ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Flevox 50 mg Spot-On Solution for Cats

PuAR correct as of 04/02/2019 when RMS was transferred to ES.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0358/001/DC
Name, strength and pharmaceutical form	Flevox 50 mg Spot-On Solution for Cats
Applicant	Vetoquinol UK Limited Steadings Barn Pury Hill Business Park Nr Alderton Towcester Northamptonshire NN12 7LS
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Cat
Indication for use	Treatment of flea (*Ctenocephalides spp.*) and tick (*Rhipicephalus sanguineus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for up to 4 weeks. Newly arriving fleas are killed within 48 hours of landing on the animal. The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD) where this has previously been diagnosed by a veterinary surgeon. The product has a persistent acaricidal efficacy for up to 1 week against ticks (*Rhipicephalus sanguineus* and *Dermacentor reticulatus)*. If ticks of *Dermacentor reticulatus* are present when the product is applied, all the ticks may not be killed within the first 48 hours, but they may be killed within a week.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13.3 of Directive 2001/82/EC as amended by Directive 2004/28/EC
Date of completion of the original decentralised procedure	23 February 2011
Concerned Member States for original procedure	Austria Belgium Bulgaria Cyprus Czech Republic Denmark Estonia Finland France Germany Greece Hungary Ireland Italy Latvia Lithuania Luxembourg Malta The Netherlands Norway Poland Portugal Romania Slovakia Slovenia Spain Sweden

I. SCIENTIFIC OVERVIEW

The application was submitted using the Decentralised Procedure in accordance with Article 13(3) of Directive 2001/82/EC as amended by 2004/28/EC, as hybrid application. The reference product is Frontline Spot on Solution, marketed by Merial.

The product is indicated for use in cats for the treatment of flea (*Ctenocephalides spp*.) and tick (*Rhipicephalus sanguineus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for up to four weeks. Newly arriving fleas are killed within 48 hours of landing on the animal. 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. The product has a persistent acaricidal efficacy for up to one week against *Rhipicephalus sanguineus and Dermacentor reticulatus.* If ticks of *Dermacentor reticulatus* are present when the product is applied, all the ticks may not be killed within the first 48 hours, but they may be killed within a week.

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[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 of the product was demonstrated according to the claims made in the SPC.

II. QUALITY ASPECTS

A. Composition

The product contains 50 mg/pipette fipronil as an active substance and butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone (K17) and diethyl glycol monoethylether as excipients.

The container/closure system consists of pipettes made of a polyacrylonitrile/ polypropylene – cyclic olefin co polymer –polypropylene/polypropylene thermoforming foil sealed with a polyacrilonitrile/aluminium/polyethylene terephthalate lid foil. Each pipette is included in one individual blister and placed in a carton box. Carton boxes contain 1, 3, 6, 30, 36 or 50 pipettes.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

[1] Summary of product characteristics

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 products have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance, fipronil, is almost unabsorbed through the skin and the formulation is designed to deposit the active substance easily onto the animal.

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.

There are four excipients used in the formulation and each has been used previously in veterinary medicines.

All the excipients used in the final product have monographs in the Ph. Eur. and each complies with the requirements of the current edition of the Ph. Eur.

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 sites have been provided demonstrating compliance with the specification.

G. 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.

H. Genetically Modified Organisms

Not applicable.

J. Other information

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

Special precautions for storage
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The studies described in this section do not reflect a normal course of treatment. Reactions to the active substance and the excipients are extremely rare when the product is used in accordance with the Summary of Product Characteristics. No adverse effects were observed in target animal safety studies in cats and kittens aged 8 weeks and older and weighing about 1 kg treated once up to five times the recommended dose.

III.A Safety Testing

Pharmacological Studies

There was no requirement to provide data for this section as the product has the same qualitative and quantitative composition of the active substance and has the same pharmaceutical form as the reference product. The pharmacodynamic and pharmacokinetic properties were comparable to those of the reference product. However, the applicant provided additional data to support this part of the application.

Pharmacodynamics:
Fipronil is a phenylpyrazole which blocks insect γ-amino butyric acid receptors, interrupting the passage of chloride ions, causing erratic central nervous system activity resulting in death of the insects or ascarids. Fipronil may block glutamate-activated chloride channels in invertebrates, increasing selective toxicity.

Pharmacokinetics:
After a local application of fipronil to the dog, it is slightly absorbed through the skin. Low levels of fipronil may be detected in the plasma, with a very high variability between dogs. After application, there is a good distribution of the chemical in the hair, presenting a good gradient of concentration between the application zone and the peripheral area.
The principal metabolite is the sulfone derivative of fipronil, which also possesses insecticidal and acaricidal properties. The concentrations of fipronil on the hair decrease with time.

Toxicological Studies

Single dose toxicity:
A series of acute single dose toxicity studies were conducted in rat, mouse and rabbit by oral, inhalation and dermal route. Clinical signs were generally noted within 24 hours of treatment and included tremors and convulsions, effects on activity or gait, hunched posture, wetness in various body parts and seizures.

