Veterinary Medicines Directorate

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# MUTUAL RECOGNITION

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

## Vetflea 50 mg Spot-On Solution for Cats

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

# MODULE 1

## PRODUCT SUMMARY

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|---|---|
| EU Procedure number | UK/V/0397/001/DC |
| Name, strength and pharmaceutical form | Vetflea 50 mg Spot-On Solution for Cats |
| Applicant | ALFAMED<br>13ème Rue – L.I.D.<br>06517 CARROS CEDEX<br>FRANCE |
| Active substance | Fipronil |
| ATC Vetcode | QP53AX15 |
| Target species | Cats |
| Indications for use | Treatment of flea (*Ctenocephalides* spp.) and tick (*Dermacentor reticulatus*) infestations.<br><br>The product has a persistent insecticidal efficacy for up to 5 weeks against fleas (*Ctenocephalides felis*).<br>The product has a persistent acaricidal efficacy for up to 2 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.<br>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

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| Legal basis of original application | 'Hybrid' application 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

This application was submitted using the Decentralised Procedure, in accordance with Article 13 (3) as amended, as a 'hybrid' application, where bioequivalence could not be demonstrated via bioavailability studies, but was demonstrated by clinical equivalence. The reference product was Frontline Spot On 10% w/v Spot-On Solution, first authorised in the UK in 1996. The product is a spot-on solution intended for use in cats, 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 5 weeks. There is persistent activity of up to 2 weeks against The specified tick species, however if Rhipicephalus sanguineus and Ixodes ricinus are already when the product is applied, all ticks may not be killed within the first 48 hours, but will be killed within a week. The product is presented in a range of pack sizes.

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 products consist of the active substance fipronil at 50 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 delivering 50 ml of solution. 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 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 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*

This application was 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 (1), 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 this product was considered identical to those of the reference product, Frontline Spot On 10% w/v Spot-On Solution.

Pharmacokinetics

No additional data were presented as the pharmacokinetic properties of this product was considered identical to those of the reference product, Frontline Spot On 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 cats 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 product, 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 in cats. Additional studies were also presented from studies in dogs performed to provide data for the relevant dog products, showing the efficacy of the product used after shampooing and water immersion. These last two studies were also considered relevant.

### *Dose determination studies:*

A number of dose confirmation studies were presented:-

Study 1 (A second study using the same parameters provided additional information)

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|---|---|
| Study title | Comparative immediate efficacy of Frontline spot-on and 104.07[4] a generic fipronil spot-on formulation against fleas *(Ctenocephalides felis)* in cats |
| Objectives | To evaluate the efficacy of a topically applied spot-on formulation of fipronil against fleas (*Ctenocephalides felis*) on cats 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 0.5 ml. |
| Control product/placebo | Control product, Frontline Spot On 10% w/v topical solution, at 0.5. Reference product Frontline Spot-On for Cats.<br><br>Negative control group (no treatment). |
| Animals | Healthy cats, 8 animals each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas on cats. Efficacy of the test product was compared to the negative control and reference product upon weekly infestation of fleas, up to Day 2. |
| Randomisation | Randomised. |
| Blinding | Blinded. |
| Method | This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 40 fleas per cat), at various time points, and given treatment according to their respective groups. Flea counts were performed 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] Equivalent to Vetflea 50 mg Spot-On Solution for Cats.

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|---|---|
| | 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

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|---|---|
| Study title | Comparative study on the efficacy of a generic fipronil spot-on formulation (104.07) and Frontline Top Spot against fleas *(Ctenocephalides felis)* on cats |
| Objectives | to determine and compare the persistent efficacy of a fipronil spot-on formulation (104.07) with that of Frontline spot-on against fleas *(Ctenocephalides felis)* on cats. |
| 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 0.5 ml. |
| Control product/placebo | Control product, Frontline Top Spot, at 0.5ml<br>Negative control group (no treatment). |
| Animals | Healthy cats, 8 animals each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas on cats. Efficacy of the test product was compared to the negative control and reference product upon weekly infestation of fleas, up to Day 2. |
| Randomisation | Randomised. |
| Blinding | Blinded. |
| Method | This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per cat), at various time points, and given treatment according to their respective groups. Flea counts were performed 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 3

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| Study title | The efficacy of a single application of the spot-on 104.07 (Fipronil) compared to Frontline Spot On Cat and a no treatment control against artificially induced infestations of ticks (*Ixodes ricinus*) on cats |
| Objectives | to confirm the efficacy of a fipronil spot-on formulation (104.07) against the tick *Ixodes ricinus* on cats compared to Frontline Spot On Cat and a no treatment control when applied once topically at a rate of 0.5 ml per cat. |
| 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 0.5 ml. |
| Control product/placebo | Control product, Frontline Spot-On Cat, at 0.5ml<br>Negative control group (no treatment). |
| Animals | Healthy cats, 6 animals each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against ticks on cats. Efficacy of the test product was compared to the negative control and reference product upon weekly infestation of fleas, up to Day 2. |
| Randomisation | Randomised. |
| Blinding | Blinded. |
| Method | This was a parallel-grouped study. After acclimatisation, animals were infested as appropriate (approximately 100 fleas per cat), at various time points, and given treatment according to their respective groups. Flea counts were performed 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 4 (Dog Study)

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| 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.<br>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 5 (Dog Study)

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|---|---|
| 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).<br><br>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)