United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Wilko Flea Drops 50 mg Spot-on Solution for Cats

Updated: May 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Wilko Flea Drops 50 mg Spot-on Solution for Cats
Applicant	Bob Martin (UK) Ltd. Wemberham Lane Yatton Somerset BS49 4BS
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats
Indication for use	Treatment of flea (*Ctenocephalides* spp.) infestations. The product has a persistent insecticidal efficacy for up to 5 weeks against fleas (*Ctenocephalides* spp.). Although no immediate killing effect against ticks has been demonstrated, the product has shown an acaricidal efficacy against *Dermacentor reticulatus*. If ticks of this species are present when the product is applied, all the ticks may not be killed within the first 48 hours but they will be killed within a week.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

The product is a spot-on solution, developed as a generic of Frontline Spot-On Cat. However, bioequivalence could not be demonstrated by appropriate studies, and therefore the product was deemed to be a generic hybrid, whereby it was necessary for clinical endpoints to be produced. The product is administered topically to cats, (solution contains 10% fipronil), at 0.5 ml per animal.

The product is indicated for the treatment of flea (*Ctenocephalides* spp.) and tick (*Dermacentor reticulatus*) infestations. The products are available in blister cards or boxes of 1, 2, 3, 4, 5 or 6 pipettes, and are contraindicated for kittens less than 2 months of age or weighing less than 1 kg, convalescent animals, and other species, particularly rabbits.

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 fipronil as active substance and excipients butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethylene glycol monoethyl ether.

The container system consists of the product packed at 0.50 ml in blister cards or boxes of 1, 2, 3, 4, 5 or 6 pipettes, packaged in a clear PVC blister closed by

[1] SPC – Summary of Product Characteristics

heat sealing with aluminium foil. 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

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 (Ph. Eur). The active substance, fipronil, is sourced from two active substance manufacturers. Data on the active substance was provided in the form of an Active Substance Master File (ASMF). The active substance is manufactured in accordance with the principles of good manufacturing practice (GMP).

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 comply with their respective Ph. Eur monographs. Certificates of analysis were received from each manufacturer, and testing of the excipients is performed on receipt.

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 sites have been provided demonstrating compliance with the specification. Tests on the finished product include those for identification and assay of the active substance and

anti-oxidants, quantification of related impurities, uniformity of dosage units, moisture and microbial purity.

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 2 years was established for the active substance from one supplier, whilst a retest period of 3 years was established for the active substance from the other supplier. The shelf-life of the finished product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the finished product as packaged for sale: 2 years.
- Store below 25°C.
- Do not store above 25 °C.
- Store in a dry place.
- Store in the original package.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Data were required for this section, as bioequivalence demonstrated by bioavailability was not demonstrated with a reference product.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant provided bibliographical data and an *in-vivo* laboratory study, which had relevance to the Safety and Efficacy sections of the report. Fipronil is a phenylpyrazole which acts against the target parasite gamma-amino butyric acid (GABA) receptors, disrupting the passage of chloride ions. Uncontrolled nervous system activity occurs, followed by death of the parasite. The selective toxicity of fipronil for insect receptors are thought to be due to the putative blocking of glutamate-activated chloride channels, which are absent in vertebrates.

Pharmacokinetics

The applicant has provided bibliographical data which show that fipronil is poorly absorbed through the skin. Fipronil spreads over the skin via translocation

following application, and is stored in the sebaceous glands, prior to being slowly eliminated with hair and sebum.

Toxicological Studies

The applicant has provided bibliographical data.

- Single Dose Toxicity

  One study found fipronil to be moderately toxic in rodents via the oral route. Clinical signs of toxicity are hunched posture, piloerection, diarrhoea, abnormal gait and excitation of the central nervous system (CNS), including convulsions. The active substance is a slight dermal irritant, but was not found to be a sensitiser in a guinea pig dermal sensitisation test.

- Repeated Dose Toxicity

  Several studies were included, which outlined the NOEL[2] in various species following administration, via oral and dermal routes. A 13-week study of neurotoxicity, where fipronil was administered orally to rats, found an NOAEL[3] of 0.3 mg/kg/day. In dogs, a one year study found a NOAEL of 0.3 mg/kg/day when fipronil was administered orally. One study in rabbits showed a NOAEL of 5mg/kg/day when fipronil was administered over 21 days via dermal administration.

- Reproductive Toxicity, including Teratogenicity:

  Suitable references were supplied for this section. In one study of reproductive toxicity, fipronil was added to the rats' diet. Fetal and reproductive toxic effects were noted at the NOEL for parental toxicity, established as 0.25 mg/kg/day. The NOAEL for reproductive effects was 2.5 mg/kg/day. In a further study developmental toxicity was not observed in rats administered fipronil by gavage on days 6-15 of gestation but there were signs of maternal toxicity. The NOAEL for maternal toxicity was 4 mg/kg/day whilst for developmental toxicity the NOAEL was established as 20 mg/kg/day, the highest dose tested. A similar study using rabbits developmental toxicity was not observed, a NOAEL of 1 mg/kg/day was established, but maternal toxicity occurred however an NOAEL was not identified.

