College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fiprotec 50 mg Spot On Solution for Cats

Date Created: September 2014

Updated: October 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0274/2DC
Name, strength and pharmaceutical form	Fiprotec 50 mg Spot On Solution for Cats
Applicant	Beaphar B.V. Drostenkamp 3 8101 BX Raalte The Netherlands
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats
Indication for use	Treatment and prevention of flea infestations (*Ctenocephalides felis*). The duration of protection against flea infestation is 5 weeks. Treatment of tick infestations (*Ixodes ricinus*). Ticks (*Ixodes ricinus*) on the animal at time of treatment will be killed within 48 hours. Treatment does not protect against new tick infestations.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

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 completion of the original decentralised procedure	23rd April 2014.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia,, Spain, Sweden.

I. SCIENTIFIC OVERVIEW

This application was submitted as a generic 'hybrid' application, as defined under Article 13 (3) of Directive 2001/82/EC as amended. The product is intended for the treatment and prevention of flea (*Ctenocephalides felis*) infestations in cats. The duration of protection against flea infestations is 5 weeks. The products also protect against tick (*Ixodes ricinus*) infestations. Ticks on the animal at time of treamtment will be killed within 48 hours. The product does not protect against new infestations.

The product is administered topically to the skin, at 0.5 ml of product (1 pipette) per cat. The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto 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.

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

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 50 mg/ml fipronil and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), benzyl alcohol (E1519) and diethylene glycol monoethyl ether.

One container/closure system consists of a blue pipette composed of a heat-formed shell (polypropylene and acrylonitrile methyl acrylate copolymer/cyclic olefin copolymer polypropylene/polypropylene) and a film (acrylonitrile methyl acrylate copolymer/aluminium/polyester), with 1, 2, 3 or 6 pipettes in a cardboard box. Another container/closure system consists of a blue pipette is composed of a heat-formed shell (polypropylene/cyclic olefin copolymer/ethylene-vinyl alcohol copolymer/polypropylene) and a film (polyethylene terephthalate/aluminium/polypropylene).
The blue pipette is enclosed in an aluminium blister (polyethylene/polyamide/aluminium/polyamide/polyethylene and polyamide/aluminium/polyethylene), with 1, 2, 3, 4 or 6 pipettes in a cardboard box.

The choice of the formulation and the presence 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. Process validation data on the product have been presented in accordance with the relevant European guidelines. The manufacturing process is a simple mixing and adding procedure, followed by loading into pipettes.

II.C. Control of Starting Materials

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. All excipients are described in the Ph. Eur.

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. A suitable declaration was provided.

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.

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. Three batches were stored for 24 months at 25ºC/60% RH and at 6 months at 40ºC/75% RH in commercial packaging. No obvious degradation occurred.

G. Other Information

Do not store above 25°C.
Keep pipette within blister until ready for use, in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Fipronil is a phenylpyrazole which blocks gamma-amino buyric acid (GABA) receptors within the cell membranes of target parasites. The active substance is more toxic to insects than animals, partially because of the difference in sensitivity in GABA receptors.

Pharmacokinetics

A concentration gradient of fipronil passes throughout the fur of the animal. A metabolite of fipronil, fipronil sulfone also possesses insecticidal and acaricidal activity. Fipronil is shed with the fur and sebum and level decrease within the fur to approximately 3 – 4 mg/kg two months after treatment. After topical application of the active substance, adsorption of fipronil through the skin is minimal.

Toxicological Studies

No data were supplied for this section apart from a user risk assessment, as, in accordance with Article 13 (3) of Directive 2001/82/EC, these were not required. Some toxicological data were included in the user risk assessment.

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:

- Keep pipettes in original packaging until ready for use
- This product can cause mucous membrane and eye irritation. Therefore, contact of the product with mouth and eyes should be avoided.
- Persons with known hypersensitivity to fipronil or any of the excipients (see section 6.1)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 plain water.
- Do not smoke, drink or eat during application.
- 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.
- 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

A Phase I risk assessment was provided in accordance with VICH and CVMP guidelines.

Phase I:

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 directions as cited on the SPC are acceptable:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

- The product may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because the product is not intended for use in food-producing species.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

A summary of the pharmacodynamics of fipronil was presented. These data are identical to those presented for the reference product, and the omission of pharmacodynamic data from this section of the dossier was accepted. Efficacy was demonstrated by means of a dose confirmation study.

Pharmacokinetics

An overview of absorption, distribution, metabolism and elimination was provided. Target animal safety and dose confirmation studies addressed this point, and the proposed product will be used in the same species and with the same posology as the reference product. The omission of pharmacokinetic data from this section of the dossier were therefore acceptable.

Tolerance in the Target Species

The applicant conducted a controlled target animal tolerance, GCP/GLP[3]-compliant study in young animals, using multiples of the recommended dose in the target species, (1x, 3x and 5x the recommended dose). A placebo containing no active substance, but containing the excipients was used as a control. All doses were administered by the dermal route at monthly intervals for 3 consecutive months. Parameters evaluated were systemic and/or local toxicity, behaviour, physical appearance, feed intake and mortality/viability. Clinical tests were performed at various time points. No adverse effects were seen following doses up to 5x the recommended dose.

[3] GLP/GCP – Good Laboratory Practice. Good Clinical Practice.

Resistance

The bibliography provided suggested that although some resistance to fipronil has been noted, adequate warnings and precautions appear on the product literature, stating that all pets in a household be treated and that the immediate household environment and bedding should be treated.

