Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bob Martin Fipronil 67mg Spot-on Solution for Small Dogs
Bob Martin Fipronil 134mg Spot-on Solution for Medium Dogs
Bob Martin Fipronil 268mg Spot-on Solution for Large Dogs
Bob Martin Fipronil 402mg Spot-on Solution for Extra Large Dogs

PuAR correct as of 21/01/2020 when RMS was transferred to FR. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0468/001-005/MR
Name, strength and pharmaceutical form	Bob Martin Fipronil 67mg Spot-on Solution for Small Dogs Bob Martin Fipronil 134mg Spot-on Solution for Medium Dogs Bob Martin Fipronil 268mg Spot-on Solution for Large Dogs Bob Martin Fipronil 402mg Spot-on Solution for Extra Large Dogs
Applicant	Bob Martin (UK) Ltd
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Rhipicephalus sanguineus* and *Ixodes ricinus*) infestations. Fleas will be killed within 24 h. Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. The product has a persistent acaricidal efficacy for 4 weeks against ticks (*Rhipicephalus sanguineus*, *Ixodes ricinus, Dermacentor reticulatus*). Ticks will usually be killed within 48 h after contact with Fipronil. However, if ticks of some species (*Dermacentor reticulatus)* are already present when the product is applied, all of the ticks may not be killed within the first 48 hours.

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.
Date of completion of the original mutual recognition procedure	20th March 2013
Date product first authorised in the Reference Member State (MRP only)	14th December 2011
Concerned Member States for original procedure	Austria, Cyprus, Czech Republic, France, Germany, Hungary, Malta, Netherlands, Portugal, Slovakia

I. SCIENTIFIC OVERVIEW

The products are spot-on solutions, developed as generics of Frontline Spot-On Dog. However, bioequivalence could not be demonstrated by appropriate studies, and therefore the products were deemed to be generic hybrids, whereby it was necessary for clinical endpoints to be produced. The products are administered topically to dogs, (solutions containing 10% fipronil), according to the following regimen: 1 pipette of 0.67 ml (67 mg fipronil) for dogs weighing over 2 kg and up to 10 kg bodyweight, 1 pipette of 1.34 ml (134 mg fipronil) for dogs weighing over 10 kg and up to 20 kg, 1 pipette of 2.68 ml (268 mg fipronil) for dogs weighing over 20 kg and up to 40 kg, and 1 pipette of 4.02 ml (4.2 mg fipronil) for dogs over 40 kg and up to 60 kg. Dogs over 60 kg require 2 pipettes of 2.68 ml (536 mg fipronil).

The indication is for the treatment of flea (*Ctenocephalides* spp.) and tick (*Rhipicephalus sanguineus* and *Ixodes ricinus*) infestations. Fleas will be killed within 24 h. Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. The product has a persistent acaricidal efficacy for 4 weeks against ticks (*Rhipicephalus sanguineus*, *Ixodes ricinus*, *Dermacentor reticulatus*). Ticks will usually be killed within 48 h after contact with Fipronil. However, if ticks of some species (*Dermacentor reticulatus*) are already present when the product is applied, all of 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.

The products are available in blister cards or boxes of 1, 2, 3, 4, 5 or 6 pipettes, and are contraindicated for puppies less than 2 months of age, animals outside the specified weigh range, convalescent animals, and other species, particularly rabbits.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products 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 SPC.[1]

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. 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 single-dose pipettes containing an extractable volume of 0.67 ml, 1.34 ml, 2.68 ml or 4.02 ml packaged in a clear PVC blister closed by heat sealing with aluminium foil placed in blister cards or boxes of 1, 2, 3, 4, 5 or 6 pipettes, The particulars of the containers and controls performed are provided and conform to the regulation. The absence of preservative is justified.

The products are an established pharmaceutical form and development is adequately described in accordance with the relevant European guidelines.

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, an established active substance, not described in the European Pharmacopoeia (Ph. Eur). Data on the active substance was provided in the form of an Active Substance Master File (ASMF). The active

[1] SPC – Summary of Product Characteristics.

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 and a certificate of analysis was 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 products. 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 products include those for identification of the active substance and excipients, identification 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, the shelf-life of the product as packaged for sale is 2 years.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- Shelf life of the product as packaged for sale 2 years.
- Store below 25^{o}C in a dry place in the original packaging.

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, which had relevance to both 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 provided bibliographical data, which had relevance to both the Safety and Clinical sections of the report. In the dog, fipronil spreads over the skin via translocation following application, and is stored in the sebaceous glands, prior to being slowly illiminated with hair and sebum.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

  One review stated that technical grade fipronil is acutely toxic to mammals via the inhalation and oral routes. Clinical signs of toxicity are hunched posture, piloerection, diarrhoea and abnormal gait. The active substance is a slight dermal and eye irritant, but was not found to be a sensitiser in a guinea pig dermal sensitisation test. The NOEL[2] in rats was stated as being 0.5 mg/kg. Two further studies in rats established the NOAEL[3] as being 2.5 mg/kg and 5.0 mg/kg respectively.

- Repeated Dose Toxicity

  A table was presented which outlined the NOEL in various species after administration, which was performed either dermally or orally. One 21-

  day study in rabbits found a NOEL of 5.0 mg/kg/day when fipronil was given via the oral route. In dogs, a 13-week study found a NOEL of 2.0

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

mg/kg/day for males and 0.2 mg/kg/day for females. Further dog studies performed over a year found NOELs of between 0.2 mg/kg/day (capsules) and 0.3 mg/kg/day (diet). A further study in rats given fipronil via the oral route showed a NOEL of 0.019 mg/kg/day, over a 2-year study.

