid' application according to Article 13 (3), and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. Dissolution tests were performed as appropriate for the original application.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

No additional data were presented as the pharmacodynamic properties of these products were considered identical to those of the reference product, Frontline Spot On Dog 10% w/v Spot-On Solution.

Pharmacokinetics

No additional data were presented as the pharmacokinetic properties of these products were considered identical to those of the reference product, Frontline Spot On Dog 10% w/v Spot-On Solution.

Tolerance in the Target Species of Animals

The applicant conducted a GLP[3]-compliant target animal safety study. A suitable number of young dogs received the product in a suitably controlled study. The animals were divided into groups, and received no treatment, 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

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

[3] GLP – Good Laboratory Practise.

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[4] against fleas (*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 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

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

	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 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	After 48 hours, the therapeutic efficacies of the products

endpoints	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, 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)