Veterinary Medicines Directorate

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

NATIONAL PROCEDURE
PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Chanonil Spot-on Solution Dog 67 mg
Chanonil Spot-on Solution Dog 134 mg
Chanonil Spot-on Solution Dog 268 mg
Chanonil Spot-on Solution Dog 402 mg

Eziflea Spot-on Solution Dog 67 mg
Eziflea Spot-on Solution Dog 134 mg
Eziflea Spot-on Solution Dog 268 mg
Eziflea Spot-on Solution Dog 402 mg

Fiprene Spot-on Solution Dog 67 mg
Fiprene Spot-on Solution Dog 134 mg
Fiprene Spot-on Solution Dog 268 mg
Fiprene Spot-on Solution Dog 402 mg

Fipronil EU Pharmaceuticals Spot-on Solution Dog 67 mg
Fipronil EU Pharmaceuticals Spot-on Solution Dog 134 mg
Fipronil EU Pharmaceuticals Spot-on Solution Dog 268 mg
Fipronil EU Pharmaceuticals Spot-on Solution Dog 402 mg

Zerotal Spot-on Solution Dog 67 mg
Zerotal Spot-on Solution Dog 134 mg
Zerotal Spot-on Solution Dog 268 mg
ZerotalSpot-on Solution Dog 402 mg

Johnson's Fipronil Spot-on Solution for Small Dogs 67 mg
Johnson's Fipronil Spot-on Solution for Medium Dogs 134 mg
Johnson's Fipronil Spot-on Solution for Large Dogs 268 mg
Johnson's Fipronil Spot-on Solution for Extra Large Dogs 402 mg

Date Created: October 2018

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Chanonil Spot-on Solution Dog 67 mg Chanonil Spot-on Solution Dog 134 mg Chanonil Spot-on Solution Dog 268 mg Chanonil Spot-on Solution Dog 402 mg Eziflea Spot-on Solution Dog 67 mg Eziflea Spot-on Solution Dog 134 mg Eziflea Spot-on Solution Dog 268 mg Eziflea Spot-on Solution Dog 402 mg Fiprene Spot-on Solution Dog 67 mg Fiprene Spot-on Solution Dog 134 mg Fiprene Spot-on Solution Dog 268 mg Fiprene Spot-on Solution Dog 402 mg Fipronil EU Pharmaceuticals Spot-on Solution Dog 67 mg Fipronil EU Pharmaceuticals Spot-on Solution Dog 134 mg Fipronil EU Pharmaceuticals Spot-on Solution Dog 268 mg Fipronil EU Pharmaceuticals Spot-on Solution Dog 402 mg Zerotal Spot-on Solution Dog 67 mg Zerotal Spot-on Solution Dog 134 mg Zerotal Spot-on Solution Dog 268 mg ZerotalSpot-on Solution Dog 402 mg Johnson's Fipronil Spot-on Solution for Small Dogs 67 mg Johnson's Fipronil Spot-on Solution for Medium Dogs 134 mg Johnson's Fipronil Spot-on Solution for Large Dogs 268 mg Johnson's Fipronil Spot-on Solution for Extra Large Dogs 402 mg
Applicant	EU Pharmaceuticals Ltd, 37 Geraldine Road, London, SW18 2NR
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Rhipicephalus sanguineus* and *Ixodes Ricinus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. The product has a persistent acaricidal efficacy

	for 4 weeks against ticks (*Rhipicephalus sanguineus*, *Ixodes ricinus*, *Dermacentor reticulatus*). If ticks of some species (*Dermacentor reticulatus*) are already present when the product is applied, all of the ticks may not be killed within the first 48 hours. <u>Zerotal products only:</u> The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon.

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	1st October 2018

I. SCIENTIFIC OVERVIEW

These applications were for generic 'hybrid' products, submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended. They are indicated for use in dogs of different weights, as described in the relevant Summaries of Product Characteristics, (SPCs).

