Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

**Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)**
**Federal Office of Consumer Protection and Food Safety**
**Mauerstraße 39-42**
**10117 Berlin**
**(Germany)**

**DECENTRALISED PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**Amflee 67 mg Spot-on Solution for Small Dogs**
**Amflee 134 mg Spot-on Solution for Medium Dogs**
**Amflee 268 mg Spot-on Solution for Large Dogs**
**Amflee 402 mg Spot-on Solution for Extra Large Dogs**

**Date: 08 March 2018**

# MODULE 1

**PRODUCT SUMMARY**

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|---|---|
| EU Procedure number | DE/V/0191/002<br>DE/V/0191/003<br>DE/V/0191/004<br>DE/V/0191/005 |
| Name, strength and pharmaceutical form | Amflee 67 mg Spot-on Solution for Small Dogs<br>Amflee 134 mg Spot-on Solution for Medium Dogs<br>Amflee 268 mg Spot-on Solution for Large Dogs<br>Amflee 402 mg Spot-on Solution for Extra Large Dogs |
| Applicant | TAD Pharma GmbH<br>Heinz-Lohmann-Str. 5<br>27472 Cuxhaven<br>Germany |
| Active substance(s) | Fipronil |
| ATC Vetcode | QP53AX15 |
| Target species | Dogs |
| Indication for use | Treatment of flea (*Ctenocephalides spp*.) and tick (*Dermacentor reticulatus*) infestations.<br>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.<br>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.<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 Veterinary Medicinal Agencies website (www.hma.eu).

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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|---|---|
| Legal basis of original application | Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 24th December 2014 |
| Date product first authorised in the Reference Member State (MRP only) | Not applicable |
| Concerned Member States for original procedure | Belgium, France, Greece, Italy, The Netherlands, Portugal, Spain, United Kingdom (former RMS) |

## I. SCIENTIFIC OVERVIEW

Amflee Spot-on Solution for Dogs has been developed as a generic hybrid of Frontline Sot-on Dogs. The reference product was first authorised in the UK in November 1996. Amflee contains 100 mg/ ml fipronil and is authorised for use in dogs. The product is indicated for the treatment of flea, tick and biting lice infestations. It is contraindicated for puppies less than 2 months old and/or weighing less than 2 kg or on sick or convalescent animals. The product should not be used on rabbits or cats, or in cases of hypersensitivity to the active substance or any of the excipients.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the 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.
[2] Efficacy – The production of a desired or intended result.

# II. QUALITY ASPECTS

## *II.A. Composition*

The product contains 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 a white polypropylene pipette closed with either a polyethylene or polyoxymethylene cap. The pipettes are packaged in a polyethylene terephthalate/ aluminium/ low density polyethylene triplex bag and placed in boxes of 1, 3, 6, 10, 20 or 30 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 a preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

## *II.B. Description of the Manufacturing Method*

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the excipients before and fipronil until dissolved. The solution is then filtered and filled into the pipettes. Process validation data on the product have been presented in accordance with the relevant European guidelines.

## *II.C. Control of Starting Materials*

The active substance is fipronil, an established active substance not described in a Pharmacopoeia. Data on the active substance were supplied in the form of an Active Substance Master File. 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 the excipients comply with their respective European Pharmacopeia (Ph. Eur.) Monographs. Certificates of analysis have been provided.

## *II.C.4. Substances of Biological Origin*

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

## *II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process*

Not applicable.

## *II.E. Control Tests on the Finished Product*

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for identification and assay of the active substance, identification and assay of excipients, appearance, density and microbiological purity.

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.

## *II.F. Stability*

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. A retest period of 3 years has been determined.

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. Data have been provided for batches of the finished product stored at 25°C/60% RH for 36 months and at 40°C/75% RH for 6 months. A shelf life of 36 months has been established.

## *II.G. Other Information*

Shelf life of the finished product as packaged for sale is 36 months except for the 67 mg strength where the shelf life is 30 months.
Store in the original container in order to protect from light and moisture. Do not remove from bag until required for use.
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)

## *III.A Safety Documentation*

### *Pharmacological Studies*

Pharmacodynamics
Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It works by blocking gamma-amino butyric acid (GABA) receptors which affects the movement of chloride ions across the cell membrane. This results in uncontrolled central nervous system (CNS) activity which leads to death of the insect or acarid. Fipronil is more toxic to insects than mammals due to differences in the GABA receptor sensitivity.

Pharmacokinetics
A radiolabelled study performed in rats, demonstrated that following dermal application of fipronil, less than 1% was absorbed in 24 hours. A comparative *in vitro* study looked at absorption across human, rat and rabbit epidermal membranes. At high doses absorption through rat and rabbit membranes was greater than humans, but comparable at low doses. The absorption increased with time but only 0.01% had crossed the human membrane in 8 hours.

