DEPARTAMENTO DE
MEDICAMENTOS
VETERINARIOS

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 Ornamental Birds 0.75 mg/ml cutaneous spray solution

CORREO ELECTRÓNICO

mresvet@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 54 01
FAX: 91 822 5443

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0399/001/DC
Name, strength and pharmaceutical form	Diptron Ornamental Birds 0.75 mg/ml cutaneous spray solution
Applicant	QUIMICA DE MUNGUÍA S.A. Derio Bidea, 51 48100 Munguía- Vizcaya SPAIN
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Ornamental Birds
Indication for use	Treatment of mite's infestations by Dermanyssus gallinae in ornamental birds. In canaries, one application provided insecticidal efficacy up to 21 days: The test item showed 74.1% efficacy 16/17 days after treatment and 99.2% after 21 days.

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 12.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	24/03/21
Date product first authorised in the ReferenceMemberState (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.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 0.75 mg/ml of fipronil as active substance and povidona, isopropanol and purified water as excipients.

The container/closure system is white opaque HDPE bottle equipped with mechanical dosing pumps of HDPE/LDPE.

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.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is fipronil an established substance described in the European 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.

Scientific data have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

D. Control on intermediate products

Not applicable.

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.

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.

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 when stored under the approved conditions.

The claim of one year stability after broaching is based on the demonstration of stability for a batch broached and stored.

G. Other Information

Not applicable

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL) (*for pharmaceuticals only)*

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, it is slightly absorbed through the skin in rodents and no rodents. After topical application in dogs, fipronil spreads in the lipids of the skin and hair follicles in a short period of time (between 24 to 48 h) and continues to be released onto the skin and coat, resulting in long-lasting residual activity.
In all species fipronil is mainly metabolised to its sulphone derivative (RM 1602), which also possesses insecticidal and acaricidal properties.

Toxicological Studies

The applicant has provided bibliographical data which show that:

- 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

Routes	Species	Duration	Results
Oral	Rat	13 weeks	NOAEL: 0,3 mg/kg bw/d
Oral	Rat	2 years	NOAEL:0,02 mg/kg bw/d
Oral	Dog	4 weeks 6 weeks	NOEL: 1 mg/kg bw/d
Oral	Dog	13	NOEL:0,5 mg/kg bw/d

Routes	Species	Duration	Results
		weeks	
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.

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 in compliance with the relevant guideline which shows that the main risk of exposure is the acute indirect and direct oral contact for a child. Moreover, the product may cause eye and skin irritation. Due to the presentation of the product in the form of spray and due to the form of application of this; additional measures have been added to reduce user exposure with this product.

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

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Several bibliographic references were provided by the applicant dealing with the pharmacological properties of fipronil: the general mechanism of action is reviewed and also some aspects of the Pharmacokinetic behaviour of the compound after topical administration, in other species different to the target one, but it is acknowledged that PK information is difficult to find and very limited in general.

Tolerance in the Target Species of Animals

No target animal safety studies in accordance with the VICH GL43 have been developed with the formulation as, *if systemic exposure is known to be negligible, and there are no safety concerns, no specific tolerance study is needed, and tolerance can be demonstrated based on the field study or from published literature data*.

IV.B Clinical Studies

One DOSE CONFIRMATION STUDY has been carried out in canaries to determine the efficacy and safety of the treatment of birds infested with *Dermanyssus gallinae* with the test item.

Male and female canaries (*Serinus canaria domesticus*) were included in the study, and were artificially infested once with *Dermanyssus gallinae* mites.

The Test Item showed 74.1% efficacy 16/17 days after treatment and 99.2% after 21 days. The test item is considered to be effective at a certain time point if efficacy is at least 90%.

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.

Sequence of significant variations

Summary of change (Application number)	Approval date
Change in shelf-life of the veterinary medicinal product as packaged for sale: 3 years (ES/V/XXXX/A/070/G)	24/03/2023