The products are indicated for the treatment of flea (*Ctenocephalides* spp.) and tick (*Rhipicephalus sanguineus* and *Ixodes Ricinus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for 8 weeks.

The product has a persistent acaricidal efficacy for 4 weeks against ticks (*Rhipicephalus sanguineus*, *Ixodes ricinus* and *Dermacentor reticulatus*).

If ticks of some species (*Dermacentor reticulatus*) are already present when the product is applied, all of the ticks may not be killed within the first 48 hours.

Zerotal products only: the product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon.

These were determined a generic 'hybrid' applications because bioequivalence could not be demonstrated or inferred through bioavailability studies/waivers from bioequivalence study requirements. Bioequivalence was established via clinical equivalence. The reference product was Frontline Spot-On Dog marketed in the UK since November 1996. The proposed products were considered to have the same pharmaceutical form, active substance and similar excipients to the reference product.

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. 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 [1] of the products was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains fipronil at varying concentrations, (0.67 mg, 1.34 mg, 2.68 mg, 4.02 mg), and the excipients butylhydroxyanisole E320, butylhydroxytoluene E321, benzyl alcohol and diethylene glycol monoethyl ether

The container/closure system consists of a white opaque, pink translucent or green translucent polypropylene/cyclic olefin copolymer/polypropylene layer, polyethylene/ethylenevinyl alcohol/polyethylene layer single-dose pipette, containing an extractable volume of 0.67 ml, 1.34 ml, 2.68 ml or 4.02 ml. 1, 2, 3, 4 or 6 pipettes per pack. The pipettes are packed into individual foils and placed in a carton box. 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:
Calculation of the amount of fipronil required, add the fipronil, and excipients to a mixing vessel, mix, filter into a holding vessel, collect samples for QC, fill into labelled pipettes and pack.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is fipronil, an established active substance which is not described in a pharmacopoeia, but is presented in accordance with an active substance master file. 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 Suitability were provided.

Excipients comply with monographs within the European Pharmacopoeia, (Ph. Eur). Packaging was suitably described and justified.

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: identification and assay of the active substance and key excipients, detection of impurities, uniformity of dosage units, moisture and microbial purity.

II.F. Stability

Stability data on the active substance 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

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.

Do not store above 25°C. Store in a dry place in the original package.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Due to the nature of the applications, pharmacological and toxicological data were not required. Minor changes in the formulation of the products in comparison to the reference products were not expected to impact the safety profile of the products.

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. Therefore the following applicant's user recommendations are appropriate:

- Keep pipettes in original packaging until ready to use.
- This product can cause mucous membrane and eye irritation. Therefore, contact between the product and the mouth or eyes should be avoided.
- In the case of accidental eye contact, immediately and thoroughly flush the eyes with water. If eye irritation persists seek medical advice and show the package leaflet or the label to the physician.
- Do not smoke, drink or eat during application.
- Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. Wash hands after use.
- Ingestion of the product is harmful. Prevent children getting access to the pipettes and discard the used pipettes immediately after applying the product. In case of accidental ingestion of product seek medical advice immediately.
- Animals or people with a known hypersensitivity (allergy) to fipronil or any of the other ingredients should avoid contact with the product.
- 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 should not be allowed to sleep with owners, especially children.

Environmental Safety

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

The applicant submitted a Phase I ERA concluding that the assessment ended at Phase I, question 3. Fipronil is known to be toxic to the aquatic environment, and adequate risk mitigation is provided warning the user not to allow dogs to enter watercourses for 2 days after application. The disposal advice stated in SPCs is satisfactory. The products are not expected to pose a risk to the environment when used as recommended.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Due to the nature of the application, additional pharmacodynamic and pharmacokinetic studies were not required. The applicant provided literature reviews of the pharmacodynamic and pharmacokinetic aspects of the fipronil.

