Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fipronil/S-methoprene Krka 50 mg Spot-on Solution for Cats
RSPCA FleaAway Combo 50 mg/60 mg Spot-on Solution for Cats

Date Created: February 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fipronil/S-methoprene Krka 50 mg Spot-on Solution for Cats RSPCA FleaAway Combo 50 mg/60 mg Spot-on Solution for Cats
Applicant	Krka d.d., Novo mesto
Active substance	Fipronil, S-methoprene
ATC Vetcode	QP53AX65
Target species	Cats
Indication for use	To be used against infestations with fleas, alone or in association with ticks and/or biting lice: - Treatment of fleas (*Ctenocephalides* spp.). Insecticidal efficacy against new infestations with adult fleas persists for 4 weeks. Prevention of the multiplication of fleas by inhibiting the development of eggs (ovicidal activity), larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for six weeks after application. - Treatment of ticks (*Ixodes ricinus, Dermacentor variabilis, Rhipicephalus sanguineus*). The product has a persistent acaricidal efficacy for up to 2 weeks against ticks (based on experimental data). - Treatment of biting lice (*Felicola subrostratus*).

MODULE 2

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

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic duplicate applications in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	17th December 2018

I. SCIENTIFIC OVERVIEW

This application was for a generic duplicate product in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference product is Frontline Combo Spot-on Cat, authorised in the UK since January 2004. Data presented in this report are based on a subsequent product, Fleascreen Combo Spot-On Cat 50, authorised in the UK since February 2018.

The proposed product is indicated in cats against infestations with fleas, alone or in association with ticks and/or biting lice. For treatment of flea infestations (*Ctenocephalides* spp.) Insecticidal efficacy against new infestations with adult fleas persists for 4 weeks. The product inhibits the development of eggs (ovicidal activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for six weeks after application, preventing the multiplication of fleas. For treatment of tick infestations (*Ixodes ricinus, Dermacentor variabilis, Rhipicephalus sanguineus),* the product has persistent acaricidal efficacy for up to 2 weeks (based on experimental data). The product can also be used for treatment of infestations with biting lice (*Felicola subrostratus*).

The product is for administration by topical application. The minimum recommended dose is 5 mg/kg for fipronil and 6 mg/kg for S-methoprene. Dosage is one pipette of 0.5 ml per cat. The minimum treatment level is 4 weeks.

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

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

according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting marketing authorisations.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 50 mg fipronil and 60 mg S-Methoprene. The excipients are butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone (K25), polysorbate 80, ethanol 96 per cent, and diethylene glycol monoethyl ether.

The container/closure system consists of polypropylene single-dose pipettes, in aluminium foil sachets packaged in cardboard boxes containing 1, 3 or 6 pipettes. 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 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 product is manufactured by mixing the excipients to form a solution before dissolving fipronil in the solution followed by S-methoprene. The final volume is then made up with remaining diethylene glycol monoehtyl ether, the solution is filtered and finally the pipettes are filled. 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, established active substances not described in the European Pharmacopoeia. Active Substance Master Files (ASMF) have been provided for both of the active substances. The active substances are manufactured in accordance with the principles of good manufacturing practice.

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 are manufactured in accordance with their respective Ph. Eur. monographs. Certificates of analysis have been provided, and testing of the excipients is performed on receipt.

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 these products.

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 specifications control 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 include those for: appearance, density, uniformity of dosage units of the active substances, identification of the active substances, identification of excipients, related substances of the active substances, content of the active substances, content of excipients, 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. A retest period of three years has been determined for fipronil and two years for S-methoprene.

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. Data were provided for the finished product stored for 24 months and 36 months at 25°C/60%RH, and at 40°C/75%RH. A shelf life of two years has been established for the finished product.

G. Other Information

- Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
- This veterinary medicinal product does not require any special temperature storage conditions.
- Store in the original package in order to protect from light and moisture.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic duplicate application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because both the proposed product and the reference product are pharmaceutically equivalent, results of pharmacological studies are not required.

Toxicological Studies

As this is a generic duplicate application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because both the proposed product and the reference product are pharmaceutically equivalent, results of toxicological studies are not required.

User Safety

The applicant provided a User Risk Assessment (URA). The user risks are the same as those identified for the reference products and the same warnings have been included on the SPC and product literature:

- This product can cause mucous membrane, skin and eye irritation. Therefore, contact of the product with mouth, skin and eyes should be avoided.
- 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 ocular exposure the eye should be rinsed carefully in clean water.
- If the product is accidentally swallowed, seek medical advice immediately and show the package leaflet to the physician.
- Wash hands after use.
- Do not smoke, drink or eat during application.
- 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.

- Keep pipettes in original packaging until ready to use.
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Ecotoxicity

The Phase I environmental risk assessment concluded that as the product is for use in non-food animals only they pose minimal risk to the environment. Fipronil may adversely affect aquatic organisms therefore warnings and precautions are included on the product literature to ensure safety to the environment when the product is used as directed:

- Fipronil and S-methoprene may adversely affect aquatic organisms.
- Do not contaminate ponds, waterways or ditches with the product or empty container.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

As this is a generic duplicate application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because both the proposed product and the reference product are pharmaceutically equivalent, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a generic duplicate application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because both the proposed product and the reference product are pharmaceutically equivalent, results of studies investigating tolerance in the target species are not required.

Resistance

A bibliography provided for the reference product was applicable to the proposed product. The publications submitted suggested that there has been no significant change to the level of fipronil resistance in *Ctenocephalides felis* populations. No data were provided for resistance to S-methoprene or for any other ectoparasites. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials/Field Trials

As this is a generic duplicate application submitted according to Article 13 (1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be assumed because both the proposed product and the reference product are pharmaceutically equivalent, results of laboratory and field trials are not required.

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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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.

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