Following dermal application fipronil spreads over the skin and can be detected in the stratum corneum and sebaceous glands for up to 56 days after application. The concentration of fipronil on hair decreases over time. Absorption of fipronil is low in the dog.

### *Toxicological Studies*

Data were provided on the toxicology of fipronil. The studies referenced demonstrated the established use of fipronil and that it is safe to use when administered as per the instructions.

- Single Dose Toxicity

The $LD_{50}$[3] following oral administration to rats has been reported as 97 mg/kg and for mice is 95 mg/kg. The clinical signs observed in these studies were tremors, convulsions, gait abnormalities, hunched posture and seizures.

The $LD_{50}$ following dermal administration in distilled water was more than 2000 mg/kg in rats and 354 mg/kg in rabbits. No clinical signs were seen in rats but in rabbits the signs included convulsions, sluggishness, spasms, tremors, hyperactivity, diarrhoea and emaciation.

[3] $LD_{50}$ – Dose that kills half a population

- Repeated Dose Toxicity

The NOEL[4] following oral administration for 13 weeks to rats was reported as 0.33 mg/kg and as 0.5 mg/kg in dogs. A year-long study in dogs fed fipronil found an NOEL of 0.2 mg/kg. In all studies clinical signs of toxicity included neurological symptoms. A study in rabbits looked at repeated dermal applications over 21 days and found a NOEL of 5 mg/kg. Systemic signs were observed towards the end of the study but not skin irritation was seen.

- Reproductive Toxicity, including Teratogenicity:

One study in rats reported that reproductive effects were only observed at doses above those that cause parental systemic toxicity. A published study was provided in which fipronil was applied dermally as a single dose of 70, 140 or 280 mg/kg. The results indicate high doses of fipronil may affect the endocrine system and cause adverse reproductive effects in the rat.

In a developmental study female rats were given up to 20 mg/kg on day 6-15 of gestation and no treatment effects were observed. A similar study was performed in rabbits, dosed on day 6-19 of gestation, and no effects were seen at the highest dose of 1 mg/kg.

- Mutagenicity:

Published studies were provided. Fipronil and its metabolites were negative in a range of genotoxity tests.

- Carcinogenicity:

In one study in mice no evidence of carcinogenicity was seen and the NOAEL[5] was reported as 0.055 mg/kg. A similar study in rats reported an NOAEL of 0.019 mg/kg and effects on the thyroid gland were observed. Alterations to T3, T4 and thyroid-stimulating hormone were noted and at high doses fipronil induced follicular-cell tumours of the thyroid. However, rats are known to be more sensitive than humans to thyroid changes.

Information regarding the metabolites was provided. There are two major metabolites of fipronil; fipronil sulfone and desulfinyl fipronil. Desulfinyl fipronil is a photo degradation product of fipronil that can be found on treated pets and can have a greater toxicity than fipronil or fipronil sulfone.

### *Studies of Other Effects*

Dermal irritation, ocular irritation and neurotoxicity studies were provided. Fipronil was not a dermal or ocular irritant in rabbits and was a weak skin sensitizer in one study using guinea-pigs.

[4] NOEL – No observed effect level
[5] NOAEL – No observed adverse effect level

In a single dose study for neurotoxicity in rats the NOAEL was 0.5 mg/kg following administration of 5 mg/kg fipronil. In a 13 week study in rats the NOEL was 0.3 mg/kg for neurotoxicity and systemic toxicity.

A neurotoxicity study in dogs was also referenced. Severe neurotoxic signs were observed after 5-13 days of daily oral dosing of 20 mg/kg fipronil. No NOAEL was determined.

### *Observations in Humans*

Bibliographical information was provided. The data show that following ingestion of fipronil the main symptoms are vomiting, agitation and seizures. Other symptoms following exposure include headache, nausea, vertigo and weakness. The reported cases all recovered, often without medication.

### *User Safety*

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature (similar to those of the reference product), 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 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.
- Do not smoke, drink or eat during application.
- Avoid contents coming into contact with the fingers. If this occurs, wash off immediately with soap and water.
- Wash hands after use.
- People with a known hypersensitivity to fipronil or dimethyl sulphoxide 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.

### *Environmental Safety*

An environmental risk assessment (ERA) was provided. The ERA was in accordance with VICH and CVMP guidelines.

**Phase I:**
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not 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.

- 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.I. Pre-Clinical Studies*

### *Pharmacology*

Pharmacodynamics
Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It works by blocking gamma-amino butyric acid (GABA) receptors which affects the movement of chloride ions across the cell membrane. This results in uncontrolled central nervous system (CNS) activity which leads to death of the insect or acarid. Fipronil is more toxic to insects than mammals due to differences in the GABA receptor sensitivity.

