Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

EL, IT, PL, UK: DIXIE 50 mg Spot-On solution for cats

ES, FR, PT: DIXIE Fipronil 50 mg Spot-On solution for cats

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0256/001/DC
Name, strength and pharmaceutical form	DIXIE 50 mg Spot-On solution for cats DIXIE Fipronil 50 mg Spot-On solution for cats
Applicant	QUIMICA DE MUNGUÍA S.A.
Active substance(s)	Fipronil
ATC Vet code	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.'

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

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F-DMV-25-03

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	This application is submitted in accordance with Article 13(3) of Directive 2001/82/EC, amended by Directive 2004/28/EC, so called hybrid application and it is presented under the Decentralised Procedure (according to Article 32(3) of Directive 2001/82/EC) for DIXIE fipronil 100 mg/mL Spot-On solution for Cats.
Date of completion of the original decentralised procedure	18/10/2017
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	EL, FR, IT, PL, PT, UK

I. SCIENTIFIC OVERVIEW

***For public assessment reports for the first authorisation in a range**:*

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

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The product contains fipronil (100 mg/ml) as active substance and BHT and BHA as antioxidants. Other ingredients are povidone, polysorbate 80, ethanol 96%, diethylene glycol monoethyl eter.

The container/closure system consists on 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. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is 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, which is not described in a 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.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

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

Satisfactory TSE information has been provided in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

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 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 (18 months), when stored under the approved conditions.

H. Genetically Modified Organisms

J. Other Information

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

The applicant has provided bibliographical data which show that fipronil acts by inhibiting the GABA complex, binding to the chloride channel and thereby blocking pre- and post-synaptic transfer of chloride ions across the membrane. This results in uncontrolled activity of the central nervous system and death in insects and acarids.

Pharmacokinetics

The applicant has also provided bibliographical data which show that after a local application of fipronil to the dog, it is slightly absorbed through the skin. After topical application, the product will spread from the site of treatment to cover the entire surface of the animal within 24 hours. Fipronil is mainly metabolised to its sulfone derivative (RM1602), which also possesses insecticidal and acaricidal properties. The concentrations of fipronil on the hair decrease with time.

Toxicological Studies

- Single Dose Toxicity

The applicant has provided bibliographical data, which show that fipronil exhibits moderate acute toxicity by oral route in rats and mice. Toxicological signs included hyperactivity, abnormalities of gait and posture, tremors and convulsions. By the dermal route, it is of moderate toxicity in rabbits and low toxicity in rats. The assays carried out with the formulation revealed that it is a slight skin irritant and a moderate eye irritant in rabbits and was not a skin sensitizer in guinea pigs.

  - Oral LD50[1] rats = 97 mg/kg bw
  - Oral LD50 mice = 91 mg/kg bw
  - Dermal LD50 in rabbits > 354 mg/kg bw
  - Dermal LD50 in rats > 2000 mg/kg bw.

- Repeated Dose Toxicity

Route	Specie	Duration	Results
Oral	Rat	13 weeks	NOAEL[2]: 0,3 mg/kg bw/day
Oral	Rat	2 years	NOAEL: 0,02 mg/kg bw/day
Oral	Dog	4 and 6 weeks	NOEL[3]: 1 mg/kg bw/day
Oral	Dog	13 weeks	NOEL: 0.5 mg/kg bw/day
Dermal	Rabbits	21 days	Decreased food intake and decreased bodyweight gain at 10 mg/kg and extreme hyperactivity in 2 rabbits.

- Reproductive Toxicity, including Teratogenicity:

The information on reproductive and developmental toxicity provided show that signs of maternal toxicity appear in rabbits at all doses and at relatively low doses in rats. The NOEL for developmental toxicity, however, was established at the highest dose tested.

- Mutagenicity/carcinogenicity

The information submitted show that neither fipronil nor its metabolites exhibit genotoxic potential, and, in terms of mutagenicty/carcinogenicity, can be considered equal as that of the reference product.

[1] LD50 – Lethal dose at which 50% mortality observed.
[2] NOAEL– No observed adverse event limit.
[3] NOEL – No observed effect limit.

Other Studies

The applicant has provided bibliographical data. Some signs of neurotoxicity have been detected in rats after repeated oral administration of the active substance. The formulation was a slight skin irritant and a moderate eye irritant in rabbits and was not a skin sensitizer in guinea pigs.

User Safety

The applicant has provided a user safety assessment (URA) in compliance with the relevant guidelines, which shows that DIXIE 50 mg Spot-On solution for cats might entail risk for children in the scenario where the content of an entire pipette is accidentally ingested. In order to mitigate this risk, a secondary child-resistant packaging compliant with BS EN 14375 was added. This approach is consistent with the requirements established by the EMA guideline EMA/CVMP/SWP/721059/2014, currently on draft status. The child-resistant secondary packaging permits to access only one dosage unit.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the ERA could stop in question 3 of Phase I, since the product will be used only in non food-producing animals. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

No residue depletion studies were conducted since the product is intended to be administered to a non-food producer specie.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies (pharmaceuticals only)

Tolerance in the Target Species of Animals

The applicant has conducted a controlled target animal tolerance study using multiples of the recommended dose in the target species. A placebo was used as a control. All doses were administered by topic route on 3 occasions.
Parameters evaluated were weight, behaviour, physical conditions, blood biochemistry, hematology and urinalyses.
No adverse effects were seen following doses up to 5 times the recommended dose.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The bibliography provided suggests that there are no problem in the development of resistance and no lack of efficacy due to development of resistance is expected.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

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.

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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 veterinary Heads of 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.

<None>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- *Changes to pharmacokinetic data leading to a change in the SPC*
- *Changes to toxicological data leading to a change in the SPC*
- *Changes to user safety warnings*
- *Changes to ecotoxicological information as given in the SPC or changes to disposal warnings*
- *New residue studies in new target species or tissues*
- *Reassessment of residue data or new studies resulting from changes to MRL*
- *Changes to withdrawal period*
- *Changes to target species*
- *Changes to target species tolerance data leading to change in warnings/precautions for target species*
- *New or changed indications*

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- *Name of product [Type IA: 2]*
- *Name of active substance [Type IA: 3}*
- *MAH [Type IA: 1]*
- *Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]*
- *Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]*
- *Method of preparation [Type 1B: 33]*
- *Active substance specification [Type IB: 25]*
- *CEP [Type IA/B: 15]*
- *Re-test period or storage conditions of active substance [Type IB: 17]*
- *Excipient specifications [Type 1A/B: 25]*
- *Packaging materials[Type 1A/B: 28, 29, 36, 41, 43]*
- *TSE [Type 1A: 16, 22]*
- *Shelf-life or storage conditions of the finished product [Type 1B: 42]*

Quality changes

Summary of change (Application number)	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change (Type; application number)	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	

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