Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

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

Date: 08 March 2018

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/
Name, strength and pharmaceutical form	Flevox 2.5 mg/ml Cutaneous Spray, Solution for Cats and Dogs
Applicant	KRKA d.d. NOVO mesto Smarjeska cesta 6 8501 Novo mesto Slovenia
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats and Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Ixodes ricinus*, *Rhipicephalus sanguineus*) infestations in dogs and cats. Treatment of biting lice infestations in dogs (*Trichodectes canis*) and cats (*Felicola subrostratus*). The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). 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 4 weeks 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 Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	25th July 2012
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom (former RMS)

I. SCIENTIFIC OVERVIEW

This was an application for a generic product, for which the reference product was Frontline Spray 0.25% w/v Cutaneous Spray Solution, marketed in the UK for more than 10 years. The product is for the treatment and prevention of flea and tick infestation in cats and dogs and may be used as part of a treatment strategy for Flea Allergy Dermatitis in these animals. The product has efficacy against *Ixodes* spp. including *Ixodes ricinus* and controls infestation caused by *Trichodectes canis* in dogs and *Felis subrostratus* in cats.

The product is applied in a pump sprayer, with suitable delivery settings available. Instructions on use are provided in the SPC, and several precautions are advised for proper administration to animals. The indicated dose is dependent on bodyweight and hair length, with the recommendation being to apply 3 to 6 ml per kg bodyweight, (7.5 mg to 15 mg of active ingredient per kg bodyweight). This equates to 6 to 12 pump applications of the 100 ml presentation, 2 to 4 pump applications of the 250 ml presentation, or 1 to 2 pump applications of the 500 ml presentation. The minimum treatment interval is four weeks, and the treatment regimen should be based on the local epidemiological situation.

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. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 2.5 mg fipronil and excipients copovidone, isopropyl alcohol and purified water.

The container/closure system consists of opaque, white, high density polyethylene bottles fitted with a pump sprayer, and comes in 100 ml, 250 ml or 500ml sizes, delivering respectively 0.5 ml, 1.5 ml or 3.0 ml of product. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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.

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 for which an Active Substance Mater File was provided. The active substance is manufactured in accordance with the principles of good manufacturing practice. All excipients are monographed in the European Pharmacopoeia.

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.

[1] SPC – Summary of Product Characteristics.

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. Tests include those relevant for the pharmaceutical form.

G. Stability

Stability data on the active substance was provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. The re-test period for the active substance was identified. Stability tests were performed on a variety of batches at long term and accelerated conditions.

H. Genetically Modified Organisms

Not applicable.

J. 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

Store below 25°C.
Highly flammable.
Protect from direct sunlight.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and essential similarity with a reference product has been successfully claimed, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III.A Safety Testing

Pharmacological Studies

As essential similarity with a reference product has been successfully claimed, results of pharmacological tests were not required.

Toxicological Studies

As essential similarity with a reference product has been successfully claimed, results of toxicological tests were not required.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which shows that because essential similarity was claimed with the reference product, no further assessment was required. Warnings and precautions as listed on the product literature 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.
- After accidental ocular exposure the eye should be rinsed carefully with plain water.
- Operators with a known hypersensitivity to the active substance or alcohol or with asthma should avoid contact with the product. Avoid contents coming into contact with the fingers. If this occurs, wash hands with soap and 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. People with known sensitivity or asthma may be particularly sensitive to the product. Do not use product if you have previously experienced a reaction to it.
- 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.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed, these matched those of the reference product.

IV CLINICAL ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, efficacy studies were not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, tolerance studies were not required. The tolerance claims for this product are equivalent to those of the reference product.

Resistance

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, resistance studies were not required. The resistance claims for this product are equivalent to those of the reference product.

IV.B Clinical Studies

Laboratory Trials

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, laboratory studies were not required.

Field Trials

As this is a generic application according to Article 13, and bioequivalence with a reference product has been successfully claimed, field studies were not 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 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 Heads of Veterinary Medicinal 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.

•	08 March 2018	Change of RMS from UK to DE
•	30 July 2015	Addition of a manufacturer of the active substance
•	28 February 2014	Addition of a site responsible for batch control testing of the finished product.
•	28 February 2014	Change in the invented name of the veterinary medicinal product in France and Spain.
•	14 February 2014	Change in the re-test period of the active substance.
•	06 February 2014	Addition of a distributor.
•	04 October 2013	Change to the invented name of the product from Amflee 2.5 mg/ml to Flevox 2.5 mg/ml.