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

ITCH FLEA Combo 50 mg/60 mg Spot-on Solution for Cats

Fipnil Plus 50 mg/60 mg Spot-on Solution for Cats

VetUK Flea & Tick Treatment Plus for Cats 50 mg/60 mg Spot-on Solution (Fipronil and S-Methoprene)

On Defence Plus 50 mg/60 mg Spot-on Solution for Cats

Date Created: August 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	ITCH FLEA Combo 50 mg/60 mg Spot-on Solution for Cats Fipnil Plus 50 mg/60 mg Spot-on Solution for Cats VetUK Flea & Tick Treatment Plus for Cats 50 mg/60 mg Spot-on Solution (Fipronil and S-Methoprene) On Defence Plus 50 mg/60 mg Spot-on Solution for Cats
Applicant	EU Pharmaceuticals Ltd 37 Geraldine Road London SW18 2NR
Active substance	Fipronil, S-methoprene
ATC Vetcode	QP53AX65
Target species	Cats
Indication for use	In cats: - To be used against infestations with fleas, alone or in association with ticks and/or biting lice. - Elimination 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. - Elimination 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). - Elimination 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 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	8th 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 applications were determined as generic 'hybrid' applications because bioequivalence could not be demonstrated or inferred through bioavailability studies/waivers from bioequivalence study requirements. The principle of 7.1.d) of the guideline EMA/CVMP/016/00-Rev.2 was applied for these applications, in conjunction with the data requirements outlined in section 7 of guideline EMEA/CVMP/EWP/005/2000-Rev.3 (Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats). The applicant demonstrated that there are no differences in the qualitative or quantitative composition of the test product which are expected to affect absorption, the rate and extent of distribution and persistence of the active substances. It was therefore considered that the test and reference products can be used interchangeably, and it is acceptable that the applicant has not provided any pharmacological, tolerance or clinical data. The reference product is Frontline Combo Spot-on Cat, first authorised in the UK in January 2004.

The products are indicated for the treatment of the following:

In cats:
- To be used against infestations with fleas, alone or in association with ticks and/or biting lice.
- Elimination 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.
- Elimination 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).
- Elimination of biting lice (*Felicola subrostratus*).

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 product contains 50 mg fipronil and 60 mg s-methoprene and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), ethanol anhydrous, polysorbate 80 (E433), povidone, and diethylene glycol monoethyl ether.

The container/closure system consists of a white pipette composed of a heat-formed shell of composed of polypropylene/cyclic olefin copolymer/polypropylene layer and polyethylene/ethylene vinyl alcohol/polyethylene layer. The products are presented in a variety of pack sizes from between 1 to 160 pipettes in individual foil sachets. 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.

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: addition and mixing of excipients, followed by the addition and mixing of the active substances. The product are analysed and filtered before loading into pipettes.

II.C. Control of Starting Materials

The active substances are fipronil and s-methoprene, established active substances which are not described in a pharmacopoeia but are in accordance with in-house specifications. The active substance is 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 certificates of Analysis were provided.

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

All excipients are monographed within the European Pharmacopoeia. Packaging components comply with EU specifications.

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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those for: appearance, condition of packaging, moisture content, identification and assay of the active substances, impurities, uniformity of dosage and microbial purity.

II.F. Stability

Stability data on the active substances and the finished products 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

Shelf life of the veterinary medicinal product as packaged for sale: 1 year.
Do not store above 30°C.
Store in the original package.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the applications, no toxicological or pharmacological data were required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. These were the same as those of the reference 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 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 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

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

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. The SPC and product literature carry suitable warnings:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.
- Fipronil and (S)-methoprene should not enter water courses as this may be dangerous for fish and other aquatic organisms.

IV. CLINICAL DOCUMENTATION

Pharmacology

Pharmacodynamics properties

Fipronil is an insecticide and acaricide of the phenylpyrazole family. It acts by interacting with ligand-gated chloride channels, thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of the target organisms. Fipronil kills fleas within 24 hours and ticks and lice within 48 hours of treatment.

(S)-Methoprene is a juvenile hormone analogue that inhibits the development of immature stages of insects.

5.2 Pharmacokinetic properties

Studies of metabolism of fipronil have demonstrated that the major metabolite is the sulfone derivative of fipronil.

The pharmacokinetic profiles after topical application of fipronil and (S)-methoprene in combination were studied in cats, in comparison to intravenous dosing of fipronil or (S)-methoprene alone. Topical application, with additional potential oral exposure from licking, resulted in overall systemic absorption of fipronil.

Peak fipronil plasma concentrations are rapidly attained and decline with a mean terminal half-life of approximately 25 h. Fipronil is slightly metabolised to fipronil sulfone in cats. Plasma concentrations of (S)-methoprene were generally below the limit of quantitation cats after topical application.

Both (S)-methoprene and fipronil, together with its major metabolite, are well-distributed in the haircoat of cats within one day after application. The concentrations of fipronil, fipronil sulfone and (S)-methoprene in the hair coat decrease with time and are detectable for at least 59 days after dosing. Parasites are killed through contact rather than by systemic exposure.
No pharmacological interaction between fipronil and (S)-methoprene was noted.

IV.I. Pre-Clinical Studies

Due to the nature of the applications, no pre-clinical data were required.

Tolerance in the Target Species

Due to the nature of the applications, no tolerance data were required.

Resistance

A review of the current literature was conducted. No current evidence suggests resistance to the active substances.

IV.II. Clinical Documentation

Due to the nature of the applications, no pre-clinical data were 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 product(s) is favourable.

MODULE 4

POSTAUTHORISATION 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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