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

Fyperix 67 mg Spot-On Solution for Dogs
Fyperix 134 mg Spot-On Solution for Dogs
Fyperix 268 mg Spot-On Solution for Dogs
Fyperix 402 mg Spot-On Solution for Dogs

Date: 08 March 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0189/002 DE/V/0189/003 DE/V/0189/004 DE/V/0189/005
Name, strength and pharmaceutical form	Fyperix 67 mg Spot-On Solution for Dogs Fyperix 134 mg Spot-On Solution for Dogs Fyperix 268 mg Spot-On Solution for Dogs Fyperix 402 mg Spot-On Solution for Dogs
Applicant	KRKA d.d. NOVO mesto Smarjeska cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides spp.*) and tick (*Dermacentor reticulatus*) infestations. 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. 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. 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	21th March 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Denmark, Finland, France, Italy, The Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

These applications were approved according to Article 13(3) for 'hybrid' products. For this type of application, bioequivalence has not been demonstrated by bioavailability studies but by clinical equivalence. The products were developed as generics of Frontline Spot On Dog 10% w/v Spot on Solutions, produced by Merial Animal Health Ltd.

The products are indicated for the treatment of flea (*Ctenocephalides* spp), tick (*Dermacentor reticulatus* and *Ixodes ricinus), and* biting lice *(Trichodectes canis)*) infestations in dogs. For biting lice, most are killed within 2 days, there is insecticidal activity for up to 8 weeks against new infestations with adult fleas, and persistent acaricidal activity against *Ixodes ricinus* for up to 3 weeks, and up to 4 weeks against *Rhipecephalus sanguineus* and *Dermacentor reticulatus*. Where ticks of some species, *Rhipecephalus sanguineus* and *Ixodes ricinus* are present when the product is applied, all ticks may not be killed within the first 48 hours. The products can be used as part of the treatment for the control Flea Allergy Dermatitis, (FAD), where this has been diagnosed by a veterinary surgeon.

The active substance, fipronil, is an insecticide and ascaricide of the phenylpyrazole family. The action of fipronil is the inhibition of the GABA[1] complex, blocking pre-

[1] GABA – Gamma-amino butyric acid.

and post-synaptic transfer of chloride ions across cell membranes, resulting in loss of control of central nervous system activity and subsequent death of the parasite.

II. QUALITY ASPECTS

A. Composition

The product contains fipronil, and excipients butylhydroxyanisole E320, butylhydroytoluene E321, polysorbate 80, povidone K25 and dimethyl sulfoxide.
The container/closure system consists of white polypropylene pipettes closed with either a polyethylene or polyoxymethylene cap. Each pipette is packed in a polyethylene terephthalate/aluminium/low density polyethylene triplex bag, and a box may 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 choice of the formulation and the presence of preservative are 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

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 described in the European Pharmacopoeia (Ph. Eur). The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

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

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

E. Control on intermediate products

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 retest period of 3 years was supported for the active substance.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the 36 months stability of the formulation when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the product as packaged for sale: 3 years.
Store in the original container in order to protect from light and moisture.
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 Testing

Pharmacological Studies

Pharmacodynamics

Fipronil is a phenylpyrazole which blocks insectoid gamma-amino butyric acid receptors, compromising the action of chloride ions. The ensuing uncontrolled central nervous system activity results in the death of the organism. Fipronil is also thought to have an effect on glutamate-activated chloride channels, which are not present in vertebrates.

Pharmacokinetics

Published data were submitted for this section. Subsequent to topical application in the dog, fipronil spreads over the skin via translocation, being stored in the oil glands of the skin and shed with the hair and sebum. The concentration of the active substance decreases over time.

Toxicological Studies

- Single Dose Toxicity

The acute toxicity of fipronil was studied, with LD_{50}[2] values reported via the oral route in rats of 97 mg/kg, 95 mg/kg via the oral route in mice and an LC50 of 0.36- 0.42 mg/L in rate after a single inhalation exposure. Adverse effects noted were convulsions, effects on behaviour, and wetness in various body areas. It was discerned that the dermal LD_{50} when given in distilled water to rats was higher than 2000 mg/kg, and 345 mg/kg when the test material was moistened with corn oil and applied to rabbits. No clinical observations were seen in rats, but they were observed in rabbits, and comprised salivation, tremors, spasms, diarrhoea and emaciation.