Pharmacokinetics
As this is a generic hybrid application according to EU Directive 2001/82/EC as amended, not further data were required. Bibliographical data were provided in support of the application.

Studies were provided for the pharmacokinetics of fipronil in the dog. In one study the plasma concentration of fipronil was measured following single topical administration. Collars were fitted to prevent grooming and ingestion of the product. Blood samples were taken pre-treatment and at regular intervals up to day 56 post-treatment. The $C_{max}$[6], $T_{max}$[7] and AUC[8] were calculated. The pharmacokinetic parameters varied between animals but by day 56 the fipronil concentration was below the level of quantification in all animals. The pharmacokinetic profile was as expected and no adverse events were observed.

A second study was provided which looked at the hair coat distribution of fipronil following single topical application to dogs. Again collars were fitted to prevent grooming and ingestion of the product. Hair samples were taken from three areas; lumbar, right side of thorax and left side of neck. Samples were collected pre-

[6] $C_{max}$ – Maximum plasma concentration
[7] $T_{max}$ – Time to maximum concentration
[8] AUC – Area under the curve

treatment and at 4 time points up to day 56 after treatment. Samples were homogenised and fipronil concentration determined. The results showed that fipronil was detected in all zones sampled within 24 hours of application. Fipronil could still be detected, at low levels, on day 56.

The two pharmacokinetic studies provided in support of the application demonstrated the pharmacokinetic parameters of the test product were as expected. Fipronil concentration was almost 1000 times greater on the hair than in the plasma, showing very little is absorbed. The studies also demonstrated that distribution across the coat does occur within 24 hours of single topical administration and remains detectable up to 56 days after treatment.

### *Tolerance in the Target Species*

A controlled target animal tolerance study was performed using multiples of the recommended dose in the target species. A placebo was used as a control. All doses were administered by the dermal route. The study was performed at a GLP[9]-compliant target animal species study unit, using 10% fipronil. Doses of 1x, 3x and 5x the nominal product dose were given to young dogs, (or a negative control was used). This was a, parallel group, randomised, blind, negative controlled study. Observations were performed as appropriate throughout the trial, with blood being analysed periodically and tissue samples being analysed. No adverse reactions relating to use of the product were seen. Suitable warnings are given in the SPC.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

### *Resistance*

A literature search had been performed and information provided on the resistance to fipronil. Very little evidence of resistance in ectoparasites in dogs has been identified. Adequate warnings and precautions appear on the product literature.

## *IV.II. Clinical Documentation*

### *Laboratory Trials*

Six dose confirmation studies were provided in support of the application. The studies demonstrated efficacy against the fleas, ticks and lice at the selected dose.

[9] GLP – Good Laboratory Practice.

***Dose confirmation studies:***

Study 1

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| Study title | Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On Solution for Dogs (10% fipronil) 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. |
| 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).<br><br>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. |

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| RESULTS | |
| Outcomes for endpoints | <u>Flea Counts</u><br><br>Where either product had been used, there was 100% efficacy against fleas on all assessment days.<br>Both products therefore had 4 weeks persistent efficacy against fleas (*C. Felis*). No treatment-related adverse effects were noted.<br><br><u>Efficacy against *R. sanguineus*</u><br>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*.<br><br><u>Efficacy against *D. reticulatus*</u><br>There was no evidence of a statistically significant difference between the two treated groups.<br>No treatment-related adverse effects were noted.<br>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. |

<u>Study 2</u>

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| Study title | A study to determine the efficacy of a single application of Fipronil Spot-On Solution for Dogs (10% fipronil) when compared to a comparator 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).<br>Negative control group (no treatment). |

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| 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<br>There was no evidence of a statistically significant difference between the two treated groups.<br>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

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| Study title | A controlled, randomised study to evaluate a single application of Fipronil Spot-On Solution for Dogs (10% fipronil) 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). |

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| 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<br><br>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

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| Study title | Water immersion stability study of topically applied Fipronil Spot-On Solution for Dogs (10% fipronil) 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. |

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| 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<br>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

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| 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). |

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| 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<br>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

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| 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. |

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| 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<br>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*

As this is a generic hybrid application submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended, the results of field trials are not required.

## V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the product(s) is favourable.

# MODULE 4

## POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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.

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| • | 08 March 2018 | Change of RMS from UK to DE. |
| • | 22 February 2018 | Change in contact details for local representative. |
| • | 03 March 2016 | Addition of a site of manufacture for the active substance |
| • | 05 February 2015 | Change of Marketing Authorisation Holder from KRKA d.d. NOVO mesto to TAD Pharma GmbH. |