- Mutagenicity

  Suitable references found that fipronil was not mutagenic at specified concentrations.

- Carcinogenicity:

[2] NOEL – No observable effect limit
[3] NOAEL – No observable adverse effect limit

Suitable references found that fipronil was not carcinogenic at specified concentrations.

Other Studies

The applicant has provided bibliographical data which found that fipronil is neurotoxic in repeat dose studies in rats and dogs. In a one year study dogs were administered fipronil in the diet on a daily basis. When fipronil was administered at a rate of 1 mg/kg/ day clinical signs of neurotoxicity were observed in females. The NOAEL was 0.3 mg/kg/day. In a further single dose study, rats were given fipronil by gavage and a NOAEL of 0.5 mg/kg/day was established based on neurological effects 7 hours after a 5mg/kg dose.

Observations in Humans

Several references were provided describing the symptoms of fipronil poisoning in humans. Symptoms include vomiting, nausea, conjunctivitis, oropharyngeal pain, agitation and seizures.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which describes the various means by which fipronil-containing products might come into contact with the user; by petting of the animal, spillage onto the skin or hand to mouth transfer. Warnings and precautions as listed on the product literature 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.
- Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. Wash hands after use.
- Do not smoke, drink or eat during application.
- 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.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product will be used in cats, with a risk mitigation measure to protect aquatic organisms, which may be adversely affected by the products. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residues studies were not applicable for this application, which applies only to non-food species.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant provided bibliographical data and an *in-vivo* laboratory study, which had relevance to the Safety and Efficacy sections of the report. Fipronil is a phenylpyrazole which acts against the target parasite gamma-amino butyric acid (GABA) receptors, disrupting the passage of chloride ions. Uncontrolled nervous system activity occurs, followed by death of the parasite. The selective toxicity of fipronil for insect receptors are thought to be due to the putative blocking of glutamate-activated chloride channels, which are absent in vertebrates.

Pharmacokinetics

The applicant has provided bibliographical data which show that fipronil is poorly absorbed through the skin. Fipronil spreads over the skin via translocation following application, and is stored in the sebaceous glands, prior to being slowly eliminated with hair and sebum.

Tolerance in the Target Species of Animals

The applicant has provided 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 topical application on 3 occasions at monthly intervals.

Observations were made, as appropriate, throughout the trial. No adverse effects were seen following doses up to five times the recommended dose. Cosmetic changes (spiking, crystallisation and scale formation) were observed in

all study groups, which spontaneously resolved. Suitable warnings are given in the SPC.

Bibliographical data have also been provided which identify transient drooling and intermittent vomiting as clinical effects following oral exposure to fipronil-containing products. The literature also identifies mild reactions after ocular exposure to fipronil, as well as possible hypersensitivity reactions and superficial dermal inflammation. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography provided suggests that there is very little evidence of resistance to fipronil in fleas and ticks. Adequate warnings and precautions appear on the product literature:-

- Fleas from pets often infest the animal's basket, bedding and regular resting areas such as carpets and soft furnishings which should be treated, in case of massive infestation and at the beginning of the control measures, with a suitable insecticide and vacuumed regularly.
- Avoid frequent swimming or shampooing the animal because the maintenance of effectiveness of the product in these cases has not been tested.
- For optimum control of flea problems in a multi-pet household, all dogs and cats in the household should be treated with a suitable insecticide.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted dose determination and confirmation studies. The dosage and method of administration is the same as that of the reference product.

Dose confirmation studies:

Study title	A study to determine the efficacy of a single application of a flea and tick treatment (fipronil 10% w/v topical spot on) when compared to an untreated control group against artificially induced infestations of fleas (*Ctenocephalides felis*) and ticks (*Ixodes ricinus*) on cats.
Objectives	To evaluate the efficacy of a topically applied spot on formulation of fipronil against C*tenocephlides felis* and *Ixodes ricinus* on cats under laboratory conditions.
Test site(s)	Laboratory environment, single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Fipronil 10% w/v topical spot on administered to cats, delivered at 0.50 ml per cat.

Control product/placebo	Negative control (no treatment)
Animals	Healthy young cats, 8 per group.
Outcomes/endpoints	Determine the efficacy of a hybrid spot on formulation against fleas on cats. Efficacy of the test product was compared to the negative controls up to Day 58.
Randomisation	Randomised.
Blinding	Partially blinded.
Method	After acclimatisation, animals were infested as appropriate (approximately 100 fleas per cat), or not infested, and given treatment according to their respective groups. Infestations occurred before and after application of the product, and remained on the animals for 48 hours. Flea counts were performed on several occasions, up to Day 58 for fleas.
Statistical method	Comparisons for efficacy between treated and control groups were made by two tailed tests, with a level of significance of 5%.
RESULTS	
Outcomes for endpoints	Persistent efficacy (5 weeks) against fleas was 100%.
DISCUSSION	The product was shown to be effective against the target parasites.

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 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)