



**ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES**

**United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS**

NATIONAL PROCEDURE

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

**Fipnil Spot-on Solution Dog 67 mg
Fipnil Spot-on Solution Dog 134 mg
Fipnil Spot-on Solution Dog 268 mg
Fipnil Spot-on Solution Dog 402 mg**

EU Pharmaceuticals Ltd.

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fipnil Spot-on Solution Dog 67 mg Fipnil Spot-on Solution Dog 134 mg Fipnil Spot-on Solution Dog 268 mg Fipnil Spot-on Solution Dog 402 mg
Applicant	EU Pharmaceuticals Ltd. 37 Geraldine Road London SW18 2NR UK.
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	<p>Treatment of flea (<i>Ctenocephalides</i> spp.) and tick (<i>Rhipicephalus sanguineus</i> and <i>Ixodes Ricinus</i>) infestations.</p> <p>Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. The product has a persistent acaricidal efficacy for 4 weeks against ticks (<i>Rhipicephalus sanguineus</i>, <i>Ixodes ricinus</i>, <i>Dermacentor reticulatus</i>).</p> <p>If ticks of some species (<i>Dermacentor reticulatus</i>) are already present when the product is applied, all of the ticks may not be killed within the first 48 hours.</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>

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Application for National Procedure
Publicly Available Assessment Report

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
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I. SCIENTIFIC OVERVIEW

These applications were submitted 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) and tick (*Rhipicephalus sanguineus* and *Ixodes ricinus*) infestations in dogs. The products have insecticidal activity against new infestations with adult fleas for 8 weeks, and have a persistent acaricidal activity against *Rhipicephalus sanguineus*, *Ixodes ricinus* and *Dermacentor reticulatus* for 4 weeks. If some tick species (*Dermacentor reticulatus*) are present when the product is applied, not all ticks may be killed within 48 hours. The products can be used as part of the treatment for the control Flea Allergy Dermatitis, where this has been diagnosed by a veterinary surgeon.

The products are 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 products can be safely used in the target species; the slight reactions observed are indicated in the SPC¹. The products are 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 products was demonstrated according to the claims made in the SPC.

¹ Summary of Product Characteristics

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II. QUALITY ASPECTS

A. Composition

Fipnil Spot-on Solution dog 67 mg

The product contains 67 mg/pipette fipronil as active substance and butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system consists of a white pipette composed of a heat-formed shell of a polypropylene/cyclic olefin copolymer/polypropylene layer and a polyethylene/ethylene vinyl alcohol/polyethylene layer. Boxes contain 1, 2, 3, 4, 6, 8, 9, 10, 12, 15, 18, 20, 21, 24, 30, 60, 90 or 150 pipettes in individual foil schets.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

Fipnil Spot-on Solution dog 134 mg

The product contains 134 mg/pipette fipronil as active substance and butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system consists of a white pipette composed of a heat-formed shell of a polypropylene/cyclic olefin copolymer/polypropylene layer and a polyethylene/ethylene vinyl alcohol/polyethylene layer. Boxes contain 1, 2, 3, 4, 6, 8, 9, 10, 12, 15, 18, 20, 21, 24, 30, 60, 90 or 150 pipettes in individual foil sachets.

Fipnil Spot-on Solution dog 268 mg

The product contains 268 mg/pipette fipronil as active substance and butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system consists of a white pipette composed of a heat-formed shell of a polypropylene/cyclic olefin copolymer/polypropylene layer and a polyethylene/ethylene vinyl alcohol/polyethylene layer. boxes contain 1, 2, 3, 4, 6, 8, 9, 10, 12, 15, 18, 20, 21, 24, 30, 60, 90 or 150 pipettes in individual foil sachets.

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Fipnil Spot-on Solution dog 402 mg

The product contains 402 mg/pipette fipronil as active substance and butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system consists of a white pipette composed of a heat-formed shell of a polypropylene/cyclic olefin copolymer/polypropylene layer and a polyethylene/ethylene vinyl alcohol/polyethylene layer. Boxes contain 1, 2, 3, 4, 6, 8, 9, 10, 12, 15, 18, 20, 21, 24, 30, 60, 90 or 150 pipettes in individual foil sachets.

B. Method of Preparation of the Product

The products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the products have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is fipronil which is almost unabsorbed through the skin and the formulation is designed to deposit the active substance easily onto the animal.