Tolerance in the Target Species

A brief overview of the current literature was provided by the applicant. The SPCs provide details on expected adverse reactions associated with fipronil – containing products, which may include transient drooling, intermittent vomiting, mild reactions to ocular exposure, hypersensitivity and dermal inflammation. None are considered serious and in some instances may be related to the excipients. An *in vivo* target animal safety study was conducted using the proposed formulation, which concluded that the formulation was well tolerated in pups from 8 weeks of age and 2 kg in bodyweight when applied at up to 5 times the recommended treatment dose on 3 occasions separated by 28 days.

Resistance

It was concluded that there is currently little or no evidence to support the occurrence of resistance by target organisms to fipronil.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted 2 *in vivo* dose confirmation studies:

Dose confirmation studies:

Study title	**Study to determine the efficacy of a single application of a flea and tick treatment (fipronil 10% w/v topical spot on) when compared to an untreated control group against artificially induced infestations of fleas (*Ctenocephalides felis*) and ticks (*Ixodes ricinus*) on dogs**
Objectives	To determine the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control against artificially induced infestation of ticks (*Ixodes ricinus)* and fleas (*Ctenocephalides felis)* in dogs.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	VICH – GL9. Good Clinical Practice.

Test Product	Proposed product delivered once as a spot-on application to each dog on study day 0.
Control product/placebo	Untreated control group – 8 animals, 4 male 4 female.
Animals	8 animals in untreated control group, 4 male 4 female. 8 animals in proposed product treatment group, 4 male 4 female. Animals were 11-87 months old on study day – 8 and weighed 11.6 – 18.1 kg on day – 2. Animals included were: • healthy based on a veterinary examination on study day -8, • bodyweight range between 10 kg and 20 kg on study days -8 and -2, • a minimum of 25% ticks recovered as live attached during a selection test, • a minimum of 50% retention of fleas during a selection test, • male dogs and female dogs, not known to be pregnant, • not treated with an ectoparasiticide, endoparasiticide with ectoparasiticide activity, or any other insecticide within three months prior to enrolment; • no evidence of skin disease at the site of application of the IVP or if they had a history of clinical signs of flea allergy dermatitis.
Outcomes/endpoints	<u>Ticks</u> Primary efficacy was the group arithmetic mean live and dead engorged tick reduction in the IVP group when compared to the control group at all time points post-treatment. <u>Fleas</u> Primary efficacy was defined as the group arithmetic mean live flea reduction in Group 2 when compared to the Control Group at all time points post treatment.
Randomisation	Randomised.
Blinding	Partially blinded.
Method	Fleas and ticks were counted and removed from the dogs approximately 48 h after infestation (48±2 h), except after the study day -2 infestation. Fleas and ticks applied on study day -2 were counted and removed on study day 2, approximately 48 h (±2 h) after application of the invented veterinary product (IVP). Study procedures: Selection test: Animals were combed free of fleas and ticks on study day -8. On study day -7 (selection test), approximately 50 *Ixodes ricinus* and approximately 100 (±3) fleas were applied to each dog.

