Veterinary Medicines Directorate

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

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bob Martin Clear Spot On Solution 67 mg for Small dogs
Bob Martin Clear Spot On Solution 134 mg for Medium dogs
Bob Martin Clear Spot On Solution 268 mg for Large dogs
Bob Martin Clear Spot On Solution 402 mg for Extra Large dogs

Bob Martin Clear Fipronil 67 mg solution spot on for Small dogs
Bob Martin Clear Fipronil 134 mg solution spot on for Medium dogs
Bob Martin Clear Fipronil 268 mg solution spot on for Large dogs
Bob Martin Clear Fipronil 402 mg solution spot on for Extra Large dogs
(ES)

Bob Martin Vetcare Spot on Fipronil solution 67 mg for Small dogs
Bob Martin Vetcare Spot on Fipronil solution 134 mg for Medium dogs
Bob Martin Vetcare Spot on Fipronil solution 268 mg for Large dogs
Bob Martin Vetcare Spot on Fipronil solution 102 mg for Extra Large dogs
(FR)

Bob Martin Clear 67 mg Spot On Solution for Small dogs
Bob Martin Clear 134 mg Spot On Solution for Medium dogs
Bob Martin Clear 268 mg Spot On Solution for Large dogs
Bob Martin Clear 402 mg Spot On Solution for Extra Large dogs
(PL)
Fleaclear Spot-on Solution 67 mg for Small dogs
Fleaclear Spot-on Solution 134 mg for Medium dogs
Fleaclear Spot-on Solution 268 mg for Large dogs
Fleaclear Spot-on Solution 402 mg for Extra Large dogs
(IT)

Kruidvat Flea Drops 67 mg solution for Small dogs
Kruidvat Flea Drops 134 mg solution for Medium dogs
Kruidvat Flea Drops 268 mg solution for Large dogs
Kruidvat Flea Drops 402 mg solution for Extra Large dogs
(NL)

Date Created: June 2011

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/0590/002-5/MR
Name, strength and pharmaceutical form	Bob Martin Clear Spot On Solution 67 mg for Small dogs Bob Martin Clear Spot On Solution 134 mg for Medium dogs Bob Martin Clear Spot On Solution 268 mg for Large dogs Bob Martin Clear Spot On Solution 402 mg for Extra Large dogs
Applicant	Bob Martin (UK) Ltd Wemberham Lane Yatton North Somerset BS49 4BS
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea infestations (*Ctenocephalides felis*). Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. Treatment of tick (*Rhipicephalus sanguineus* and *Ixodes ricinus*) infestations. The product has persistent acaricidal efficacy for up to 4 weeks against ticks (*Rhipicephalus sanguineus, Ixodes ricinus, Dermacentor reticulatus*). If *Dermacentor reticulatus* ticks are already present when the product is applied, not all of the ticks may be killed within 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.
Date of completion of the mutual recognition procedure	27 July 2016
Date product first authorised in the Reference Member State	27 May 2011
Concerned Member States for original procedure	United Kingdom

I. SCIENTIFIC OVERVIEW

These were generic hybrid applications submitted, for four strengths, in accordance with Article 13 (3) of Directive 2001/82/EC. The reference product was Frontline Spot on Dog 10% w/v spot on solution which has been marketed in the UK since 1996. Bioequivalence with the reference product was not demonstrated by bioavailability studies but by clinical equivalence.

These products (all 10% w/v) are indicated for:

The treatment of flea infestations (*Ctenocephalides felis*); insecticidal efficacy against new infestations with adult fleas persists for 8 weeks.

The treatment of tick (*Rhipicephalus sanguineus* and *Ixodes ricinus*) infestations; the product has persistent acaricidal efficacy for up to 4 weeks against ticks (*Rhipicephalus sanguineus, Ixodes ricinus, Dermacentor reticulatus*). If *Dermacentor reticulatus* ticks are already present when the product is applied, not all of the ticks may be killed within 48 hours, but they will be killed within a week.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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 [2] 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.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

These products contain fipronil 67 mg, 134 mg, 268 mg or 402 mg per pipette and excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), propylene glycol, benzyl alcohol and diethylene glycol monoethyl ether.

The container/closure system consists of a polypropylene single-dose pipette containing an extractable volume packaged in a clear PVC blister closed by heat sealing with aluminium foil and placed in a carton box or blister card. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of a simple mixing and filling process.

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

II.C. Control of Starting Materials

The active substance is fipronil an established active substance for which data was provided in the form of an active substance master file. The active substance is manufactured in accordance with the principles of good manufacturing practice and full testing of each batch is undertaken on receipt from the suppliers.

