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

Eliminall 50 mg Spot-On Solution for Cats (AT, FR, DE, GR, IT, IE, LU, NL, UK, PT, ES)
Exproline vet 50 mg spot-on solution for cats (NO, DK, FI, SE)

Date: 06 May 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0189/001
Name, strength and pharmaceutical form	Eliminall 50 mg Spot-On Solution for Cats
Applicant	KRKA d.d. NOVO mesto Smarjeska cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats
Indication for use	Treatment and prevention of flea (*Ctenocephalides* spp.) and tick (*Ixodes ricinus*) infestations in cats. The product has a persistent insecticidal efficacy for up to 4 weeks against fleas (*Ctenocephalides* spp.) and acaricidal efficacy for up to 4 weeks against *Ixodes ricinus* and for up to 1 week against *Dermacentor reticulatus* and *Rhipicephalus sanguineus*. If ticks of some species (*Dermacentor reticulatus* and *Rhipicephalus sanguineus*) 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 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 Mutual recognition procedure Decentralised procedure	28th September 2011
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

This application was submitted under the criteria for 'hybrid' applications, where bioequivalence cannot be demonstrated due to the nature of the product, (in this case, a cutaneous solution with little or no trans-cutaneous absorption). The reference product was Frontline Spot On Cat 10% w/v Spot-On Solution, authorised in the UK since November 1996.

The indication for the product is as follows: treatment and prevention of flea (*Ctenocephalides* spp.) and tick (*Ixodes ricinus*) infestations. The product has a persistent insecticidal efficacy for up to 4 weeks against fleas (*Ctenocephalides* spp.) and acaricidal efficacy for up to 4 weeks against *Ixodes ricinus* and for up to 1 week against *Rhipicephalus sanguineus* and *Dermacentor reticulatus*. If ticks of some species (*Dermacentor reticulatus*, *Rhipicephalus sanguineus*) 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. The products are not to be used in kittens less than two months old and/or weighing less than 1 kg. Do not use the products in sick or convalescent animals, do not use in 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 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.

II. QUALITY ASPECTS

A. Composition

The product contains 100 mg/ml fipronil as an active substance and excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), polysorbate 80, povidone K25 and dimethyl sulfoxide.

The container system is a white polypropylene pipette closed with either a polyethylene or polyoxymethylene cap. 0.5 ml pipettes are packed individually into a polyethylene terephthalate/aluminium/low density polyethylene triplex bag. Boxes contain 1,3,6,10,20 or 30 pipettes. The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative is justified.

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

Dimethyl sulfoxide, polysorbate, povidone, butylyhydroxytoluene and butylhydroxyanisole are mixed with fipronil. The product is then filtered and packaged.

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.

C. Control of Starting Materials

The active substance is fipronil, an established active substance not described in the European Pharmacopoeia, (an Active Substance Master File was provided).
The active substance is manufactured in accordance with the principles of good manufacturing practice.

[1] SPC – Summary of Product Characteristics.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. All excipients are monographed in the European Pharmacopoeia, and all comply with relevant requirements.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

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

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product.

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. This includes relevant general characteristics, identification, quantitative determination and purity tests.

G. 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 re-test period of two years was deemed acceptable. Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the 30 months stability of the formulation when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale 30 months.
Store in the original container in order to protect from light and moisture.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This was a hybrid application according to Article 13 (3). Pharmacological and toxicological data were required and were provided in the form of published data for this section.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

A series of published references were presented, which showed that fipronil was effective in reducing the numbers of the target organisms. The active substance works by the disruption of the functioning of the nervous system of the target parasite. It is understood that the action of the GABA[2]-gated chloride ion channel or the glutamate-gated channel is blocked. Neuronal excitation and death are the ensuing results on the target insects.

Pharmacokinetics

A series of studies, the majority performed in rats, were taken from published literature provided data for this section with regard to absorption, distribution, metabolism and elimination. The dose absorbed appeared dependent on the type of treatment, and once absorbed fipronil was quickly metabolised and residues widely distributed. The main route of elimination was via the faeces.

Toxicological Studies

A series of published studies were presented for the results of toxicological studies.

Single Dose Toxicity

Acute toxicity studies in rats showed that moderate toxicity was caused by fipronil via the inhalation and oral routes. Using 95.6% technical grade fipronil via the oral route, an average LD_{50}[3] of 97 mg/kg was seen in rats, and an average LD_{50} of 95 mg/kg was seen in mice. Via the inhalation route, the LC_{50} for rats was 0.36 mg/L for males and 0.42 mg/L for females. The active substance was shown to be

[2] GABA – Gamma-amino butyric acid.
[3] LD_{50} – Median lethal dose.

relatively non-hazardous to rats via the dermal route, but proved moderately hazardous to rabbits. Doses were fatal at greater than 50 mg/kg in rodents.

Repeated Dose Toxicity

Reports from published literature were provided which cited the investigation of repeated dose toxicity for fipronil in rodents and dogs. All treatments were given via the oral route. In one study, an increase in the incidence of liver cell periacinar hypertrophy was noticed in male rats at a dose of 1 ppm (0.13 mg/kg/day), when the animals were fed at doses of 0.1,3,10 or 25 ppm fipronil over 13 weeks. No NOAEL[4] was established. In a further study, an increase in liver and thyroid weights was seen when fipronil was fed at 30 ppm, along with evidence of changes to plasma glucose and urea levels, and thyroid follicular cell epithelial hypertrophy in males. The NOAEL was 5 ppm, equivalent to 0.33 mg/kg/day.