	On study day -5 the number of live attached ticks was counted and recorded and all ticks were removed. The number of live fleas was counted and recorded and all fleas were removed. At least 25% of the ticks placed on the dog on study day -7 (and counted on study day -5) had to be recovered as live attached. At least 50% of the fleas placed on the dog on study day -7 (and counted on study day -5) had to remain on the host. Tolerance: Clinical observations were carried out on study day 0 at various timepoints. Dogs were sedated for tick infestation and tick counts. The examination for the tick count was completed before combing and flea counting. Attachment rate was calculated on the attachment of female ticks only (n=35), with at least 25% of the infested ticks required to attach to each animal at each time point to demonstrate that the tick population used was vigorous.
Statistical method	The experimental unit was the individual animal. Software SAS (Version 9.2); two tailed tests with level of significance 5% was used. Ticks: primary efficacy for ticks was defined as the group arithmetic mean live and dead engorged tick reduction in the treated group when compared to the control group at all time points post-treatment. To calculate efficacy, the following counts were used for each animal: Count of control group = number of live attached ticks (engorged or unengorged) + live free ticks. Count of test group = number of live attached ticks (engorged or unengorged) + live free ticks + number of killed attached engorged ticks The arithmetic and geometric mean tick counts were calculated for the test group on each day ticks were counted and used to calculate the percent reduction for each day ticks were counted. An effective dose was expected to provide > 90% reduction in tick counts compared to control using the following formula (Abbott's): % reduction (efficacy) = 100*[(mc – mt)/mc] Mc = geometric or arithmetic mean count of Group 1 (control); Mt = geometric or arithmetic mean count of Group 2 (product treated). Efficacy was declared at > 90% reduction compared to the Control Group. Fleas: efficacy was defined as the group arithmetic

	mean live flea reduction in Group 2 when compared to the Control Group at all time points post treatment. The arithmetic and geometric mean flea counts were calculated for each group on each day fleas were counted and used to calculate the percent reduction for each day fleas were counted. An effective dose was expected to provide ≥ 95% reduction in flea counts compared to control using the following formula (Abbott's): % reduction (efficacy) = 100*[(mc – mt)/mc] Mc = geometric or arithmetic mean count of untreated group,; Mt = geometric or arithmetic mean count of treated group (product treated). Efficacy was declared at ≥ 95% reduction compared to the Control Group. Note: determination of efficacy was based on arithmetic means only.
RESULTS	The results of this study demonstrated that the IVP was effective against *Ctenocephalides felis* from study day 2 to study day 72 inclusive, and effective *against Ixodes ricinus* from study day 2 to study day 30 inclusive, when applied once topically as a spot on to dogs. In addition, a single topical application of Fipronil 100 mg/ml topical spot on at a dose rate of 1.34 ml per dog in the bodyweight range of 10 kg to 20 kg was well tolerated. All treated animals had a greasy appearance and clumping of hair to the coat, at one or both of the application sites at various times. Minor changes in weight occurred in a small minority of animals. No abnormal clinical observations were detected during the course of the study. No clinically significant abnormal general health observations were reported for any animal during the study. Six adverse events were reported during the study. No treatment was required for five of the adverse events. One adverse event involving a lick granuloma required treatment for five days.
DISCUSSION	The results of this study supported the claims for treatment of *Ctenocephalides* spp. and *Ixodes Ricinus* infestations in dogs.

Study title	**Study to determine the efficacy of a single application of a flea and tick treatment (fipronil 10% w/v topical spot on) when compared to an untreated control group against artificially induced infestations of two species of ticks (*Dermacentor reticulatus* and *Rhipicephalus sanguineus*) on dogs**
Objectives	To determine the efficacy of a single topical application of a tick and flea treatment (Fipronil 10% w/v topical spot on) when compared to an untreated control against artificially induced infestation of two species of ticks (*Dermacentor reticulatus* and *Rhipicephalus sanguineus)* in dogs.
Test site(s)	Single-centre, EU country.
Compliance with Regulatory guidelines	VICH – GL9. Good Clinical Practice.
Test Product	Proposed product delivered once as a spot-on application to each dog on study day 0.
Control product/placebo	Untreated control group – 8 animals, 4 male 4 female.
Animals	8 animals in untreated control group, 4 male 4 female. 8 animals in proposed product treatment group, 4 male 4 female. Animals were 7-40 months old on study day – 11 and weighed 10.1 – 16.4 kg on day – 2. Animals included were: • healthy based on a veterinary examination on study day -11, • bodyweight range between 10 kg and 20 kg on study days -11 and -4, • a minimum of 25% ticks recovered as live attached during a selection test, • a minimum of 50% retention of fleas during a selection test, • male dogs and female dogs, not known to be pregnant, • not treated with an ectoparasiticide, endoparasiticide with ectoparasiticide activity, or any other insecticide within three months prior to enrolment; • no evidence of skin disease at the site of application of the IVP or if they had a history of clinical signs of flea allergy dermatitis.
Outcomes/endpoints	Primary efficacy was defined as the group arithmetic mean live and dead engorged tick reduction in the IVP group when compared to the control group at all time points post-treatment.
Randomisation	Randomised.
Blinding	Partially blinded.

