Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DIXIE 50 mg Spot-on Solution for Cats

Date Created: May 2021

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	DIXIE 50 mg Spot-on Solution for Cats, Spot-on solution
Applicant	Sinergic Chemical S.L., C/ Zurbaran n9 piso LC Pta.DCH, Local Derecha, Madrid, 28010, Spain
Active substance	Fipronil
ATC Vetcode	QP53AX15
Target species	Cats
Indication for use	Treatment and prevention of flea infestations (*Ctenocephalides felis*). Fleas present on the animal at the time of product application will be killed within 48 hours. The product has persistent insecticidal efficacy lasting for 4 weeks against *Ctenocephalides felis* fleas. Treatment and prevention of tick infestations (*Rhipicephalus turanicus*). Ticks present on the animal at the time of product application will be killed within 48 hours. The product has persistent acaricidal efficacy for 4 weeks against *Rhipicephalus turanicus* ticks.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

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 conclusion of the procedure	17th March 2021

I. SCIENTIFIC OVERVIEW

The product is intended for use in cats, for the indications cited above. This was a generic hybrid application, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

This was determined a generic 'hybrid' application because bioequivalence could not be demonstrated or inferred through bioavailability studies, or waivers from bioequivalence study requirements. The product is not systemically acting, and bioequivalence cannot be demonstrated between the test and reference product.

The reference product is Frontline Spot On Dog 10% w/v Spot On Solution, authorised in the UK in November 1996. The dose is one pipette of 0.5 ml, per cat. The product must not be used on kittens less than 9 weeks old and/or weighing less than 1 kg, on sick (systemic diseases, fever), or convalescent animals, administered as described under 'Indications' above. The product must not be used in rabbits, as adverse reactions and even death could occur. Do not apply on wounds or damaged skin. Do not use in case 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, 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 CONSTITUENTS

II.A. Composition

The product contains 50 mg of fipronil, butylhydroxyanisole (E320), and butylhydroxytoluene (E321). Other excipients are povidone K25, polysorbate 80, 96% ethanol and diethylene glycol monoethyl ether.

The container/closure system consists of white, opaque plastic spot-on pipettes of COEX- High Density Polyethylene-Extrusion material. Each pipette is packaged in blisters composed by plastic supports (PVC-PE) to hold them and covered by a polyester / polyethylene complex. Package sizes: 1,2,3,4,5 or 6 pipettes in carton box. The particulars of the containers and controls performed are provided and conform to the regulation.

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. The manufacturing method consists of a sequential addition and mixing of the ingredients.

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 have Ph. Eur monographs. Packaging materials are acceptably controlled, and Certificates of Suitability were provided where required.

II.C.4. Substances of Biological Origin

Acceptable documentation in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products were 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. Control tests on the finished product are those for: appearance, physical properties, closure system, microbial limits, identification of active substance and content of product in the pipette.

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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Supportive pharmacodynamic and pharmacokinetic references were provided. Due to the nature of the application, (generic hybrid, the profile can be considered equal to that of the reference product), these were deemed acceptable.

Toxicological Studies

Supportive references, and consideration that the safety profile of the reference product can be considered equal to that of the reference product were acceptable.

Studies of Other Effects

Supportive references were provided for reproductive toxicity, mutagenicity, carcinogenicity, specific target organ toxicity, metabolites/impurities and immunotoxicity. The product was considered to have a positive risk/benefit profile, as outlined in the SPC and product literature.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. A NOEL[3] of 0.02 mg/kg was accepted as the oral exposure toxicological reference value for dermal exposure. All the excipients used in the formulation are found in other authorised veterinary spot-on products and are not considered of toxicological concern in the levels found in the proposed products.

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 may cause neurotoxicity. Keep stored pipettes in the original packaging until ready to use. In order to prevent children from getting access to used pipettes, dispose of used pipettes immediately.
- People with a known hypersensitivity to fipronil or any of the excipients should avoid contact with the veterinary medicinal 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 ocular exposure or irritation of the eyes during administration, these should be rinsed immediately and thoroughly with plain water. If eye irritation persists, seek medical advice immediately and show the package leaflet or the label to the physician.
- Avoid contents coming into contact with the fingers. In case of dermal exposure, wash immediately with soap and water.
- Wash hands after use.
- Do not smoke, drink or eat during application.
- Treated animals should not be handled, and children should not be allowed to play with them 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

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines. The applicant submitted a Phase I ERA containing sufficient information to conclude that assessment ends at Phase I, based on use in non-food animals only. Fipronil is known to be toxic to the aquatic

[3] NOEL – No observed effect limit.

environment and the applicant has included appropriate additional disposal advice in the SPC and product literature, advising that the product is not disposed of in waterways.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Bibliographic references were provided. Fipronil is a broad spectrum phenylpyrazole ectoparasiticide. The principal mechanism of action is blocking the passage of chloride ions through GABA-gated and glutamate-gated chloride channels in ectoparasites. This results in uncontrolled activity of the nervous system and ultimately death.

Pharmacokinetics

The applicant provided a target animal safety study and two dose confirmation studies, which supported the following statements:

Absorption
After local application of the product in the cat, absorption of fipronil through the skin is negligible.

Distribution
After topical application, the product will spread from the site of treatment to cover the entire surface of the animal. A concentration gradient of fipronil is set up on the fur of the animal extending from the point of application to the peripheral areas (lumbar zones, flanks, …).

Biotransformation
Fipronil is mainly metabolised to its sulfone derivative (RM1602), which also possesses insecticidal and acaricidal properties.

Elimination
The concentrations of fipronil on the hair decrease with time.

Tolerance in the Target Species

The applicant conducted a local tolerance study in cats, using multiples of the recommended dose in the target species. Sterile saline was used as a control.
Based on the study, the SPC and product literature accurately reflect the type and incidence of adverse effects which might be expected.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted two dose confirmation studies.

Dose confirmation studies:

Study title	Efficacy of an ectoparasitic spot-on, Dixie Fipronil 100 mg/ml Spot-on for Cats, against experimental tick (*Rhipicephalus turanicus*) and flea (*Ctenocephalides felis*) infestations on cats
Test site(s)	Single laboratory study practices, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Dixie 100 mg/ml Spot-on for Cats. The test item was applied directly to the skin between the shoulder blades. All animals received 0.5 ml of the test item.
Control product/placebo	Negative control (no treatment).
RESULTS	
Outcomes for endpoints	Sufficient efficacy was observed.
DISCUSSION	The SPC and product literature contain appropriate information for use of the product.

Study title	Efficacy of an ectoparasitic spot-on, Dixie Fipronil 100 mg/ml Spot-on for Cats, against experimental flea (*Ctenocephalides felis*) infestations on cats
Test site(s)	Single laboratory study practices, third country.
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Outcomes for endpoints	Sufficient efficacy was observed.
DISCUSSION	The SPC and product literature contain appropriate information for use of the product.

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 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 Product Information Database of the Veterinary Medicines Directorate website.

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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.

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