IV.II. Clinical Documentation

Laboratory Trials

Efficacy was satisfactorily assessed via dose determination studies.

Dose confirmation studies:

Study title	Efficacy testing of a fipronil spot-on formulation against artificial flea and tick infestations on cats
Objectives	An *in vivo* dose confirmation study to assess the efficacy of 100 mg/ml fipronil against fleas and ticks on cats
Test site(s)	Single-centre site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP) Good Laboratory Practice (GLP)
Test Product	An invented medicinal product (IVP) containing fipronil at 100 mg/ml
Control product/placebo	Positive control (Frontline Spot-on Cat) and placebo containing excipients only
Animals	24 mixed breed cats, male and female.
Outcomes/endpoints	Measurement of parasites destroyed and assessment of health of animals.
Randomisation	Randomised
Blinding	Blinded
Method	12 cats in negative control group, 6 each in positive control and IVP groups. 25 ticks *(I. ricinus*) were initially administered to each animal (day -7). At day 28 50 ticks were also added. Tick counts were performed at various time points. At day -7 each animal was infested with 50 fleas, At various follow-up infestation days, a further 100 fleas were added. Fleas were combed out at various time points, and assessed as being dead or alive.
Statistical method	Ticks For the IVP and positive CP, efficacy was calculated at each time point using Abbott's formula below. Arithmetic means were used. Efficacy against ticks (%) = 100 x (m_c – m_t) / m_c where m_c is the mean number of live ticks on the

	negative control animals and m_t is the mean number of live ticks (categories t1 - t3) on IVP or positive CP treated animals. An effective dose was defined as giving >90% efficacy against ticks. <u>Fleas</u> For the IVP and positive CP, efficacy was calculated at each time point using the formula below. Arithmetic means were used. Efficacy against fleas (%) = 100 x (m_c – m_t) / m_c where m_c is the mean number of live fleas on negative control animals and m_t is the mean number of live fleas on the IVP and positive CP treated animals. An effective dose was defined as giving >95% efficacy against fleas.
RESULTS	
Outcomes for endpoints	On specific days, the mean number fleas on IVP and positive control treated animals was significantly lower than on placebo-treated animals. Efficacy was not demonstrated against ticks.
DISCUSSION	After additional data had been provided, the citation in the SPC with regard to indications was approved. Two further studies were provided.

Study title	Controlled study of the efficacy of Fiprotec 50 mg Spot-On Solution for Cats against artificial infestations of fleas ((*Ctenocephalides felis*) and ticks (*Ixodes ricinus*) in cats
Objectives	An *in vivo* dose confirmation study to assess the efficacy of a 50 mg fipronil product against fleas and ticks on cats. To test immediate and persistent efficacy
Test site(s)	Single-centre site
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	An invented medicinal product (IVP) containing fipronil at 50 mg.
Control product/placebo	Placebo containing excipients only.
Animals	16 mixed breed cats for total study, male and female.
Outcomes/endpoints	Measurement of parasites destroyed and assessment of health of animals.
Randomisation	Randomised

Blinding	Blinded
Method	IVP and placebo administered once, 7 cats selected for each group, were infested with 100 adult fleas (*C.felis*), and 50 ticks (*D. reticulatus*) at various time points. After 48 hours parasites were counted and engorgement evaluated.
Statistical method	<u>Ticks</u> Efficacy was calculated using Abbott's formula, as follows: Efficacy against ticks (%) = 100 x (m_c – m_t) / m_c where m_c is the arithmetic mean number of live ticks (categories 1-3) on dogs in the negative control group and m_t is the arithmetic mean number of live ticks (categories 1-3) and killed, engorged ticks (category 6) on dogs in the treatment group. An effective dose was defined as giving >90% efficacy against ticks. <u>Fleas</u> Efficacy was calculated using Abbott's formula, as follows: Efficacy against fleas (%) = 100 x (m_c – m_t) / m_c Where m_c is the arithmetic mean number of live fleas on the negative control group and m_t is the arithmetic mean number of live fleas on the treated group. An effective dose was defined as giving >95% efficacy against fleas.
RESULTS	
Outcomes for endpoints	On specific days, the mean number of live ticks and fleas on IVP-treated animals was significantly lower than on placebo-treated animals. For fleas 100% immediate and persistent efficacy was demonstrated. For ticks, between 34% and 97% efficacy was demonstrated (attached/engorged ticks) and 60%
DISCUSSION	The data supported the claim for immediate and persistent efficacy for fleas, showing 100% efficacy. Data were provided which supported a claim for treatment of ticks already attached to the animal; killed within 48 hours. The product does not protect against new tick infestations.

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

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

•	8 May 2020	Replace Active Substance Manufacturer
•	4 April 2019	Renewal
•	24 July 2018	Change in RMS from UK to NL.
•	29 March 2018	Change in type of container for the finished product. Change in type of container for the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack within the range of the currently approved pack sizes of the finished product. Changes to the package leaflet.
•	09 February 2018	Increase in batch size (including batch size range*) of the finished product. Addition of a manufacturer responsible for importation batch release including batch control/testing. Change in the QPPV of an existing pharmacovigilance system as described in the DDPS.
•	28 June 2016	Change in the SPC, labelling or package leaflet due to new data.
•	20 May 2015	Updates to SPC and product labelling, including the removal of flea allergy dermatitis claim. Change in pack size of the finished product.