IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Zeronil 50 mg Spot-on Solution for cats

PRODUCT SUMMARY

EU Procedure number	IE/V/0276/005/DC
Name, strength and pharmaceutical form	Zeronil 50 mg Spot-on Solution for cats
Active substance(s)	Fipronil
Applicant	Chanelle Pharmaceuticals Manufacturing Limited, Loughrea, Co. Galway, Ireland.
Legal basis of application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of Authorisation of procedure	21/12/2011
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp) infestations The product has a persistent insecticidal efficacy for up to 5 weeks against fleas (*Ctenocephalides* spp.). The product has not demonstrated an immediate acaricidal effect against ticks but has demonstrated persistent acaricidal efficacy for up to 2 weeks against *Ixodes ricinus* and 1 week against *Dermacentor reticulatus* and *Rhipicephalus sanguineus*. 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 a treatment strategy for Flea Allergic Dermatitis, where this has been previously diagnosed by a veterinary surgeon.
ATCvet code	QP53AX15
Concerned Member States	CY, CZ, DK, EE, EL, ES, FI, HU, IS, IT, LI, LT, LU, NL, PT, RO, SE, SI, SK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

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; only slight reactions of a cosmetic nature were observed in studies with the product and are adequately reflected 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 and were supported by proprietary dose confirmation studies.

The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A.Qualitative and Quantitative Particulars

The product contains fipronil 50 mg and the excipients butyhydroxyanisole (E320), butylhydroxytoluene (E321), benzyl alcohol and diethylene glycol monoethyl ether.
The product is packaged in white opaque, pink translucent or green translucent polypropylene single-dose pipettes containing an extractable volume of 0.5 ml packaged in a clear PVC blister closed by heat sealing with aluminium foil and placed in a carton.
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 at a licensed manufacturing site.
The product is manufactured using conventional manufacturing techniques.

C.Control of Starting Materials

The active substance is fipronil, an established active substance. 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.

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 has 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 approvedconditions.
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.

G.Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This is a generic (hybrid) application according to Article 13.3 for a spot-on formulation containing fipronil as active substance. Although this is a generic application and reference is made to a reference product Frontline Spot-on Cat (VPA 10857/004/001), *in-vivo* bioequivalence with the reference product cannot be demonstrated by means of bioavailability studies and so the applicant has provided appropriate safety/efficacy data in support of the product.

The safety and pharmaco-toxicological aspects of this product are considered to be essentially similar to those of the reference product.

Warnings and precautions as listed on the product literature are in line with those approved for the reference product and are adequate to ensure safety of the product to users, the target species (cats) and the environment.

III.A Safety Testing

Pharmacological Studies

The applicant has provided bibliographical data which show that the active substance fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA complex. This results in uncontrolled activity of the central nervous system and death of insects or acarids. Absorption of Fipronil through skin is slight and the active substance spreads to other parts of the skin in a short period of time (typically 24 to 48 hours) where it is stored in and gradually released from the sebaceous glands and hair follicles. Highest concentrations of Fipronil are to be expected at the site of application with concentrations decreasing with distance from the application site and over time.

Toxicological Studies

The applicant adequately characterised the toxicological profiles of the active substance and excipients by means of reference to published literature.
From the data provided, it could be concluded that in most animal studies, the central nervous system appears to be the target organ of toxicity. Data was also provided to characterise the toxicity profile of fipronil in a range of animals following exposure via the oral and dermal routes. Significant oral exposure has been shown to produce neurotoxic effects in rats and dogs in acute and sub-acute toxicity studies. Studies cited by the applicant indicate that fipronil affects reproductive parameters in rodents at high doses.
All excipients included in the product are considered to have well established use in veterinary medicinal products.

Observations in Humans

The applicant provided bibliographical information which showed that conjunctivitis, oro-pharyngeal pain, vomiting, headache, dizziness, abdominal pain, cough or drowsiness may occur in humans following exposure to fipronil.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline which showed that the active substance fipronil and the photodegradation product fipronil desulfinyl are considered to be the primary hazard for the user.