There are four excipients used in the formulation and each has been used previously in veterinary medicines.

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 used in the final product have monographs in the Ph. Eur. and each comply with the requirements of the current edition of the Ph. Eur.

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.

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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 sites have been provided demonstrating compliance with the specification.

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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

Special precautions for storage

Store below 25°C.

Store in a dry place in the original package.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Published data were submitted for this section, which were also relevant to Part IV, Clinical Aspects. Fipronil is a phenylpyrazole which blocks insect 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. A metabolite of fipronil, fipronil sulfone is also considered to have an effect.

Pharmacokinetics

Published data were submitted for this section, which were also relevant to Part IV, Clinical Aspects. 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

Published data were submitted for this section. A review of chronic and subchronic toxicity found that technical grade fipronil is acutely toxic to mammals via the inhalation and oral routes of exposure. Side effects include a hunched posture, abnormal gait, diarrhoea and piloerection. Further data stated that mild dermal and eye irritation occurred, but that the active substance was not a sensitiser in the guinea pig sensitisation test.

Additional data showed that fipronil caused neurotoxicity in rats at a NOEL² of 0.5 mg/ml. Two other studies showed NOAELs³ of 5.0 mg/kg, and 2.5 mg/kg and 7.5 mg/kg respectively.

Repeated Dose Toxicity

Data provided showed that in rats, repeated dosing of fipronil caused seizure, inappetance, decrease bodyweight, liver dysfunction and changes in blood cell biochemistry. In dogs, fipronil toxicity caused neurotoxicological signs and low bodyweight.

² NOEL – No Observable Effect Limit.

³ NOAEL – No Observable Adverse Effect Limits.

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Other Studies

Reproductive Toxicity

Published evidence of reproductive toxicity was seen, with a reproductive toxicity for rats described as being at a NOEL of 2.54 mg/kg/day and 2.74 mg/kg/day, and a developmental toxicity study where a NOEL of 20 mg/kg was displayed with a maternal toxicity of 4/mg/kg/day. The SPC⁴ states that 'Studies have not been carried out with this product in pregnant and lactating bitches. Use in pregnancy and lactation only in accordance with professional veterinary advice and a benefit/risk assessment.'

Carcinogenicity and Mutagenicity

Suitable references were submitted with regard to these topics.

Special Studies

No reports of immunotoxicity were found in published literature. Fipronil was found to be developmentally neurotoxic in repeat dose studies in rats and dogs.

Observations in Humans

In most cases, exposure to fipronil in reported cases caused vomiting, oropharyngeal pain, abdominal pain, coughing, headache and drowsiness. Symptoms resolved spontaneously.

Microbiological Studies

Studies on Metabolites, Impurities, Other Substances and Formulation

Suitable reference data were submitted. Specific eye and skin irritation studies for fipronil were not submitted, and this was considered acceptable as the proposed products contain well-known spot on formulations. Data were also submitted with regard to the irritant properties of the excipients. The SPC contains suitable warnings.

User Safety

A satisfactory user risk assessment was provided. It was established that the products should not pose any greater risk to the user than the reference product, when used as described on the SPC and product literature.

The following warnings and precautions are listed on the SPC and product literature:

⁴ SPC – Summary of Product Characteristics.

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- Keep pipettes in original packaging until ready to use.
- 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 hands with soap and water. Wash hands after use.
- Ingestion of the product is harmful. Prevent children getting access to the pipettes and discard the used pipettes immediately after applying the product. In case of accidental ingestion of product seek medical advice immediately.
- Animals or people with a known hypersensitivity to fipronil or any of the other ingredients should avoid contact with the 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.

Other precautions

- Fipronil may adversely affect aquatic organisms. Dogs should not be allowed to swim in water courses for 2 days after application.
- The product may have adverse effects on painted, varnished or other household surfaces or furnishings.

Ecotoxicity

A satisfactory environmental risk assessment was provided. It was established that the products should not pose any greater risk to the environment than the reference product, when used as described on the SPC and product literature:

- 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.

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IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Published data were submitted for this section, which were also relevant to Part III, Safety. 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. A metabolite of fipronil, fipronil sulfone is also considered to have an effect.

Pharmacokinetics

Published data were submitted for this section, which were also relevant to Part III, Safety. 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 hair and sebum. The concentration of the active substance decreases over time.