- Reproductive Toxicity, including Teratogenicity

  Suitable references were provided for this section. A series of studies performed in rats where fipronil-containing product was applied topically at 70, 140 or 180 mg/kg saw an alteration to the endocrine system along with adverse reproductive effects in female rats. A further study in rats saw a NOEL for reproductive toxicity of 2.54 mg/kg (males) and 2.74 mg/kg (females), which was above the level for parental toxicity. Another developmental study saw a NOEL in rats of 20 mg/kg/day, with a maternal toxicity NOEL of 4 mg/kg/day. No teratogenic effects were observed.

- Mutagenicity

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

- Carcinogenicity

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

Other Studies

The applicant provided bibliographical data which found that fipronil is neurotoxic in repeat dose studies in rats and dogs. In one study a 90 oral repeat study in rats established a NOAEL of 8.9 – 10.8 mg/kg/day, with the NOEL for toxicity based on bodyweight and food consumption changes being lower at 0.3 – 0.35 mg/kg/day. In a further single dose oral acute neurotixicity study in rats, a NOAEL of 2.5 mg/kg/day was established, based on neurological effects 7 hours after a 7.5 mg/kg/day dose.

Observations in Humans

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

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which described 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.
- 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.
- 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.
- Keep pipettes in the original packaging and dispose of used pipettes immediately.

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 the products will be used in dogs, 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 products are used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant provided bibliographical data which related to both the Safety and Efficacy sections. 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 are thought to be due to the putative blocking of glutamate-activated chloride channels, which are absent in vertebrates.

Pharmacokinetics

The applicant provided bibliographical data, which had relevance to both the Safety and Clinical sections of the report. In the dog, fipronil spreads over the skin via translocation following application, and is stored in the sebaceous glands, prior to being slowly illuminated with hair and sebum.

Tolerance in the Target Species of Animals

The safety of a 10% fipronil w/v spot on solution was tested in young dogs, administered at x1, x3 and x5 the nominal dose. The product was administered at monthly intervals, on three occasions. This was a three-phase, parallel group, randomised, blind, negative controlled study performed in a suitable number of male and female dogs. Clinical examinations and blood tests were performed at various time points, up to Day 66. No adverse reactions attributable to the product were seen.

Resistance

The conclusion that little or no evidence of resistance to fipronil has been found to date was supported. Adequate warnings and precautions appear on the product literature:-

- Avoid frequent swimming or shampooing the animal because the maintenance of effectiveness of the product in these cases has not been tested.
- 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.
- For optimal control of flea infestation in 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 conducted dose determination and dose confirmation studies. The dosage matches that of the reference product, but is administered slightly differently, to two points on the dog's back.

Dose confirmation studies:

Study 1

Study title	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

	(C*tenocephlides felis*) and ticks (*Ixodes ricinus*) on dogs
Objectives	To evaluate the efficacy of a topically applied spot on formulation of fipronil against C*tenocephlides felis* and *Ixodes ricinus* on dogs 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 dogs of 10-20 kg, delivered at 1.34 ml per dog.
Control product/placebo	Negative controls (no treatment).
Animals	Healthy young dogs, 8 dogs per group
Outcomes/endpoints	Determine the efficacy of a hybrid spot on formulation against fleas and ticks on dogs. Efficacy of the test product was compared to the negative controls up to Day 30 (ticks) and Day 72 (fleas).
Randomisation	Randomised.
Blinding	Partially blinded.
Method	After acclimatisation, animals were infested as appropriate (approximately 100 fleas per dog, or approximately 50 fleas per dog), 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. Tick and flea counts were performed on several occasions, from Day 2 up to Day 30 for ticks and from Day 2 to Day 72 for fleas, after treatment.
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 (2 months) against fleas was 100%, with 95% immediate efficacy. Persistent efficacy against ticks (4 weeks) was >90. No treatment-related adverse events were seen.
DISCUSSION	The product was shown to be effective against the target parasites.

Study 2

Study title	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 two species of tick (*Dermacentor reticulatus* and *Rhipecephalus sanguineus*) on dogs
Objectives	To evaluate the efficacy of a topically applied spot on formulation of fipronil against *Dermacentor reticulatus* and *Rhipecephalus sanguineus* on dogs 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 dogs of 10-20 kg, delivered at 1.34 ml per dog.
Control product/placebo	Negative controls (no treatment).
Animals	Healthy young dogs, 8 dogs per group
Outcomes/endpoints	Determine the efficacy of a hybrid spot on formulation against ticks on dogs. Efficacy of the test product was compared to the negative controls up to Day 30.
Randomisation	Randomised.
Blinding	Partially blinded.
Method	After acclimatisation, animals were infested as appropriate (approximately 50 ticks per dog), and treated according to their respective groups. Infestations occurred before and after application of the product, and remained on the animals for 48 hours. Tick counts were performed on several occasions, up to Day 30
Statistical method	Comparisons for efficacy between treated and control groups were made by two tailed tests, with a level of significance of 5%. ANOVA was also utilised.
RESULTS	
Outcomes for endpoints	Persistent efficacy against ticks (4 weeks) was >90%. No treatment-related adverse events were seen.
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)