The routes of possible exposure were considered to be skin contact/dermal absorption during handling, administration and disposal of the product in addition to exposure following petting of the treated animal before the application site is dry. Transfer from hand to mouth is considered possible as is ocular exposure.

Based upon the user safety assessment provided, it could be concluded that the product:

- includes the same concentration of active substance (fipronil) as the reference product (Frontline Spot-on Cat)
- is intended to be administered in an identical manner and at the same frequency as approved for the reference product
- is presented in an identical pipette size as authorised for the reference product (i.e. user will be exposed to the same volume of product), and
- the same user safety advice is proposed for the product as is approved for the reference product.

It was accepted that the product will not pose any greater risk to the user than the reference product and warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline. Given that the product is intended for use in non-food producing animals, it was accepted that the risk assessment could end in Phase I of the assessment. Whilst it is known that fipronil may adversely affect aquatic organisms, the same warnings in respect of the environment as appear in the SPC of the reference product are included in the SPC for Zeronil 50 mg Spot-on Solution for Cats. In addition, the applicant has included the same disposal advice as approved for the reference product.

It was concluded that the product will not present an unacceptable risk for the environment when used in accordance with the proposed SPC.
Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13.3 and it is not possible to demonstrate bioequivalence with the reference product by means of bioavailability studies, the applicant provided the results of proprietary dose confirmation studies and a target animal tolerance study.

The efficacy claims for this product are in line with the outcomes of the studies conducted by the applicant.

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data which show that the active substance fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. It acts by inhibiting the GABA complex. This results in uncontrolled activity of the central nervous system and death of insects or acarids. Absorption of Fipronil through skin is slight and the active substance spreads to other parts of the skin in a short period of time (typically 24 to 48 hours) where it is stored in and gradually released from the sebaceous glands and hair follicles. Highest concentrations of Fipronil are to be expected at the site of application with concentrations decreasing with distance from the application site and over time.

Tolerance in the Target Species of Animals

The applicant conducted a randomised 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 topically on three occasions at four weekly intervals.
Effects were studied for clinical, biochemical, haematological and local tolerance parameters.
No adverse effects were seen following doses of up to five times the recommended dose. Skin/hair changes of a cosmetic nature were observed in the majority of animals with a trend for a higher incidence in the higher dose groups. The SPC is considered to adequately reflect the observations reported.

Resistance

The bibliographical information provided suggests that no documented cases of fipronil resistance in the label-indicated species have been reported in the literature.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant conducted two dose confirmation studies in cats.

One study was a randomised controlled study investigating the efficacy of the product against fleas (*Ctenocephalides felis*) and the tick *Ixodes ricinus*on cats. Eight animals were included in each arm of the study. The control group was untreated.Efficacy against fleas (*Ctenocephalides felis*) and the tick *Ixodes ricinus*was demonstrated and the indications included in the SPC reflect the data provided.

Another study was a randomised controlled study investigating the efficacy of the product against the tick *Dermacentor reticulatus*on cats.

Eight animals were included in each arm of the study. The control group was untreated.Efficacy against the tick *Dermacentor reticulatus*was demonstrated and the indications included in the SPC reflect the data provided.

In addition to the two dose confirmation studies, the applicant conducted an *in-vitro*laboratory study to investigate the susceptibility of the ticks *Rhipicephalus sanguineus*and *Dermacentor reticulatus* to different concentrations of the proposed formulation. The results of this study in combination with the *in-vivo* findings of the dose confirmation studies conducted by the applicant in dogs and cats were considered adequate to support the indication included in the SPC against the tick *Rhipicephalus sanguineus*.

Field Trials

Given the nature of the application (generic hybrid) no field studies were required.

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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. 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 HPRA website.

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.

Changes:
None.