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.

The excipients are butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol, diethylene glycol monoethyl ether and propylene glycol. All comply with their respective European Pharmacopoeial monographs. Certificates of analysis from the supplier of each excipient were provided.

II.C.4. Substances of Biological Origin

The information provided from both the suppliers of the active substance and the suppliers of the excipients confirms that there are no substances of risk. All the excipients are of non-animal origin and the manufacturing process of the final

product introduces no other substances.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. Control tests on the finished product include identification and assay of fipronil, butylhydroxyanisole and butylhydroxytoluene, visual characteristics, impurities, uniformity of dosage, moisture and microbial purity.

II.F. Stability

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product.

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. Batches were stored under VICH[3] conditions of 25°C/60% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provide in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Store below 25°C.
Store in the original packaging.
Store in a dry place.

[3] VICH – International Cooperation on Harmonisation of Technical requirements for Veterinary Medicinal Products.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

These were generic applications according to Article 13 (3), and bioequivalence with a reference product was not demonstrated by bioavailability studies but by clinical equivalence, therefore safety studies were provided.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which shows that fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA (Gamma-Amino Butyric acid) complex, binding to the chloride channel and thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarids.

Fipronil exhibits an insecticidal and acaricidal activity against fleas (*Ctenocephalides felis*), ticks (*Rhipicephalus* spp., *Ixodes* spp. including *Ixodes ricinus*) in the dog.

Fleas will be killed within 24 hours and ticks will usually be killed within 48 hours 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 applicant has also provided bibliographical data which shows that fipronil is mainly metabolised to its sulfone derivative, which also possesses insecticidal and acaricidal properties. The concentrations of fipronil on the hair decrease with time.

Toxicological Studies

The applicant has provided bibliographical data which shows that the product will not pose a risk when used as recommended. The following results were reported:

- Single Dose Toxicity

One study referenced stated that technical grade fipronil is acutely toxic to mammals via the oral and inhalation routes. In another study, the active substance was shown to cause slight dermal and eye irritation, but not sensitisation. A no observed adverse effect levels (NOAEL) in rats of 5 mg/kg was determined in both studies.

- Repeated Dose Toxicity

The studies referenced indicate that fipronil, on repeat oral dosing, causes changes in the thyroid and liver in rat studies and neurotoxicity in dogs. In the repeat dermal study in rabbits, systemic toxicity was noted. The no observed effect levels (NOEL) have been established in various studies and range from 0.2 mg/kg/day to 5 mg/kg/day.

- Reproductive Toxicity, including Teratogenicity:

The studies referenced indicate that fipronil causes reproductive effects, at doses above that causing maternal toxicity, but no teratogenic effects were reported.

- Mutagenicity

The studies referenced indicate that fipronil is not mutagenic and does not cause chromosome aberrations.

- Carcinogenicity

The studies referenced indicate that fipronil is not carcinogenic in humans.

Studies of Other Effects

The applicant has provided bibliographical data which show that fipronil induces neurotoxicity in rats, in repeat dose studies at a variety of NOEL and NOEAL.

Observations in Humans

Bibliographical data were provided which show that following exposure to fipronil via ingestion, inhalation or contact, show mild symptoms including vomiting, headaches, dizziness, drowsiness, coughing, abdominal pain and skin reactions. The user safety warnings in the SPC are adequate.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows:

This product can cause mucous membrane and eye irritation.

The following warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- 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.
- People with a known hypersensitivity to fipronil or any of the other ingredients 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.

Environmental Safety

An environment risk assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The phase one assessment concluded at question three of the VICH decision tree. The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV CLINICAL DOCUMENTATION

As this is a generic application according to Article 13 (3), and bioequivalence with a reference product has not been demonstrated by bioavailability studies, efficacy studies were required.

IV.I. Pre-Clinical Studies

Pharmacology

Bibliographical data has been provided which shows that fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA (Gamma-Amino Butyric acid) complex, binding to the chloride channel and thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarids.

Fipronil exhibits an insecticidal and acaricidal activity against fleas (*Ctenocephalides felis*), ticks (*Rhipicephalus* spp., *Ixodes* spp. including *Ixodes ricinus*) in the dog. Fleas will be killed within 24 hours and ticks will usually be killed within 48 hours 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 applicant has also provided bibliographical data which shows that fipronil is mainly metabolised to its sulfone derivative, which also possesses insecticidal and acaricidal properties. The concentrations of fipronil on the hair decrease with time.

