Veterinary Medicines Directorate

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

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Amflee Combo 67 mg/ 60.3 mg spot-on solution for small dogs (CY, IE)
Dadektin Combo 67 mg/ 60.3 mg spot-on solution for small dogs (UK)
Fyperix Combo 67 mg/ 60.3 mg spot-on solution for small dogs (PT)
Fyperix Comp vet 67 mg/ 60.3 mg spot-on solution for small dogs (FI)
Fypermid Combo 67 mg/ 60.3 mg spot-on solution for small dogs (IT)

Amflee Combo 134 mg/ 120.6 mg spot-on solution for medium dogs (CY, IE)
Dadektin Combo 134 mg/ 120.6 mg spot-on solution for medium dogs (UK)
Fyperix Combo 134 mg/ 120.6 mg spot-on solution for medium dogs (PT)
Fyperix Comp vet 134 mg/ 120.6 mg spot-on solution for medium dogs (FI)
Fypermid Combo 134 mg/ 120.6 mg spot-on solution for medium dogs (IT)

Amflee Combo 268 mg/ 241.2 mg spot-on solution for large dogs (CY, IE)
Dadektin Combo 268 mg/ 241.2 mg spot-on solution for large dogs (UK)
Fyperix Combo 268 mg/ 241.2 mg spot-on solution for large dogs (PT)
Fyperix Comp vet 268 mg/ 241.2 mg spot-on solution for large dogs (FI)
Fypermid Combo 268 mg/ 241.2 mg spot-on solution for large dogs (IT)

Amflee Combo 402 mg/ 361.8 mg spot-on solution for extra large dogs (CY, IE)
Dadektin Combo 402 mg/ 361.8 mg spot-on solution for extra large dogs (UK)
Fyperix Combo 402 mg/ 361.8 mg spot-on solution for extra large dogs (PT)
Fyperix Comp vet 402 mg/ 361.8 mg spot-on solution for extra large dogs (FI)
Fypermid Combo 402 mg/ 361.8 mg spot-on solution for extra large dogs (IT)

Date Created: May 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0660/002/DC UK/V/0660/003/DC UK/V/0660/004/DC UK/V/0660/005/DC
Name, strength and pharmaceutical form	Dadektin Combo 67 mg/60.3 mg Spot-on for Small Dogs Dadektin Combo 134mg/120.3 mg Spot-on Solution for Medium Dogs Dadektin Combo 268 mg/241.2 mg Spot-on Solution for Large Dogs Dadektin Combo 402 mg/361.8 mg Spot-on Solution for Extra Large Dogs
Applicant	Krka, d.d., Novo Mesto, Smarjeska 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 decentralised procedure	28th February 2018
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Cyprus, Finland, Ireland, Italy, Portugal

I. SCIENTIFIC OVERVIEW

These applications are for generic products, submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference products, authorised in the UK since January 2004, are Frontline Combo Spot-On Dog, a series of products exhibiting the same quantity of the active substances as those in the proposed products. The legal basis for the application, that the proposed and reference products are pharmaceutically equivalent, is consistent with the principles underlying exemption from the requirement to provide in vivo bioequivalence studies outlined in section 7.1(d) of that guideline (EMA/CVMP/016/00-Rev.2). A biowaiver is therefore supported.

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

For the treatment of flea infestations (*Ctenocephalides* spp.). Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. For the 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. For the 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*).

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released onto 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 fipronil and s-methoprene in pipettes as shown below:

Dadektin Combo 67 mg/60.3 mg Spot-on for Small Dogs (in 0.67 ml)

Dadektin Combo 134mg/120.3 mg Spot-on Solution for Medium Dogs (in 1.34 ml)

Dadektin Combo 268 mg/241.2 mg Spot-on Solution for Large Dogs (in 2.68 ml)

Dadektin Combo 402 mg/361.8 mg Spot-on Solution for Extra Large Dogs (in 4.02 ml)

The excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone (K25), polysorbate 80, ethanol 96 per cent and diethylene glycol monoethyl ether comprise the remainder of the product.

The container/closure system consists of white polypropylene single-dose pipette packaged in aluminium foil sachets. The product is provided in a cardboard box 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 products are an established pharmaceutical form and their 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 method consists of a series of dissolution and mixing steps, followed by filtration of the final solution and filling into pipettes.

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

The products are manufactured in accordance with the European Pharmacopoeia and 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. Acceptable assurances of suitability were provided.

All excipients are monographed in the Ph. Eur, and the quality of packaging materials is suitably controlled.

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 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 products are: appearance, density, uniformity of dosage form, Identification of active substances and related substances, content of active substances and key excipients and microbiological quality.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, under VICH[3] conditions, demonstrating the stability of the active substance when stored under the approved conditions. Results showed that the products were generally stable and was not affected by freezing and thawing.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 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)

For generics, insert in the relevant sections as appropriate:

III.A Safety Documentation

Due to the nature of the application, no data were required for toxicological or pharmacological assessment.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the products are safe to use when used as recommended. The recommendations are the same as those of the reference product, with additional advice.

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

- 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.

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

- 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

Phase I:

The products will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required. The products are not expected to pose a risk the environment when used as recommended in the SPC and product literature.

IV CLINICAL DOCUMENTATION

Due to the nature of the application, no pharmacological data were required.

Tolerance in the Target Species

Due to the nature of the application, no animal safety studies were required.

Resistance

A literature review was conducted. At present, there is no clinically-significant resistance amongst the target parasites which impacts on the benefit:risk balance of the products.

IV.II. Clinical Documentation

Due to the nature of the application, no efficacy studies were 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 product(s) 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 products. The current SPCs are 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 products.

The PAA for these products are available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)