Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Bob Martin Clear Plus 67 mg/ 60.3 mg Spot-on Solution for Small Dogs
Bob Martin Clear Plus 134 mg/ 120.6 mg Spot-on Solution for Medium Dogs
Bob Martin Clear Plus 268 mg/ 241.2 mg Spot-on Solution for Large Dogs
Bob Martin Clear Plus 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs

Date Created: September 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Bob Martin Clear Plus 67 mg/ 60.3 mg Spot-on Solution for Small Dogs Bob Martin Clear Plus 134 mg/ 120.6 mg Spot-on Solution for Medium Dogs Bob Martin Clear Plus 268 mg/ 241.2 mg Spot-on Solution for Large Dogs Bob Martin Clear Plus 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs
Applicant	Bob Martin (UK) Ltd Wemberham Lane Yatton North Somerset BS49 4BS UK
Active substance	Fipronil (S)-methoprene
ATC Vetcode	QP53AX65
Target species	Dogs
Indication for use	For the treatment of dogs weighing 10 kg to 20 kg bodyweight - To be used against infestations with fleas, alone or in association with ticks and/or biting lice. - Treatment of flea infestations (*Ctenocephalides* spp.). Insecticidal efficacy against new infestations with adult fleas persist for 8 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for eight weeks after application. - Treatment of tick infestations (*Ixodes*

	ricinus, *Dermacentor variabilis, Dermacentor reticulatus*, *Rhipicephalus sanguineus*) The product has a persistent acaricidal efficacy for up to 4 weeks against ticks. - Treatment of infestations with biting lice (*Trichodectes canis*).

MODULE 2

The Summary of Product Characteristics (SPC) for these products are 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 conclusion of the procedure	21st August 2018

I. SCIENTIFIC OVERVIEW

These were generic 'hybrid' applications submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended. The reference products are Frontline Plus Spot on Dog small, medium, large and extra large, authorised in the UK in 2015 via MRP (informed consent).

These were determined generic 'hybrid' applications because bioequivalence could not be demonstrated. The proposed products act locally, therefore bioequivalence, (which relates to systemic exposure) could not be accepted. The principles of the biowaivers stated in the guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) were applied. The applicant claimed exemption from *in vivo* studies in accordance with Section 7.1.d) of this guideline. The proposed products are quantitatively and qualitatively identical to the reference product in terms of active substances. In terms of excipients, the proposed and reference products are qualitatively identical, but not quantitatively identical. Differences in the quantitative composition of excipients are not expected to influence the absorption and distribution of active substances in the proposed products, compared to that of the reference products. Therefore, the products can be used interchangeably, and target animal safety and efficacy for the proposed products were inferred from that of the reference products.

The products are indicated for the treatment of dogs weighing between 2 kg and 40 kg bodyweight

The products are indicated for:

- To be used against infestations with fleas, alone or in association with ticks and/or biting lice.

- Treatment of flea infestations (Ctenocephalides spp.). Insecticidal efficacy against new infestations with adult fleas persist for 8 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal

activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for eight weeks after application.

- Treatment of tick infestations (Ixodes ricinus, Dermacentor variabilis, Dermacentor reticulatus, Rhipicephalus sanguineus) The products have a persistent acaricidal efficacy for up to 4 weeks against ticks.

- Treatment of infestations with biting lice (Trichodectes canis).

The products are administered topically as a spot-on, dosed according to body weight.

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, 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain (s)-methoprene and fipronil and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), ethanol, polysorbate 80 (E433), povidone and diethylene glycol monoethyl ether.

The container/closure system consists of primary packaging, which is a white opaque polypropylene single-dose tubes containing an extractable volume of 0.67 ml, 1.34 ml, 2.68 ml and 4.02 ml. The tubes, presented in packs of 1, 2, 3, 4, 5 or 6, are packed into clear blisters made of 250 µm PVC and either 20 µm hard temper aluminium foil or heat sealable coated foil. The blisters are then packed into cartons.
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.

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

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 process in which the excipients are added and mixed with the bulk of the diethylene glycol monoethyl ether until a clear solution is formed. Fipronil is added followed by (s)-methoprene, the mixing is continued for 60 minutes to ensure a clear solution is formed. The final amount of diethylene glycol monoethyl ether is then added to make up the volume.

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

II.C. Control of Starting Materials

The active substances are fipronil and (s)-methoprene, both are established active substances described in the European Pharmacopoeia (Ph. Eur.). The active substances are manufactured in accordance with the principles of good manufacturing practice.

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

The excipients used in the final product, have monographs in the Ph. Eur. They all comply with the requirement of the current edition of the Ph. Eur.

The active substance (fipronil) obtained from two sources, is packaged either in a polyethylene bag which is placed in a aluminium foil bag and then in a fibre drum or in double-layer low density polyethylene bags packed into a fibreboard drum. Each drum typically holds 25 kg of the active substance.

The active substance ((s)-methoprene) obtained from two sources is packed either in steel drums of 60 litre capacity of more lined with a pigmented phenolic resin or in 10 litre or 20 litre high density polyethylene jars with inner and outer caps.

II.C.4. Substances of Biological Origin

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

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, colour, identification of fipronil, identification of s-methoprene, identification of butylhydroxyanisole, identification of butylhydroxytoluene, assay of fipronil, assay of (s)-methoprene, content of butylhydroxyanisole, content of butylhydroxytoluene, related substances, uniformity of dosage units, moisture and microbiological quality.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

G. Other Information

The shelf life is 18 months with the storage restrictions of 'Do not store above 25°C, Store in the original packaging and store in a dry place'.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

The products have the same qualitative and quantitative composition as the reference products, therefore no further data has been provided. This was acceptable.

Toxicological Studies

The products have the same qualitative and quantitative composition as the reference products, therefore no further data has been provided. This was acceptable.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that states that the products are of the same pharmaceutical form as the reference products have the same qualitative and quantitative composition with respect to active substances, dose rate and route of administration. The qualitative and quantitative risk to the user or a child is identical to that identified for the reference product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- Keep pipettes in original packaging until ready to use.
- This product can cause mucous membrane, skin and eye irritation. Therefore, contact of the product with mouth, skin and eyes should be avoided.
- If the product is accidentally swallowed, seek medical advice immediately and show the package leaflet to the physician.
- People with a known hypersensitivity (allergy) to insecticides or alcohol should avoid contact with the product. Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water.
- After accidental occular exposure the eye should be rinsed carefully with clean water.
- Wash hands after use.
- 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 are not allowed to sleep with owners, especially children.
- Do not smoke, drink or eat during application.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

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.

Withdrawal Periods

Not applicable

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As generic 'hybrid' products, the applicant has correctly identified that there is no requirement to provide additional data in this section of the dossier.

Tolerance in the Target Species

Tolerance studies were not required because the products are classed as generic 'hybrid'. The applicant has correctly identified that there is no requirement to provide additional data in this section of the dossier.

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.

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