Method	Ticks were counted and removed from the dogs approximately 48 h after infestation (48±2 h), except after the study day -2 infestation. Ticks applied on study day -2 were counted and removed on study day 2, approximately 48 h (±2 h) after application of the investigational veterinary product. Study procedures: Selection test: Animals were combed free of ticks on study day -11. On study day -7 (selection test), approximately 50 viable *Rhipicephalus sanguineus* ticks were applied to the dogs. On study day -5 (approximately 48±2 h post-infestation), the number of live attached ticks were counted and recorded and all ticks were removed. At least 25% of the ticks placed on the dog on study day -7 (and counted on study day -5) were to be recovered as live attached. NOTE: On study day -7, dogs were only infested with *Rhipicephalus sanguineus.* 50 *D. reticulatus* were applied on day -4. Tolerance: Clinical observations were carried out at appropriate time points on study day 0. Dogs were sedated for tick infestation and tick counts with ketamine and xylazine.
Statistical method	The experimental unit was the individual animal. Software SAS (Version 9.2); two tailed tests with level of significance 5% was used. Ticks: primary efficacy for ticks was defined as the group arithmetic mean live and dead engorged tick reduction in the treated group when compared to the control group at all time points post-treatment. To calculate efficacy, the following counts were used for each animal: Count of control group = number of live attached ticks (engorged or unengorged) + live free ticks. Count of test group = number of live attached ticks (engorged or unengorged) + live free ticks + number of killed attached engorged ticks The arithmetic and geometric mean tick counts were calculated for the test group on each day ticks were counted and used to calculate the percent reduction for each day ticks were counted. An effective dose was expected to provide > 90% reduction in tick counts compared to control using the following formula (Abbott's): % reduction (efficacy) = 100*[(mc – mt)/mc] Mc = geometric or arithmetic mean count of Group 1

	(control); Mt = geometric or arithmetic mean count of Group 2 (product treated). Efficacy was declared at > 90% reduction compared to the Control Group.
RESULTS	All animals in the IVP group 2 had a greasy appearance and/or clumping of hair and/or matting and/or spiking and/or deposits at one or both of the application sites at some or all of the +1 to +4 hour time points. In all dogs these had resolved by 24 hours. From study day -11 to study day 15, five animals assigned to the control group gained weight and three animals assigned to this group lost weight (range of weight loss was 0.2 kg to 1.2 kg); five animals assigned to the IVP group gained weight and three animals assigned to this group lost weight (range of weight loss was 0.1 kg to 0.6 kg). There was no evidence of any illness associated with this weight loss. No abnormal clinical observations were detected during the course of the study. No clinically significant abnormal general health observations were reported for any animal during the study. Three adverse events were reported during the study. They involved hair loss and small wounds. The adverse events were not considered to be related to the product. Amendments and deviations: At each time point the number of 'live attached' ticks and the tick attachment rates were calculated for Group 1 (untreated control) to confirm the vigour of the ticks for each species. A minimum of 25% of the infested ticks for each species should attach to each animal at each time point to demonstrate that the tick population was vigorous. On study day 2 five animals in the untreated control group (Group 1) had an attachment rate of < 25% (10%, 18%, 20%, 6% and 10%). The mean attachment rate for the group on Day 2 was 23.8%.
DISCUSSION	The results of this study supported the claims for treatment of *Dermacentor reticulatus* and *Rhipicephalus sanguineus* in dogs.

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 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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