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

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fiprotec Combo 67 mg/ 60.3 mg Spot-On Solution for Small Dogs (UK)
Fiprotec Combo 134 mg/120.6 mg Spot-On Solution for Medium Dogs (UK)
Fiprotec Combo 268 mg/241.2 mg Spot-On Solution for Large Dogs (UK)
Fiprotec Combo 402 mg/361.8 mg Spot-On Solution for Extra Large Dogs (UK)

Fyperix Combo 67 mg/ 60.3 mg Spot-On Solution for Small Dogs (DE)
Fyperix Combo 134 mg/120.6 mg Spot-On Solution for Medium Dogs (DE)
Fyperix Combo 268 mg/241.2 mg Spot-On Solution for Large Dogs (DE)
Fyperix Combo 402 mg/361.8 mg Spot-On Solution for Extra Large Dogs (DE)

Date Created: August 2017

PuAR correct as of 01/03/2018 when RMS was transferred to DE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0632/002/MR UK/V/0632/003/MR UK/V/0632/004/MR UK/V/0632/005/MR
Name, strength and pharmaceutical form	Fiprotec Combo 67 mg/ 60.3 mg Spot-On Solution for Small Dogs Fiprotec Combo 134 mg/120.6 mg Spot-On Solution for Medium Dogs Fiprotec Combo 268 mg/241.2 mg Spot-On Solution for Large Dogs Fiprotec Combo 402 mg/361.8 mg Spot-On Solution for Extra Large Dogs
Applicant	KRKA, d.d., Novo mesto Šmarješka cesta 6, 8501 Novo mesto Slovenia
Active substance(s)	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 application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of conclusion of the mutual recognition procedure	21st February 2017
Date product first authorised in the Reference Member State (MRP only)	12th October 2015
Concerned Member States for original procedure	UK, DE

I. SCIENTIFIC OVERVIEW

Fiprotec Combo Spot-On Solutions for Dogs have been developed as generics of Frontline Combo Spot-On for Dogs products. These applications are for generic products, submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The reference products, which have been authorised in the UK since 2004 are:

Frontline Combo Spot-on Dog S, 67.00 mg/60.30 mg, Spot-on Solution
Frontline Combo Spot-on Dog M, 134 mg/120.6 mg, Spot-on Solution
Frontline Combo Spot-on Dog M, 268 mg/241.20 mg, Spot-on Solution
Frontline Combo Spot-on Dog XL, 402 mg/361.8 mg, Spot-on Solution

The products contain the active substances fipronil and S-methoprene, and are indicated for the treatment of flea, tick and biting lice infestations. The products are contraindicated in puppies less than 8 weeks old and/or less than 2 kg or in sick or convalescent animals. The use of the products in non-target species is not recommended; in particular the product should not be used in rabbits as adverse reactions even mortality could occur. Do not use in cats and ferrets, as this could lead to overdosing.

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; the slight 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 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 product contains fipronil and S-methoprene as the active substance and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone (K25), polysorbate 80, ethanol 96% and diethylene glycol monoethyl ether.

The container/closure system consists of white polypropylene single-dose pipettes in aluminium foil sachets. The product is packaged in cardboard cartons 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 is 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 product is manufactured by mixing the excipients to form a solution before dissolving fipronil in the solution and then 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.

[1] SPC – Summary of Product Characteristics

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 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. The tests performed include those for identification and assay of the active substances, identification and assay of the relevant excipients, appearance, density, uniformity of dosage units and microbiological quality.

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.

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 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

- The shelf life of the finished product as packaged for sale is 2 years.
- Store below 30°C.
- 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 application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can been assumed because of the nature of the product, results of pharmacological studies are not required.

Toxicological Studies

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

User Safety

The applicant has not provided a user safety assessment as this is a generic application in accordance with Article 13(1) of Directive 2001/82/EC. The user risks are the same as those identified for the reference product 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.

Environmental Safety

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that as the product is for use in non-food animals only it poses 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.

- Dogs should not be allowed to swim in watercourses for 2 days after application.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

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

Tolerance in the Target Species

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

Resistance

The applicant has provided a bibliography to give a current overview of fipronil resistance. The publications submitted suggest 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:

- 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.

IV.II. Clinical Documentation

Laboratory Trials

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product can be

assumed because of the nature of the product, results of laboratory 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 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.

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