Ridaflea Spot-On Solution Dog S 67 mg EU Pharmaceutical Ltd
Ridaflea Spot-On Solution Dog M 134 mg
Ridaflea Spot-On Solution Dog L 268 mg
Ridaflea Spot-On Solution Dog XL 402 mg

I. INTRODUCTION

These applications were approved according to Article 13(3) for 'hybrid' products. For this type of application, bioequivalence has not been demonstrated by bioavailability studies but by clinical equivalence. The products were developed as generics of Frontline Spot On Dog 10% w/v Spot on Solutions, produced by Merial Animal Health Ltd.

The products are indicated for the treatment of flea (*Ctenocephalides* spp) and tick (*Rhipicephalus sunguineus* and *Ixodes ricinus*) infestations in dogs. The products have insecticidal activity against new infestations with adult fleas for 8 weeks, and have a persistent acaricidal activity against *Rhipicephalus sanguineus*, *Ixodes ricinus* and *Dermacentor reticulatus* for 4 weeks. If some tick species (*Dermacentor reticulatus*) are present when the product is applied, not all ticks may be killed within 48 hours.

The active substance, fipronil, is an insecticide and ascaricide of the phenylpyrazole family. The action of fipronil is the inhibition of the GABA[1] complex, blocking pre- and post-synaptic transfer of chloride ions across cell membranes, resulting in loss of control of central nervous system activity and subsequent death of the parasite.

II. QUALITY ASPECTS

Product Development and Composition

The products were developed as generics of Frontline Spot On Dog 10% w/v Spot on Solutions produced by Merial Animal Health Ltd. The products contain the same quantitative composition, pharmaceutical form and dose volumes of active substance as the reference product. Four excipients are used in the products, each used previously in veterinary medicines. A crystallisation inhibitor prevents the crystallisation of fipronil prior to dissemination into the skin surface lipids, permitting diffusion across the entire skin surface. No antimicrobial preservative is present, this was not considered essential as bacterial growth within a non-aqueous system is very unlikely. Comparative impurity profiles of both product and reference product were provided. The data were satisfactory. Data regarding the manufacturing process, dose reproducibility, uniformity of dosage and pipette design were all acceptable.

Active Substance

The active substance, fipronil, is not cited in a pharmacopoeia. Information was provided in the form of Active Substance Master Files. Testing of batches is done appropriately, and suitable Certificates of Analysis were provided.

Other Substances

The excipients are butyldroxyanisole E320, butyldroytoluene E321, benzyl alcohol and diethylene glycol monoethyl ether.

[1] GABA – Gamma-amino butyric acid.

Date created: 6th October 2011
Last reviewed: 29th February 2016

Packaging Materials

The product is packaged as follows:-

White opaque, purple translucent or pink pipettes composed of a heat-formed shell of a polypropylene/cyclic olefin copolymer/polypropylene layer and a polyethylene/ethylene vinyl alcohol/polyethylene layer.

Box with 1, 2, 3, 4 or 6 pipettes in individual foil sachets.

Manufacture of the Finished Product

The process comprises of the dissolution of the active substance and excipients in the solvents. Data were provided demonstrating that no degradation occurs as a result of the manufacturing process. Satisfactory data on dose reproducibility and uniformity of dosage unit were provided from three batches of filled pipettes.

Finished Product Quality Control

Tests performed on the finish product are identification of fipronil, butyldroxyanisole and butyldroxytoluene, tests for impurities, uniformity of dosage, moisture content and microbial purity. High Performance Liquid Chromatography analysis is used as the detection system for the active substance related substances, and is considered appropriate. Batch analysis performed on five validation batches and data on the full range of pipettes were satisfactory.

Stability of the Product

Active substance

Appropriate stability data were provided, and supported a retest period of two years. Three batches of fipronil were stored at 25°C/60% RH for 12 months and at 40°C/75%RH for 6 months, in commercial packaging.

Finished Product

Shelf-life of the product as packaged for sale: 2 years. Do not store above 25°C. Store in a dry place in the original packaging.

CONCLUSIONS ON QUALITY

Satisfactory data were provided with regard to quality.

III. SAFETY ASPECTS

Introduction

The pipettes have a twist and snap-off top, and the pipette tip is placed onto the skin of the dog at two points along the back and squeezed to expel the product. Residues documentation was not required for these products, as they are used in a non-food species. Appropriate safety data were required for these hybrid applications.

Pharmacology

Pharmacodynamics

Published data were submitted for this section, which were also relevant to Part IV, Clinical Aspects. Fipronil is a phenylpyrazole which blocks insectoid gamma-amino butyric acid receptors, compromising the action of chloride ions. The ensuing uncontrolled central nervous system activity results in the death of the organism. Fipronil is also thought to have an effect on glutamate-activated chloride channels, which are not present in vertebrates. A metabolite of fipronil, fipronil sulfone is also considered to have an effect.

