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

DIPTRON 100 mg/ml spot-on solution for dogs

CORREO ELECTRÓNICO

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0202/001/DC
Name, strength and pharmaceutical form	DIPTRON 100 mg/ ml spot-on solution for dogs
Applicant	Química de Munguía, S.A.
Active substance(s)	Fipronil
ATC Vet code	QP53AX15
Target species	Dogs
Indication for use	The treatment and prevention of infestations by fleas (*Ctenocephalides* spp.,) and ticks (*Rhipicephalus* spp, *Ixodes* spp,) and as part of the treatment strategy for Flea Allergy Dermatitis, where has been previously diagnosed by a veterinary surgeon.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	24/01/2014
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	PT

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.

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II. QUALITY ASPECTS

Composition

The product contains 100 mg/ml of Fipronil and povidone, butylhydroxytoluene, butylhydroxyanisole, polisorbate 80, ethanol 96& and diethylene glycol monoethyl ether as excipients.

The product is packaged in white opaque plastic spot-on pipettes (single dose containers). The particulars of the containers and controls performed are provided and conform to the regulation.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

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.

Control of Starting Materials

The active substance is Fipronil, an established substance manufactured in accordance with the principles of good manufacturing practices.

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.

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.

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.

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III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

For generics, insert in the relevant sections as appropriate:

DIPTRON SPOT-ON DOGS is a hybrid application according to Article 13.3 of Directive 2001/82/EC, as modified by Directive 2004/28/EC.

Since this product is intended for companion animals only, no residue data need to be provided.

III.A Safety Testing

Pharmacological Studies

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.

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

The applicant has provided bibliographical data and results of acute toxicity studies carried out with the reference product which show that:

- Single Dose Toxicity
  Fipronil exhibits moderate acute toxicity by oral route in rats (LD_{50} = 97 mg/kg bw) and mice (LD_{50} = 91 mg/kg bw). Toxicological signs included hyperactivity, abnormalities of gait and posture, tremors and convulsions. By the dermal route, it is of moderate toxicity in rabbits (LD_{50} > 354 mg/kg bw) and low toxicity in rats (LD_{50} > 2000 mg/kg bw). 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.

- Repeated Dose Toxicity

Routes	Species	Duration	Results
Oral	Mice	6 weeks	LOEL: 2.4 mg/kg bw/d
Oral	Rat	13 weeks	NOAEL: 5 ppm (0.3 mg/kg bw/d)
Oral	Rat	2 years	NOAEL: 0.5 ppm (0.02 mg/kg bw/d)
Oral	Dog	4 – 6 weeks	NOEL: 1 mg/kg bw/d
Oral	Dog	13 weeks	NOEL:0.5 mg/kg bw/d
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:

  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
  Neither fipronil nor its metabolites exhibit genotoxic potential

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.

Studies on Metabolites

Regarding the metabolite fipronil-desulfinyl, the applicant has cited a range of references obtained from the "Australian Pesticides and Veterinary Medicines Authority, 2011" The available information indicates that fipronil-desulfinyl is highly toxic after either single-dose or long-term exposure but it is not a metabolite of fipronil in mammals. It is one of two photodegradation products of fipronil which can be formed in the presence of sunlight and could potentially appear in the environment or on treated surfaces. This metabolite seems to have a much greater tendency than fipronil to bind to sites in the chloride ion channel of the GABA receptor of the rat brain being more toxic for the central nervous system of mammals than the parent compound.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that there are several potential risks to the owner and their children during the application and post-application phases. These are appropriately identified, and adequate warnings and precautions are listed on the product literature in order 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 can stop in question 3 of Phase I, since the product will be used only in non food-producing animals. Given that this veterinary medicinal product is an ectoparasiticide applied topically to dogs, a recommendation for dogs not entering watercourses for two days after application has been included.

IV. CLINICAL ASSESSMENT (EFFICACY)

DIPTRON SPOT-ON DOGS is a hybrid application according to Article 13.3 of Directive 2001/82/EC, as modified by Directive 2004/28/EC.

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study using multiples of the recommended doses in the target species. A placebo was used as a control.

Resistance

The applicant has submitted a brief summary relating the current situation of fipronil resistance and no impact on the efficacy of the product is expected.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Field Trials

The applicant has conducted two field studies which show that the product has the same efficacy than the reference 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 risk benefit 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 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