Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Chanonil Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets

Eziflea Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets

Fipronil/(S)-methoprene EU Pharma 50 mg/60 mg Spot-on Solution for Cats and Ferrets

TermaFlea Combo 50 mg/60 mg Spot on Solution for Cats and Ferrets

Zeronil Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets

Zerotal Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets

Date Created: January 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Chanonil Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets, Spot-on solution Eziflea Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets Fipronil/(S)-methoprene EU Pharma 50mg /60mg Spot-on Solution for Cats and Ferrets TermaFlea Combo 50 mg/60 mg Spot on Solution for Cats and Ferrets Zeronil Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets Zerotal Plus 50 mg/60 mg Spot-on Solution for Cats and Ferrets
Applicant	EU Pharmaceuticals Ltd, 37 Geraldine Road, London, SW18 2NR
Active substance	(S)-Methoprene and Fipronil
ATC Vetcode	QP53AX65
Target species	Cats and Ferrets
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*). In ferrets: To be used against infestations with fleas, alone or in association with ticks. 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. Elimination of ticks (*Ixodes ricinus*,). The product has a persistent acaricidal efficacy for 4 weeks against ticks (based on experimental data).

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 Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	21/10/2021

I. SCIENTIFIC OVERVIEW

This was determined a generic 'hybrid' application as the active substances are not systemically acting, and bioequivalence cannot be demonstrated between the test and reference products. The reference product is Frontline Combo Spot-on Cat, marketed by Boehringer Ingelheim Animal Health UK Ltd (formerly Merial Animal Health Ltd) and first authorised in the UK in January 2004.

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, <the consumer of foodstuffs from treated animals> 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 CONSTIUENTS

II.A. Composition

The product contains Fipronil and (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

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

copolymer/polypropylene layer and polyethylene/ethylene vinyl alcohol/polyethylene layer.
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 several steps of solubilisation and mixing to produce the final solution that is filtered before being filled into the pipettes.

II.C. Control of Starting Materials

The active substances are Fipronil and (S)-Methoprene; established active substances described in the European Pharmacopoeia. The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the materials. Batch analytical data demonstrating compliance with this specification have been provided.

An ASMF was provided based on the European Pharmacopoeial monograph for fipronil. S-methoprene has no monograph in a pharmacopoeia; control specifications were provided by the applicant which were virtually identical to those in the ASMF and adequate batch analysis data were provided.

The excipients are butylhydroxyanisole (E320), butylhydroxytoluene (E321) ethanol, anhydrous, polysorbate 80 (E433), povidone, diethylene glycol monoethyl ether; these are all supplied in accordance with the relevant European Pharmacopoeia monographs.

The active substance is packed in low density polyethylene bags, contained within thermo-sealed aluminium foil bags and fibreboard drums. The specifications and supplier details for each component are adequate and the specification for the bag includes a specific IR identity test for the polymer. A declaration relating to the acceptability of the polyethylene with regard to EU requirements for food contact use was provided.

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 site have been provided demonstrating compliance with the specification. Control tests on the finished product are those for appearance, condition of packaging, identification of actives & excipients, assay, related impurities, uniformity of dosage form, seal integrity and microbial purity.

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.

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.

G. Other Information

Do not store above 30°C.
Store in the original package.
Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

II. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

The formulations are qualitatively and quantitatively the same as the reference products regarding active substances and have been demonstrated to be identical with respect to the choice and quantity of excipients. The proposed and

reference products also have the same pharmaceutical form. No data have been submitted to support the pharmacology and toxicology of the active substances and this is acceptable.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the products are generic products of the Frontline Combo Spot-On range of products for dogs. The proposed products have the same qualitative and quantitative composition as the reference products in terms of active substances and excipients. Both the reference and generic products are of the same pharmaceutical form, which is a spot-on. The products are used in the same species, at the same dose and using the same administration method as the reference products. As the qualitative and quantitative risk will be the same as those for the reference products and therefore there was no need to present further information.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. 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.
This product contains benzyl alcohol and may cause skin sensitisation or transient skin reactions in rare cases (for example, irritation, tingling).
People with a known hypersensitivity (allergy) to insecticides or alcohol should avoid contact with the product.
Do not smoke, drink or eat during application.
If contact with the skin occurs, wash hands with soap and water.
If the product gets into eyes, the eyes should be thoroughly rinsed with clean water. If skin or eye irritation persists, or the product is accidentally swallowed, seek medical advice.

Do not stroke, groom or 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.
Dispose of used pipettes immediately.
Wash hands after use.

Environmental Safety

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

Phase I:
The applicant submitted a Phase I ERA containing sufficient information to conclude that assessment ends at Phase I based on use in non-food animals only.
As fipronil and (S)-methoprene are known to be toxic to the aquatic environment, risk mitigation is stated advising that dogs should not be allowed to swim in watercourses. Appropriate disposal and risk mitigation advice is stated in the SPCs and package leaflets. The products are not expected to pose a risk for the environment when used as recommended in the SPCs.

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.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

The applications were submitted Article 13(3) of Directive 2001/82/EC, as amended by 2004/28/EC (so called 'hybrid' application) as bioequivalence (BE) between the reference and candidate formulations cannot be demonstrated since neither active substance acts systemically following topical application, both having a local action. For this reason, the claim of an exemption from BE studies under the bioequivalence guideline is not applicable to the proposed products. However, a basis for the omission of preclinical and clinical studies for qualifying generic ectoparasitic products was provided for in chapter 7 of the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3. This guideline states:

'Efficacy or tolerance studies are not considered necessary in the case that the composition (i.e., Quality and quantity of the active substance(s) and excipient(s)) and the physico-chemical properties of the generic product and the reference product are identical and the generic is to be administered at the same dose and route of administration as the reference product. If there is a difference in the qualitative or quantitative composition of the excipients which may affect absorption, the rate and extent of distribution and persistence of the active substance, further studies, e.g., dose confirmation and/or field studies, may be necessary.'

It is considered that there are no differences between the candidate and reference products that would be expected to alter the absorption, distribution

and persistence of the active substances. The product is to be administered using the same route of administration and at the same dose as the reference product. The exemption from efficacy and tolerance studies was considered to be applicable and consequently, no pharmacological data have been provided.

Tolerance in the Target Species

Tolerance studies were not required due to the legal basis of the application.

Resistance

Resistance studies were not required due to the legal basis of the application.
One published review on cat fleas (*Ctenocephalides felis*), which included resistance information obtained globally, including from the UK and Europe, was provided. The review concluded that there is little evidence of the development of resistance to fipronil / methoprene combinations when used on cats.

IV.II. Clinical Documentation

The absence of clinical documentation was justified due to the legal basis of the application, the similarities of the qualitative and quantitative compositions of the reference and candidate formulations and the fact that both are intended for topical administration and at the same dose. The proposed indications and posology are the same as those of the reference product.

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 are 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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