College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Fiprotec Spray 2.5 mg/ml Cutaneous Spray, Solution for Cats and Dogs

Date Created: October 2017

Updated: October 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0275/001
Name, strength and pharmaceutical form	Fiprotec Spray 2.5 mg/ml Cutaneous Spray, Solution for Cats and Dogs
Applicant	Beaphar B.V. Drostenkamp 3 8101 BX Raalte Netherlands
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats and Dogs
Indication for use	Treatment and prevention of flea (*Ctenocephalides* spp.) and tick (*Ixodes* spp., including *Ixodes ricinus*) infestations in cats and dogs. Treatment of biting lice infestations in dogs (*Trichodectes canis*) and cats (*Felicola subrostratus*). Insecticidal efficacy against new infestations with adult fleas persists for up to 2 months in cats and up to 3 months in dogs, depending on environmental challenge. The product has a persistent acaricidal efficacy for up to one month against ticks, depending on the level of environmental challenge.

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	'Hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	26th July 2017.
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Croatia, Czech Republic, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, The Netherlands, Poland, Portugal, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

This was determined a generic 'hybrid' application, in accordance with Article 13 (3) of Directive 2001/82/EC as amended, because the product is locally-acting and therefore bioequivalence with the reference product could not be demonstrated or inferred through bioavailability studies. The reference product is Frontline 0.25% w/v Cutaneous Spray Solution, authorised in the UK since December 1994.

Fiprotec Spray 2.5 mg/ml Cutaneous Spray, Solution for Cats and Dogs is indicated for use for the treatment and prevention of flea (*Ctenocephalides* spp.) and tick (*Ixodes* spp., including *Ixodes ricinus*) infestations in cats and dogs. In addition the product is indicated for the treatment of biting lice infestations in dogs (*Trichodectes canis*) and cats (*Felicola subrostratus*).

The product is additionally indicated for insecticidal efficacy against new infestations with adult fleas persists for up to 2 months in cats and up to 3 months in dogs. The product has a persistent acaricidal efficacy for up to one month against ticks. Efficacy is dependent on the level of environmental challenge.

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

[1] SPC – Summary of product Characteristics.

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 2.5 mg/ml fipronil and the excipients copovidone K28, isopropyl alcohol and purified water. The choice of the formulation is justified.

The container/closure system consists of a 100ml bottle consisting of high density polyethylene, fitted with a spray pump delivering 0.5ml per pump (dip tube consisting of low density polyethylene). The particulars of the containers and controls performed are provided and conform to the regulation.

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 a simple dissolution process, followed by mixing and filling into containers. 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 described in the European Pharmacopoeia (Ph. Eur). 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 monographed in the Ph. Eur. The container complies with appropriate requirements.

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.

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Data were provided on the bulk solution, showing that it was stable for up to 4 months at 25ºC/60% RH. The intermediate product is additionally analysed with regard to appearance, identification of active substance, pH, relative density and related substances.

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 include those for: appearance, identification of active substance, pH, relative density, related substances, volumetric content and uniformity of dosage.

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. A retest period of 3 years was identified.

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. Data confirmed that the product was sufficiently stable under the conditions defined in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 1 year.

Highly flammable.

Do not store above 25 °C.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the nature of the application, the submission of pharmacological and toxicological data were not required. User safety data were noted as being almost identical to that of the reference product. An Environmental Risk Assessment (ERA) was submitted.

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Fipronil is a member of the phenylpyrazole family. It acts by inhibiting the GABA[3] complex, binding chloride channels and thereby blocking the pre- and post-synaptic transfer of chloride ions across the membrane. In insects and acarids, this results in uncontrolled activity of the central nervous system and subsequent death. Fipronil exhibits insecticidal and acaricidal activity against fleas (*Ctenocephalides* spp.), ticks (*Ixodes* spp.) and lice (*Trichodectes canis* and *Felicola subrostratus*) in dogs and cats.

Pharmacokinetics

Absorption

After application of the spray to the coat and skin, in the dog, absorption is extremely slight to negligible.

Distribution

The persistence of fipronil on the hair is very long (on average 52.5 ± 11.5 days).

Biotransformation

In all species, fipronil is mainly metabolised to its sulphone derivative (RM1602), which also possesses insecticidal and acaricidal properties.

User Safety

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 and eye irritation. Therefore, contact of the product with mouth and eyes should be avoided
- People with asthma or a known hypersensitivity to insecticides or alcohol should avoid contact with the veterinary medicinal product. Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. If irritation occurs, seek medical advice.

[3] GABA – gamma aminobutyric acid.

- After accidental ocular exposure the eye should be rinsed carefully with plain water.
- Treated animals should not be handled until the fur is dry, and children should not be allowed to play with treated animals until the fur 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.
- Spray animals in the open air or a well ventilated room.
- Do not breathe spray. Do not smoke, drink or eat during application.
- Wear PVC or nitrile gloves during treatment of animals. It is recommended to wear a waterproof apron for the protection of clothing.
- If clothing becomes heavily wetted with the product, it should be removed and washed before re-use.
- Dispose of gloves after use and then wash hands with soap and water. Wash splashes from skin with soap and water immediately. If irritation occurs, seek medical advice
- Treatment of multiple animals: Good ventilation is particularly important where several animals are to be treated. Treat multiple animals outside, or reduce the build-up of vapour by removing the animals from the treatment room while the alcohol is evaporating and ensure that the treatment room is well ventilated between individual treatments. In addition, ensure that the drying room is well ventilated and avoid housing several recently treated animals within the same air space.

Environmental Safety

The ERA was carried out 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 therefore not required. Fipronil is dangerous to aquatic life, and suitable warnings therefore appear on the SPC and product literature:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.
- Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology and Tolerance in the Target Species

Due to the nature of the application, no studies were submitted or required.

Resistance

There is evidence that strains of fleas and ticks may develop reduced susceptibility to fipronil. The warnings are the same as those for the reference product. The SPC and product literature for the product therefore carries the following information:

- The possibility that other animals in the same household can be a source of re-infection with fleas, ticks and biting lice should be considered, and these should be treated as necessary with an appropriate product.

IV.II. Clinical Documentation

Due to the nature of the application, no studies were submitted or 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

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.

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
Renewal	IIIA and IV.I	16 September 2022
Repeat use procedure to add DE (NL/V/0275/001/E/001)	-	5 June 2019
RMS change from UK to NL	N/A	24 July 2018