Tolerance in the Target Species

Bibliographical data have been provided which shows that in general, effects seen were transient drooling, intermittent vomiting, mild reactions to ocular exposure, possible hypersensitivity and superficial dermal inflammation. Most effects were mild and self-limiting and some were probably related to the carrier.

In two dose confirmation studies, a suitable number of animals were treated the novel product. On one group, all animals had a greasy appearance to the coat and clumping of hair at applications sites, which in some cases remained at up until 24 hours post treatment. In a second group, all animals had greasy and clumped hair which resolved after 24 hours.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography provided suggests that there is little or no evidence of resistance to fipronil. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has provided two dose confirmation studies which show that the proposed dose is in line with the reference product Frontline Spot On (Merial). The product is packed into appropriate single dose pipettes that administer the correct volume of solution for the category of the dog's bodyweight.

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 dogs.
Objectives	To determine 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 (*Ixodes ricinus)* and fleas (*C. felis)* in dogs.
Test site	Single centre within an EU country.
Compliance with Regulatory guidelines	In compliance with VICH GL9 – GCP, signed final study report provided; EMEA/CVMP/EWP/005/2000-FINAL rev. 2; local ethics committee review and approval.
Test Product	Fipronil 10% w/v topical spot on, one pipette was applied once
Control product/placebo	No treatment

Animals	16 dogs weighing between 10 and 20 kg. Inclusion criteria was: • Healthy based on veterinary examination • a minimum of 25% ticks recovered as live attached during the selection test • a minimum of 50% retention of fleas during the selection test • not pregnant • no flea and tick treatment within the three months prior to the study
Outcomes/endpoints	Reduction in the presence of fleas and ticks
Randomisation	Randomised
Blinding	Partially blinded
Method	Treatment was applied up to nine days following flea and tick infestation. (Study day 2) Re-infestation at specific time points Measure number of fleas and ticks alive at specific time points
Statistical method	The experimental unit was the individual animal. Software SAS (Version 9.2); two tailed tests with level of significance 5%.
RESULTS	
Outcomes for endpoints	Fleas –efficacy was 100% against *C. felis* at all time points. Ticks – efficacy was >90 % against *Ixodes ricinus* at all time points.
DISCUSSION	The results of this study demonstrate that Fipronil 100 mg/ml topical spot on was effective against *C. felis* from study day 2 to study day 72 inclusive and effective against *Ixodes ricinus* from study day 2 to study day 30 inclusive when applied once topically as a spot on to dogs. In addition, a single topical application of Fipronil 100 mg/ml 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 SPC cites insecticidal efficacy against new infestations with adult fleas persists for 8 weeks against *C. felis.* Persistent acaricidal efficacy is cited against *Ixodes ricinus* for up to 4 weeks.

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 two species of ticks (*Dermacentor reticulatus* and *Rhipicephalus sanguineus*) on dogs.
Objectives	To determine 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 (*Dermacentor reticulatus* and *Rhipicephalus sanguineus)* in dogs.
Test site	Single centre within an EU country.
Compliance with Regulatory guidelines	In compliance with VICH GL9 – GCP, signed final study report provided; EMEA/CVMP/EWP/005/2000-FINAL rev. 2; local ethics committee review and approval.
Test Product	Fipronil 10% w/v topical spot on
Control product/placebo	No treatment
Animals	16 dogs weighing between 10 and 20 kg. Inclusion criteria was: • Healthy based on veterinary examination • a minimum of 25% ticks recovered as live attached during the selection test • not pregnant • no flea and tick treatment within the three months prior to the study
Outcomes/endpoints	Reduction in the presence of ticks
Randomisation	Randomised
Blinding	Partially blinded
Method	Treatment was applied up to nine days following tick infestation. (Study day 2) Re-infestation at specific time points Measure number of ticks alive at specific time points
Statistical method	The experimental unit was the individual animal. Software SAS (Version 9.2); two tailed tests with level of significance 5%.
RESULTS	
Outcomes for endpoints	*D. reticulatus* – efficacy was 100% from study day 9 *R. sanguineus* – efficacy was 100% against at all time points.
DISCUSSION	Fipronil 100 mg/ml topical spot on is effective against *D. reticulatus* from study day 9 to study day 30 inclusive and effective against *R. sanguineus* from study day 2 to study day 30 inclusive when applied once topically as a spot on to dogs. In addition, a single topical application of Fipronil 100 mg/ml 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 SPC cites persistent acaricidal against *R. sanguineus* and *D. reticulatus* for up to 4 weeks.

Additional supporting bibliographical data were provided, in respect to the activity of fipronil on relevant external parasites, which support the conclusions on efficacy of the dose confirmation studies provided.

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 of the products is favourable.

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)