IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

Norbrook Fipronil 268 mg Spot-On Solution for Large Dogs

PRODUCT SUMMARY

EU Procedure number	IE/V/0288/003/DC
Name, strength and pharmaceutical form	Norbrook Fipronil 268 mg Spot-On Solution for Large Dogs
Active substance(s)	Fipronil
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Legal basis of application	Hybrid application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of Authorisation	6th July 2012
Target species	Dogs
Indication for use	For the treatment of infestations by fleas (*Ctenocephalidesfelis*). The product shows immediate insecticidal effect and persistent insecticidal activity against new infestations by adult fleas for up to 5 weeks. The product has persistent acaricidal efficacy for up to 2 weeks against ticks *(Dermacentor reticulatus*). If ticks of this species are present when the product is applied, all ticks will 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 programme for Flea Allergy Dermatitis where this has been previously diagnosed by a Veterinary

	Surgeon.
ATCvet code	QP53AX15
Concerned Member States	UK

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

II. QUALITY ASPECTS

The product contains fipronil 268 mg and the excipients butylhydroxyanisole (E320), butylhydroxytoluene (E321), povidone K12, polysorbate 80, butyl alcohol and diethylene glycol monoethyl ether.
The product is presented in a 2.68 ml pipette, moulded from a film composed of 3 layers: a polypropylene/COC/polypropylene, solvent free lacquer laminate and a copolymer of polyethylene/EVOH/polyethylene. The pipettes are sealed within a child resistant 4-ply foil sachet composed of LDPE/nylon/aluminium foil/polyester film and presented in an outer box.
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.
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 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.

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

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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.

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 with a good distribution of the active substance on the hair, presenting a good gradient of concentration between the application zone and the peripheral area.Fipronil is mainly metabolised to its sulfone derivative (RM1602), which also possesses insecticidal and acaricidal properties.

Toxicological Studies

The applicant has provided bibliographical data characterising the toxicity profile of fipronil in a range of animals following exposure via the oral and dermal routes. Chronic oral exposure at high levels has resulted in signs of neurotoxicity. Laboratory studies using fipronil have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.No studies investigating such effects in the target species were conducted
It was accepted that the mutagenicity and carcinogenicity profile would be the same as for the reference product.
All excipients are considered to have well established use in veterinary medicinal products.

Other Studies

The applicant has conducted additional proprietary studies and provided bibliographical data which show that the product does not have the potential for skin sensitisation or dermal irritation. However, the product may be irritating to the eye.

Observations in Humans

The applicant has provided bibliographical data information which showed that occupational exposure to fipronil can result in headache, nausea, vertigo, and weakness.

User Safety

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.

Given 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 that
- 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 which showed that no further assessment is required. The assessment 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 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.

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 topically on one occasion.
Effects were studied for clinical, biochemical, haematological, cosmetic and local tolerance parameters.
No significant adverse effects were seen following doses of up to five times the recommended dose. Transient hair changes of a cosmetic nature were observed in the majority of animals. The SPC is considered to adequately reflect the observations reported.

Resistance
The information provided suggests that there have been no documented cases of fipronil resistance in the label-indicated species.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials
The applicant has conducted dose confirmation studies in support of the proposed indications against *Ctenocephalides felis* and *Dermacentor reticulatus* in cats.

A blinded, randomised controlled study investigating the efficacy of the product against fleas (*Ctenocephalides felis*) on cats was conducted. Six animals were included in each group. The control group was untreated.Efficacy against fleas (*Ctenocephalides felis*) was demonstrated and the indications included in the SPC reflect the data provided.

A partially blinded, randomised controlled study investigating the efficacy of the product against ticks (*Dermacentor reticulatus*) on cats was conducted. Six animals were included in each group. The control group was untreated. The results of this study in combination with the *in-vivo* findings of the dose confirmation studies conducted by the applicant in dogs were considered adequate to support the indication included in the SPC against the tick *Dermacentor reticulatus*.The indications included in the SPC reflect the data provided.

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.