Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

DIXIE 67 mg Spot-on Solution for Small Dogs
DIXIE 134 mg Spot-on Solution for Medium Dogs
DIXIE 268 mg Spot-on Solution for Large Dogs
DIXIE 402 mg Spot-on Solution for Very Large Dogs

Date Created: May 2021

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	DIXIE 67 mg Spot-on Solution for Small Dogs DIXIE 134 mg Spot-on Solution for Medium Dogs DIXIE 268 mg Spot-on Solution for Large Dogs DIXIE 402 mg Spot-on Solution for Very Large Dogs
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	Dogs
Indication for use	Treatment of existing flea (*Ctenocephalides felis*) infestations and prevention of re-infestation with fleas through insecticidal effect for up to 5 weeks. One application provides immediate and persistent insecticidal efficacy and prevents new infestations by fleas up to a maximum of 5 weeks. The product prevents new infestations of *Rhipicephalus sanguineus* ticks from day 9 to day 23 after product application. The product has not demonstrated an immediate acaricidal effect, if ticks of these species 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 can be used as part of the strategy in the treatment of flea allergy dermatitis (FAD), where this has been previously diagnosed by a veterinarian.

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 applications 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 products are intended for use in dogs, for the indications cited above. These were generic hybrid applications, submitted in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

These were determined a generic 'hybrid' application because bioequivalence could not be demonstrated or inferred through bioavailability studies, or waivers from bioequivalence study requirements. The products are 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 as follows, administered as described under 'Indications' above:

67 mg (0.67 ml per pipette) product. One per dog weighing over 2 kg and up to 10 mg bodyweight.
134 mg (1.34 ml per pipette) product. One per dog weighing over 10 kg and up to 20 kg bodyweight.
268 mg (2.68 mg per pipette) product. One per dog
402 mg product (4.02 ml per pipette) dog weighing over 40 kg and up to 60 kg bodyweight.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The products are safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPCs. The efficacy [2] of the products was

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

demonstrated according to the claims made in the SPCs. The overall benefit/risk analysis is in favour of granting marketing authorisations.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The products contain fipronil as described above and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321). Other excipients are povidone, 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 products are an established pharmaceutical form and development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The products are 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

[3] NOEL – No observed effect limit.

treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children.

- Fipronil may adversely affect aquatic organisms. Dogs should not be allowed to swim in watercourses for 2 days after application.

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 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

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 dogs, using multiples of the recommended dose in the target species. 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 provided bibliographic data, one dose confirmation study and two field studies.

Dose confirmation study:

Study title	Dose confirmation study: Efficacy of a spot-on, (DIXIE, 100 mg/ml), against experimental tick (*Rhipicephalus sanguineus*) and flea (*Ctenocephalides felis*) infestations in dogs
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 Dogs. The test item was applied directly to the skin between the shoulder blades. All animals received product appropriate to bodyweight.
Control product/placebo	Negative control (no treatment).
Method	Parallel, randomised, single centre, negative controlled efficacy study.
Statistical method	Percentage efficacy was calculated for each assessment day.
RESULTS	
Outcomes for endpoints	Sufficient efficacy was observed.
DISCUSSION	The SPC and product literature contain appropriate information for use of the product.

Field studies supported authorisation of the products.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the products are used in accordance with the Summary of Product Characteristics, the benefit/risk profile of the products 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 products. The current SPCs are 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 products.

The PAA for these products are available on the Product Information Database of the Veterinary Medicines Directorate website.

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