In dogs, fipronil was administered for one year ay doses of 0, 0.2, 2, or 5 mg/kg/day, with adverse clinical signs becoming apparent at 2 mg/kg/day and above. The NOAEL was 0.2 mg/kg/day. A further study concluded with an NOAEL of 0.3 mg/kg/day.

Other Studies

Foetotoxicity and Teratogenicity

A two-generation study in rats receiving 0, 3, 30 or 300 ppm fipronil /day saw effects that affected fertility and produced foetotoxicity. The NOAEL for parental systemic toxicity was 0.25 mg/kg/day, the NOAEL for reproductive toxicity was 2.5 mg/kg/day. A further study noted an effect on the oestrus cycle of rats at 280 mg/kg, and it was concluded that fipronil may affect the endocrine system.

Mutagenicity

No adverse effects were observed in results for genotoxicity or cytogenicity.

Carcinogenicity

Carcinogenetic effects were only noted at high levels of fipronil in rats, at 300 ppm when administered in the diet.

Other Studies

Published data investigating skin irritation, eye irritation, sensitisation potential and inhalation toxicity were presented. In general, fipronil was tolerated at lower levels. In a first study, the NOAEL in rabbits when exposed dermally to fipronil at 0, 0.5, 1, 5

[4] NOAEL – No observable adverse effect limit.

or 10 mg/kg/day was 5 mg/kg/day. In further studies, fipronil was seen to be mildly irritating to the eyes in rabbits and caused mild sensitisation in guinea-pigs tested using the Magnusson-Kligman method.

For neurotoxicity, a NOAEL of 0.5 mg/kg was seen in rats where the animals were given 0, 0.5, 5 or 50 mg/kg by gavage. IN another study where rats received 0, 0.5, 5 or 150 ppm fipronil, a NOAEL was seen at 0.3 mg/kg/day.

A study of neurotoxicity in female dogs saw fipronil given in capsules at 0 (one control animal) or 20 mg/kg/day. No NOAEL was defined, but adverse clinical signs were seen at 20 mg/kg/day.

Observations in Humans

Published reports were cited describing a variety of exposures to fipronil when used as a food-pesticide or at self-poisoning, for which symptoms were cited as being as follows: headache, nausea, vertigo, sweating vomiting and agitation. Only one death was reported in a patient who did not respond to therapeutic treatment. The SPC carries appropriate warnings.

Microbiological Studies

Not applicable.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Data were provided for the active substance in the form of published references on toxicity data, (including repeat dose studies), and a quantitative risk assessment which compared exposure levels with NOAELs[5] from repeat dose studies. Data were also received with regard to hazards presented by the excipient DMSO[6]. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that as the product is used in cats, the risk to the environment is minimal. There is potential for the active substance to affect aquatic life and therefore, warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

[5] NOAEL – No Observable Adverse Effect Limit.
[6] DMSO – Dimethyl sulfoxide.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this was a hybrid application, no further data were required for this section.

Tolerance in the Target Species of Animals

The applicant conducted a GLP[7]-compliant target animal safety study. A suitable number of young cats received the product, in a blinded, parallel grouped, randomised, and negatively controlled study in a two-phase design. The animals were divided into groups, and received treatment which consisted of placebo, 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

Published data were provided to confirm that there is a low risk of resistance developing in the target parasites. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant provided information on dose determination which mirror data relating to the reference products.

Dose confirmation studies:

A number of dose confirmation studies were provided:-

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 (*Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) on cats under laboratory conditions.

[7] GLP – Good Laboratory Practise.

Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (*Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) 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	Flea Counts Efficacy against *C. felis* 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 *C. felis.* Tick Counts Efficacy against *D. reticulatus* 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 *D. reticulatus*.
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 (*Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) on cats under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (*Dermacentor reticulatus*) and the cat flea (*Ctenocephalides felis*) 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	Flea Counts Efficacy against *C. felis* 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%), eventually providing supporting evidence for a claim for a 4 week persistent effectiveness against *C. felis.* Tick Counts Efficacy against *D. reticulatus* 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.
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 *Ixodes ricinus* on cats artificially infested with ticks under laboratory conditions.
Objectives	To evaluate a single application of a Fipronil Spot-On Solution (10% fipronil) as a tick treatment for *Ixodes ricinus* 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	Tick Counts 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. Ricinus* was provided (Study 5).
DISCUSSION	The product was shown to be effective against the target parasite. The SPC states that insecticidal efficacy is seen up to 4 weeks after dosing.

Study 4

Study title	Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation 10% fipronil against the cat flea *Ctenocephalides felis* on cats under laboratory conditions.
Objectives	To evaluate the efficacy of a topically applied spot-on formulation of 10% fipronil against the cat flea *Ctenocephalides felis* 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	Flea Counts 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 appropriate indication data; the product exhibits efficacy for up to 4 weeks against *C. felis*.

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 (*Ixodes ricinus*) 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 (*Ixodes ricinus*) 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

Field studies were not required for this hybrid application.

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 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.

•	16 March 2021	Extension of shelf-life as packaged for sale
•	08 March 2018	Change of RMS from UK to DE
•	23 March 2017	Renewal – UK as RMS.
•	03 March 2016	Addition of a site of manufacture for the active substance
•	07 February 2014	Updates to SPC and package leaflet with regard to storage of the product.
•	25 November 2013	Change of distributor.
•	18 January 2013	Addition of a new therapeutic indication to treat *Dermacentor reticulatus* infections in cats.
•	23 November 2012	Extension of a re-test period of the active substance.