

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

DECENTRALISED PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

Amflee 50 mg Spot-on Solution for Cats

Date: 21 July 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0191/001
Name, strength and pharmaceutical form	Amflee 50 mg Spot-on Solution for Cats
Applicant	TAD Pharma GmbH Heinz-Lohmann-Str. 5 27472 Cuxhaven Germany
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats
Indication for use	<p>Treatment and prevention of flea (<i>Ctenocephalides spp.</i>) and tick (<i>Dermacentor reticulatus</i>, <i>Ixodes ricinus</i>) infestations in cats.</p> <p>The product has a persistent insecticidal efficacy for up to 4 weeks against fleas (<i>Ctenocephalides spp.</i>) and acaricidal efficacy for up to 4 weeks against <i>Ixodes ricinus</i> and for up to 1 week against <i>Dermacentor reticulatus</i> and <i>Rhipicephalus sanguineus</i>. If <i>Rhipicephalus sanguineus</i> ticks 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.</p> <p>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.</p>

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

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	24 th 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, Netherlands, Portugal, Spain, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

Amflee 50 mg Spot-on Solution for Cats has been developed as a generic hybrid of Frontline Spot-on for Cats 10% w/v. The reference product has been authorised in the UK since November 1996. Amflee contains 100 mg/ ml fipronil and is authorised for use in cats. The product is indicated for the treatment of flea and tick infestations. It is contraindicated for kittens less than 2 months old and/or weighing less than 1 kg or on sick or convalescent animals. The product should not be used on rabbits 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 Pharmacopoeia (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.

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 cat.

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 LD₅₀³ 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 LD₅₀ 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 LD₅₀ – Dose that kills half a population

- **Repeated Dose Toxicity**

The NOEL⁴ 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 genotoxicity tests.

- **Carcinogenicity:**

In one study in mice no evidence of carcinogenicity was seen and the NOAEL⁵ 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. Do not contaminate ponds, waterways or ditches with the product or empty container.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.1. 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 cat. 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 60 post-treatment. The C_{max}^6 , T_{max}^7 and AUC^8 were calculated. The pharmacokinetic parameters varied between animals but by day 60 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 cats. 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-treatment and at 4 time points up to day 60 after treatment. Samples were

⁶ C_{max} – Maximum plasma concentration

⁷ T_{max} – Time to maximum concentration

⁸ AUC – Area under the curve

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 60.

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 10,000 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 60 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 GLP⁹-compliant target animal species study unit, using 10% fipronil. Doses of 1x, 3x and 5x the nominal product dose were given to young cats, (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 cats has been identified. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

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

⁹ GLP – Good Laboratory Practice.

Dose confirmation studies:

Study 1

Study title	Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml.
Control product/placebo	Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment).
Animals	Healthy adult and sub adult cats, 7 animals in each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control product and reference product up to Day 37 for fleas and Day 30 for ticks.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas and 50 ticks, at various time points treated according to their respective groups. Flea and tick counts were performed on several occasions up to Day 30/37, as appropriate.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups.

RESULTS	
Outcomes for endpoints	<p><u>Flea Counts</u></p> <p><u>Efficacy against <i>C. felis</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>95%), supporting the claim for a 4 week persistent effectiveness against <i>C. felis</i>.</p> <p><u>Tick Counts</u></p> <p><u>Efficacy against <i>D. reticulatus</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>90%), providing supporting evidence for a 1 week persistent effectiveness against <i>D. reticulatus</i>.</p>
DISCUSSION	The product was shown to be effective against the target parasites.

Study 2

Study title	Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions.
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml.
Control product/placebo	Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment).
Animals	Healthy adult and sub adult cats, 8 animals in each group.

Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control and reference product up to Day 23 for fleas and Day 16 for ticks.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas and 50 ticks, at various time points and then treated according to their respective groups. Flea and tick counts were performed at several time points up to Day 23/16, as appropriate.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups.
RESULTS	
Outcomes for endpoints	<p><u>Flea Counts</u></p> <p><u>Efficacy against <i>C. felis</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>95%), providing supporting evidence for a claim for a 3 week persistent effectiveness against <i>C. felis</i>.</p> <p><u>Tick Counts</u></p> <p><u>Efficacy against <i>D. reticulatus</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups providing supporting evidence for a claim for a 1 week persistent effectiveness.</p>
DISCUSSION	The product was shown to be effective against the target parasites.

Study 3

Study title	A controlled, randomised study to evaluate a single application of Fipronil Spot-On for Cats (10% fipronil) as a tick treatment for <i>Ixodes ricinus</i> on cats artificially infested with ticks under laboratory conditions.
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Objectives	To evaluate a single application of a Fipronil Spot-On Solution (10% fipronil) as a tick treatment for <i>Ixodes ricinus</i> on cats artificially infested under laboratory conditions.
Test site(s)	Laboratory environment. Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml.
Control product/placebo	Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment).
Animals	Healthy adult and sub adult cats, 8 animals in each group.
Outcomes/endpoints	Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control and reference product up to Day 16.
Randomisation	Randomised.
Blinding	Coded groups.
Method	The study was of a block design. After acclimatisation, animals were infested with approximately 60 ticks at various different time points and then treated according to their respective groups. Tick counts were performed on several occasions up to Day 16.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). A Mixed model Analysis of Variance was used, with a 90% reduction in ticks expected from the treatment.
RESULTS	
Outcomes for endpoints	<u>Tick Counts</u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted, a further test on <i>I. Ricinus</i> was provided (Study 5).
DISCUSSION	The product was shown to be effective against the target parasite.

Study 4

Study title	Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against the cat flea <i>Ctenocephalides felis</i> on cats under laboratory conditions.
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Objectives	To evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against the cat flea <i>Ctenocephalides felis</i> on cats under laboratory conditions.
Test site(s)	Laboratory environment. Single site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml.
Control product/placebo	Negative control group (no treatment).
Animals	Healthy adult and sub adult cats, 8 animals in 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 up to Day 37.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas at various different time points, and then treated according to their respective groups. Flea counts were performed at various time points up to Day 37.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups.
RESULTS	
Outcomes for endpoints	<u>Flea Counts</u> The results provided support for a claim for immediate efficacy (>95%) and also provided evidence for a claim of persistent efficacy for up to 4 weeks in the SPC.
DISCUSSION	The product was shown to be effective against the target species. The SPC carries specific data.

Study 5

Study title	Controlled, randomised study to evaluate the efficacy of a single application of Fipronil Spot-On for Cats (10% fipronil) when compared with an untreated control against artificially induced infestations of ticks (<i>Ixodes ricinus</i>) on cats under laboratory conditions.
Objectives	To evaluate the efficacy of a single application of Fipronil Spot-On for Cats (10% fipronil) when compared with an untreated control against artificially induced infestations of ticks (<i>Ixodes ricinus</i>) on cats under laboratory conditions.

Test site(s)	Laboratory environment. Single site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml.
Control product/placebo	Negative control group (no treatment).
Animals	Healthy adult and sub adult cats, 8 animals in 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 up to Day 37.
Randomisation	Randomised.
Blinding	Coded groups.
Method	This was a block design study. After acclimatisation, animals were infested with approximately 60 ticks at various time points, and then treated according to their respective groups. Tick counts were performed at various time points up to Day 37.
Statistical method	Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups.
RESULTS	
Outcomes for endpoints	The results provided support for a claim for immediate efficacy (>90%) and also provided evidence for a claim of persistent efficacy for up to 4 weeks in the SPC.
DISCUSSION	The product was shown to be effective against the target species. The SPC carries specific data.

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.

•	21 July 2020	Extension of the shelf life of the finished product
•	08 March 2018	Change in 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