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

NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fipronil/S-methoprene Krka 67 mg/60.3 mg Spot-on Solution for Small Dogs
Fipronil/S-methoprene Krka 134 mg/120.6 mg Spot-on Solution for Medium Dogs
Fipronil/S-methoprene Krka 268 mg/241.2 mg Spot-on Solution for Large Dogs
Fipronil/S-methoprene Krka 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs
RSPCA FleaAway Combo 67 mg/60.3 mg Spot-on Solution for Small Dogs
RSPCA FleaAway Combo 134 mg/120.6 mg Spot-on Solution for Medium
RSPCA FleaAway Combo 268 mg/241.2 mg Spot-on Solution for Large Dogs
RSPCA FleaAway Combo 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs

Date Created: February 2019

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Fipronil/S-methoprene Krka 67 mg/60.3 mg Spot-on Solution for Small Dogs Fipronil/S-methoprene Krka 134 mg/120.6 mg Spot-on Solution for Medium Dogs Fipronil/S-methoprene Krka 268 mg/241.2 mg Spot-on Solution for Large Dogs Fipronil/S-methoprene Krka 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs RSPCA FleaAway Combo 67 mg/60.3 mg Spot-on Solution for Small Dogs RSPCA FleaAway Combo 134 mg/120.6 mg Spot-on Solution for Medium RSPCA FleaAway Combo 268 mg/241.2 mg Spot-on Solution for Large Dogs RSPCA FleaAway Combo 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs
Applicant	Krka d.d., Novo mesto
Active substance	Fipronil, S-methoprene
ATC Vetcode	QP53AX65
Target species	Dogs
Indication for use	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 persists 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 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 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 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

These applications were for generic duplicate products in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. The reference products have been authorised in the UK since January 2004 and are:

Frontline Combo Spot-on Dog S
Frontline Combo Spot-on Dog M
Frontline Combo Spot-on Dog L
Frontline Combo Spot-on Dog XL

RSPCA FleaAway Combo 67 mg/60.3 mg Spot-on Solution for Small Dogs
RSPCA FleaAway Combo 134 mg/120.6 mg Spot-on Solution for Medium
RSPCA FleaAway Combo 268 mg/241.2 mg Spot-on Solution for Large Dogs
RSPCA FleaAway Combo 402 mg/ 361.8 mg Spot-on Solution for Extra Large Dogs

Data presented in this report are based on those reports created for subsequent products, Fleascreen Combo for dogs series for small, medium, large and extra large dogs respectively, authorised in the UK since February 2018.

The proposed products are indicated in dogs against infestations with fleas, alone or in association with ticks and/or biting lice. For treatment of flea infestations (*Ctenocephalides* spp.) insecticidal activity against new infestations with adult fleas persists for 8 weeks. The products inhibit the development of eggs (ovicidal activity) and larvae and pupae (larvicidal activity) originating from eggs laid by adult fleas for eight weeks after application, preventing the multiplication of fleas. For treatment of tick infestations (*Ixodes ricinus, Dermacentor variabilis, Dermacentor reticulatus, Rhipicephalus sanguineus*), the

products have persistent acaricidal efficacy for up to 4 weeks. The products can also be used for treatment of infestations with biting lice (*Trichodectes canis*).

The products are for administration by topical application. The minimum recommended dose is 6.7 mg/kg for fipronil and 6 mg/kg for S-methoprene. For small dogs (weighing over 2 and up to 10 kg) treatment is using 1 pipette of 0.67 ml (67 mg fipronil + 60.3 mg S-methoprene). For medium dogs (weighing over 10 kg up to 20 kg) treatment is using 1 pipette of 1.34 ml (134 mg fipronil + 120.6 mg S-methoprene). For large dogs (weighing over 20 kg up to 40 kg) treatment is using one pipette of 2.68 ml (268 mg fipronil + 241.2 mg S-methoprene). For extra large dogs (weighing over 40 kg) treatment is using one pipette of 4.02 ml (402 mg fipronil + 361.8 mg S-methoprene). The minimum treatment level is 4 weeks.

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, any 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[2] of the products was demonstrated 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 products contain the active substances fipronil and S-Methoprene in various quantities as specified in the relevant SPCs. 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.

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

The products are 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 products are manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing process consists of 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 products 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 products. 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 products 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 products 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 these were generic duplicate applications submitted according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference products can be assumed because both the proposed products and the

reference products are pharmaceutically equivalent, results of pharmacological studies are not required.

Toxicological Studies

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

User Safety

The user warnings are similar to those identified for the reference products:

- 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.

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 products are 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 these were generic duplicate applications submitted according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference products can be assumed because both the proposed products and the reference products are pharmaceutically equivalent, results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

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

Resistance

A bibliography provided for the reference products was applicable to the proposed products. 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 these were generic duplicate applications submitted according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with the reference products can be assumed because both the proposed products and the reference products 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 products are 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.

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