- Repeated Dose Toxicity

Studies were presented as reviews by the applicant. NOEL[3] were derived for oral studies in rats, after a 13 week study of 0.33 mg/kg bodyweight, in dogs 0.5 mg/kg bodyweight, and after year long-trials in dogs of 0.2 mg/kg bodyweight (gelatine capsules), and 0.3 mg/kg bodyweight (in diet). A NOEL of 5 mg/kg bodyweight was seen in rabbits after a 21 day trial on dermal toxicity.

[2] LD_{50} – Half the lethal dose.
[3] NOEL – No observable effect limit.

- Reproductive Toxicity, including Teratogenicity

  Published studies provided data noted that adverse effects occurred above the parental systemic toxicity level in rats in a two-generation study, and when given dermally at 70, 140 or 280 mg/kg bodyweight, there may be adverse effects to the endocrine and reproductive systems in rats. In two further studies analysed, no adverse developmental effects were seen in rabbits or rats.

- Mutagenicity

  Fipronil and its metabolites were seen to be negative in a range of genotoxicity tests.

- Carcinogenicity

  No evidence of carcinogenicity was seen in an appropriate mouse study. The NOAEL[4] was 0.55 mg/kg bodyweight based on systemic effects, liver weights and increased incidence of periacinar microvesicular vacuolation. IN rats, alterations to T-lymphocytes and thyroid-stimulation hormone were observed, along with the development of thyroid tumours. Rats are noted to be more sensitive than humans to thyroid changes. The NOAEL for

neurotoxicity was noted as being 0.019 mg/kg bodyweight for fipronil.

Other Studies

The applicant provided bibliographical data which showed that:-

Technical grade fipronil was seen not to be a dermal irritant in rabbits. Suitable reviews were provided on metabolites and impurities.

Observations in Humans

The applicant provided bibliographical data information which described the ingestion or inhalation of fipronil in humans. In all cited cases symptoms resolved spontaneously, and consisted of vomiting headache, vertigo, weakness and seizures. In one case, a man died following suspected ingestion of fipronil, but the dose was unknown and another substance may have additionally been involved.

[4] NOAEL – No adverse observable effect limit

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 original packaging and dispose of used pipettes immediately

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

- Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty container.

IV CLINICAL ASSESSMENT (EFFICACY)

Appropriate safety, pre-clinical tests and clinical trials were required for this 'hybrid' application.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics and pharmacokinetics

Suitable data were provided.

Tolerance in the Target Species of Animals

The applicant conducted a controlled target animal tolerance study 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[5]-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 organs being studied at necropsy. 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

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted six dose confirmation studies.

[5] 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 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). 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.

RESULTS	
Outcomes for endpoints	<u>Flea Counts</u> Where either product had been used, there was 100% efficacy against fleas on all assessment days. Both products therefore had 4 weeks persistent efficacy against fleas (*C. Felis*). No treatment-related adverse effects were noted. <u>Efficacy against *R. sanguineus*</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%), demonstrating a 4 week persistent effectiveness against *R. Sanguineus*. <u>Efficacy against *D. reticulatus*</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%), 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>

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). 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 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 There was no evidence of a statistically significant difference between the two treated groups. 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

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).
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 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

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.
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 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

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).
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 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

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.
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 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

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.

•	08 March 2018	Change of RMS from UK to DE
•	03 May 2017	Renewal – UK as RMS
•	03 March 2016	Addition of a site of manufacture for the active substance
•	12 June 2014	Addition of a temperature warning to the storage conditions to the SPC and product literature.
•	12 June 2014	Change of invented name from 'Ectofend' to 'Fyperix' in the UK, France, Germany, Italy, Portugal, Netherlands and Spain. Change in the invented name in Norway, Sweden, Finland and Denmark from 'Ectofend vet' to 'Fyperix vet'.
•	06 March 2014	To extend the re-test period of the product from 24 to 36 months.
•	20 November 2013	Change of distributor