Tolerance in the Target Species of Animals

Published literature was submitted for this section, in addition to data from a GLP⁵-compliant target animal species study using 10% fipronil. Doses of 1x, 3x and 5x the nominal product dose were given to young dogs, (or a negative control was used), on three occasions at monthly intervals. This was a three-phase, parallel group, randomised, blind, negative controlled study. Post-acclimatisation, the animals were examined and blood collected for analysis. Observations were performed as appropriate throughout the trial. No adverse reactions relating to use of the product were seen. Cosmetic changes occurred in all study groups, (spiking, clumping of hair with a greasy appearance), which spontaneously resolved. Suitable warnings are given in the SPC.

Resistance

The applicant's conclusion that little or no evidence of resistance to fipronil has been found to date was supported. The SPC contains appropriate information in Section 4.4, advising the end-user of the necessity of treating other household pets and the environment in order to mitigate the formation of resistance.

⁵ GLP – Good Laboratory Practice.

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IV.B Clinical Studies

Dose confirmation studies:

First study

Study title	Dose confirmation study to evaluate the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control against artificially induced infestation of ticks (<i>Ixodes ricinus</i>) and fleas (<i>Ctenocephalides felis</i>) in dogs.
Objectives	To evaluate the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control against artificially induced infestation of ticks (<i>Ixodes ricinus</i>) and fleas (<i>Ctenocephalides felis</i>) in dogs.
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil 10% w/v topical spot on
Control product/placebo	Control product, Fipronil 10% w/v topical spot on, 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 single topical application of fipronil 10% w/v as compared to untreated controls, in artificially induced tick and flea infestation. Efficacy of the test product was compared up to Day 30 for <i>Ixodes ricinus</i> , <i>Rhipicephalus sanguineus</i> and <i>Dermacentor reticulatus</i> and Day 70 for <i>Ctenocephalides felis</i> .
Randomisation	Randomised.
Blinding	Partially blinded.
Method	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 70 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 flea counts.
RESULTS	
Outcomes for	The results of this study demonstrated that Fipronil 10%

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endpoints	w/v topical spot on was effective against <i>Ctenocephalides felis</i> from Study Day 2 to Study Day 72 inclusive and effective against <i>Ixodes ricinus</i> from Study Day 2 to Study Day 30 inclusive when applied once topically as a spot on to Beagle dogs. In addition, a single topical application of Fipronil 10% w/v topical spot on at a dose rate of 1.34 mL per dog in the bodyweight range of 10 kg to 20 kg was well tolerated.
DISCUSSION	The product was shown to be effective against the target parasites.

Second study:

Study title	Dose confirmation study to evaluate the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control group against artificially induced infestation of two species of ticks (<i>Dermacentor reticulatus</i> and <i>Rhipicephalus sanguineus</i>) in dogs.
Objectives	To evaluate the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control against artificially induced infestation of two species of ticks (<i>Dermacentor reticulatus</i> and <i>Rhipicephalus sanguineus</i>) in dogs.
Test site(s)	Laboratory environment. Single site.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil 10% w/v topical spot on
Control product/placebo	Control product, Fipronil 10% w/v topical spot on, 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 single topical application of fipronil 10% w/v as compared to untreated controls, in artificially induced tick infestation. Efficacy of the test product was compared up to the Day 30 for <i>Rhipicephalus sanguineus</i> and <i>Dermacentor reticulatus</i> .
Randomisation	Randomised.
Blinding	Partially blinded.
Method	After acclimatisation, animals were infested as appropriate (approximately 50 <i>Dermacentor reticulatus</i> ticks per dog or approximately 50 <i>Rhipicephalus sanguineus</i> ticks 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.

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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 flea counts.
RESULTS	
Outcomes for endpoints	The results of this study demonstrated that Fipronil 10% w/v topical spot on was effective against <i>Dermacentor reticulatus</i> from day 9 to day 30 inclusive and effective against <i>Rhipicephalus sanguineus</i> from day 2 to day 30 inclusive when applied once topically as a spot on to Beagle dogs. In addition, a single topical application of Fipronil 10 % w/v topical spot on at a dose rate of 1.34 ml per dog in the bodyweight range of 10 kg to 20 kg was well tolerated.

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

No clinical field studies were required for these applications, suitable supporting literature was considered appropriate.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

www.gov.uk/check-animal-medicine-licensed