Repeated dose toxicity:
The repeated dose toxicity studies were conducted in rabbit, rat and dog. These studies indicated that fipronil, on repeat oral dosing, caused changes in the thyroid and liver in rat studies and neurotoxicity in dogs. In the repeat dermal study in rabbits, hyperactivity was noted at a very high dose only.

Other Studies

Reproductive toxicity, teratogenicity and embrotoxicity
An adverse effect on reproduction was seen in the two generation oral rat study at the highest dose tested and also in the published topical rat study at very high single doses. These effects were seen at very high doses only. No teratogenic effects were noted in the studies.

Mutagenicity:
No studies indicated that fipronil produces mutagenic effects.

Carcinogenicity:
Data indicated that fipronil was not carcinogenic in humans.

Studies of other effects:
The applicant submitted three studies carried out according to GLP standards. These studies indicated that Flevox spot-on solution is not irritating to the skin or eyes and is not a skin sensitiser. The applicant also submitted five specific studies of neurotoxicity. These studies confirmed that fipronil causes neurotoxic effects when administered orally to rats and dogs.

Observations in Humans

A report was submitted which included ingestion of fipronil by a suitable number of patients. Symptoms were described as CNS toxicity with seizures, sweating, nausea, vomiting and agitation. A second report cited dermal and inhalation exposure of fipronil to a number of people whilst wearing no protective clothing. Symptoms were headache, nausea, vertigo and weakness. All symptoms were resolved after 5 hours.

User Safety

The applicant has provided a user risk assessment in compliance with the relevant guideline addressing the potential exposure routes to the operator. The following warnings and precautions as listed on the product literature and SPC are adequate to ensure safety to users of the product:

- This product can cause mucous membrane and eye irritation. Therefore, contact of the product with mouth and eyes should be avoided.
- In case of accidental eye contact, rinse immediately with plenty of water. If the irritation persists, seek medical advice and show the container or the package leaflet to the physician.
- Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and water. Wash hands after use.

- Do not smoke, drink or eat during application.
- People with a known hypersensitivity to fipronil or any excipient 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.

- Keep pipettes in the original packaging and dispose of used pipettes immediately.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The product literature highlights the fact that fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty containers.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting GABA complex, binding to the chloride channel and thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarids. Fipronil also inhibits glutamate-activated chloride channels (GloCls) which are only found in invertebrates.

Pharmacokinetics

The applicant has submitted a number of references to support the pharmacokinetics of the active substance in dogs. This is considered acceptable.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study to evaluate the tolerance of an experimental flea dermal treatment when topically administered to cats at one, three and five times the recommended dose. The cats were divided into different groups. The study concluded that there were no laboratory or histological changes and no clinical signs associated with the treatment were noted when the product was administered at one, three and five times the expected therapeutic dose over an appropriate period of time.

Resistance

A review of published data was submitted in support of this section of these applications. The potential for development of resistance to these products is similar to that of the reference products.

IV.B Clinical Studies

The applicant has provided four dose confirmation studies conducted on cats. The first study was conducted to determine the efficacy of a single application of a flea treatment when compared to reference product and a control group against artificially induced infestations of *Ctenocephalides felis*. This was a blinded, randomized, single site, dose confirmation study in accordance with EMEA/CVMP/EWP/005/2000-Rev.2. The study was conducted on target animals and a suitable number of cats were divided into different groups. The study concluded that following a single topical administration, Flevox spot-on solution was well tolerated and had demonstrated efficacy against artificial *C. felis* infestations from Day 2 to Day 51 (7 weeks).

The second study was conducted to determine the efficacy of a single application of a tick treatment when compared to a control group against artificially induced infestations of *Rhipicephalus sanguineus* on cats. This was a blinded, randomized, single site, dose confirmation study in accordance with EMEA/CVMP/EWP/005/2000-Rev.2. The study was conducted on cats and a suitable number of cats were divided into different groups. The study concluded that following a single topical administration, Flevox spot-on solution was well tolerated and had demonstrated efficacy against artificial *R. sanguineus* infestations on Day 2, 9 and 23 and although on Day 16, efficacy was not above 90%, there was a significant difference in tick counts between the treated and control groups at this time point.

The third study was conducted to determine the efficacy of a single application of a tick treatment when compared to a control group against artificially induced infestations of *Dermacentor reticulatus* on cats. It was a blinded, randomized, single site, dose-confirmation study, conducted in accordance with EMEA/CVMP/EWP/005/2000-Rev.2. The study was conducted in cats and a suitable number of cats were divided into each group. The study concluded that following a single topical administration, Flevox spot-on was well tolerated and had demonstrated efficacy against artificial *D. Reticulates* infestations on Day 9 and although on Day 2, efficacy was not above 90%, there was a significant difference in tick counts between the treated and control groups at this time point.

The fourth study was conducted to determine the efficacy of a single application of a tick treatment when compared to a control group against artificially induced infestations of *Ixodes ricinus* on cats. It was a blinded, randomized, single site, dose confirmation study, in accordance with EMEA/CVMP/EWP/005/2000-Rev.2. The study was conducted in cats and a suitable number of cats were divided into different groups. The study concluded that following a single topical administration to cats, Flevox spot-on was well tolerated and had efficacy against artificial *I. ricinus* 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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.

(www.gov.uk/check-animal-medicine-licensed)