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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

SPOT-ON FIPRONIL 50MG CHATS APE (FR)
FIPROtec 50mg otopina za nakapavanje za mačke (HR)
Vitakraft gocce antiparassitarie A.P.E. 50mg soluzione per spot-on per gatti (IT)
Pipeta APE 50mg solução para unção punctiforme para gatos (PT)
FIPROtec 50mg kožni nanos, raztopina za mačke (SI)

DATE: 25/10/2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0322/001/MR
Name, strength and pharmaceutical form	SPOT-ON FIPRONIL 50MG CHATS APE
Applicant	BEAPHAR
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	CAT
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 website http://www.anmv.anses.fr/

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 completion of the original mutual recognition procedure	18th October 2017.
Date product first authorised in the Reference Member State (MRP only)	26th November 2016
Concerned Member States for original procedure	Croatia, Italy, Portugal, Slovenia

I. SCIENTIFIC OVERVIEW

This application was submitted under the criteria for 'hybrid' applications, where bioequivalence cannot be demonstrated due to the nature of the product, (in this case, a cutaneous solution with little or no trans-cutaneous absorption). The reference product was Frontline Spot On Cat 10% w/v Spot-On Solution, authorised in the UK since November 1996.

The indication for the product is as follows: 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. The product should not be used on kittens less than 8 weeks old and/or weighing less than 1 kg. Do not use on sick (systemic diseases, fever…) or convalescent animals. Do not use in non-target animals, especially not in rabbits and guinea pigs, as adverse reactions and even death could occur. Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

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, the slight reactions observed are indicated in the SPC.
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 of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 100 mg/ml fipronil (*i.e.* 50 mg/pipette) and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), benzyl alcohol (E1519) and diethylene glycol monoethyl ether.

The packaging of the finished product is as described on the SPC. 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.

B. Method of Preparation of the Product

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.

C. Control of Starting Materials

The active substance is fipronil, an established active substance described in the European Pharmacopoeia. 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.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. 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.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guideline, 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.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

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.

Ecotoxicity

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.

- Fipronil 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[1]-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.

[1] 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:

The applicant has conducted two dose confirmation studies blinded, randomised, negative controlled that support the efficacy of the product in accordance with the Summary of Product Characteristics.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.