Pharmacokinetics

Published data were submitted for this section, which were also relevant to Part IV, Clinical Aspects. Subsequent to topical application in the dog, fipronil spreads over the skin via translocation, being stored in the oil glands of the skin and shed with the hair and sebum. The concentration of the active substance decreases over time.

Toxicology

Single Dose Toxicity

Published data were submitted for this section. A review of chronic and subchronic toxicity found that technical grade fipronil is acutely toxic to mammals via the inhalation and oral routes of exposure. Side effects include a hunched posture, abnormal gait, diarrhoea and piloerection. Further data stated that mild dermal and eye irritation occurred, but that the active substance was not a sensitiser in the guinea pig sensitisation test.

Additional data showed that fipronil caused neurotoxicity in rats at a NOEL[2] of 0.5 mg/ml. Two other studies showed NOAELs[3] of 5.0 mg/kg, and 2.5 mg/kg and 7.5 mg/kg respectively.

Repeated Dose Toxicity

Data provided showed that in rats, repeated dosing of fipronil caused seizure, inappetance, decrease bodyweight, liver dysfunction and changes in blood cell biochemistry. In dogs, fipronil toxicity caused neurotoxicological signs and low bodyweight.

[2] NOEL – No Observable Effect Limit.
[3] NOAEL – No Observable Adverse Effect Limits.

Reproductive Toxicity

Published evidence of reproductive toxicity was seen, with a reproductive toxicity for rats described as being at a NOEL of 2.54 mg/kg/day and 2.74 mg/kg/day, and a developmental toxicity study where a NOEL of 20 mg/kg was displayed with a maternal toxicity of 4/mg/kg/day. The SPC[4] states that 'Studies have not been carried out with this product in pregnant and lactating bitches. Use in pregnancy and lactation only in accordance with professional veterinary advice and a benefit/risk assessment.'

Carcinogenicity and Mutagenicity

Suitable references were submitted with regard to these topics.

Special Studies

No reports of immunotoxicity were found in published literature. Fipronil was found to be developmentally neurotoxic and neurotoxic in repeat dose studies in rats and dogs.

Observations in Humans

In most cases, exposure to fipronil in reported cases caused vomiting, orophayngeal pain, abdominal pain, coughing, headache and drowsiness. Symptoms resolved spontaneously.

Studies on Metabolites, Impurities, Other Substances and Formulation

Suitable reference data were submitted. Specific eye and skin irritation studies for fipronil were not submitted, and this was considered acceptable as the proposed products contain well-known spot on formulations. Data were also submitted with regard to the irritant properties of the excipients. The SPC contains suitable warnings.

Environmental Safety

Sufficient data were provided for an appropriate Phase 1 Risk assessment, which ended at Phase I as the product is only to be used in dogs. A risk mitigation measure is placed on the SPC and label in order to protect vulnerable aquatic organisms 'Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty container.'

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

A satisfactory user risk assessment was provided. It was established that the products should not pose any greater risk to the user than the reference product, when used as described on the SPC and product literature.

[4] SPC – Summary of Product Characteristics.

Conclusions on Environmental Safety

A satisfactory environmental risk assessment was provided. It was established that the products should not pose any greater risk to the environment than the reference product, when used as described on the SPC and product literature.

IV. CLINICAL ASPECTS

Clinical Pharmacology

Pharmacodynamics

Published data were submitted for this section, which were also relevant to Part III, Safety. Fipronil is a phenylpyrazole which blocks insectoid gamma-amino butyric acid receptors, compromising the action of chloride ions. The ensuing uncontrolled central nervous system activity results in the death of the organism. Fipronil is also thought to have an effect on glutamate-activated chloride channels, which are not present in vertebrates. A metabolite of fipronil, fipronil sulfone is also considered to have an effect.

Pharmacokinetics

Published data were submitted for this section, which were also relevant to Part III, Safety. Subsequent to topical application in the dog, fipronil spreads over the skin via translocation, being stored in the oil glands of the skin and shed with hair and sebum. The concentration of the active substance decreases over time.

Tolerance in the Target Species

Published literature was submitted for this section, in addition to data from a GLP[5]-compliant target animal species study using 10% fipronil. Doses of 1x , 3x and 5x the nominal product dose were given to young dogs, (or a negative control was used), on three occasions at monthly intervals. This was a three-phase, parallel group, randomised, blind, negative controlled study. Post-acclimatisation, the animals were examined and blood collected for analysis. Observations were performed as appropriate throughout the trial. No adverse reactions relating to use of the product were seen. Cosmetic changes occurred in all study groups, (spiking, clumping of hair with a greasy appearance), which spontaneously resolved. Suitable warnings are given in the SPC.

Resistance

The applicant's conclusion that little or no evidence of resistance to fipronil has been found to date was supported. The SPC contains appropriate information in Section 4.4, advising the end-user of the necessity of treating other household pets and the environment in order to mitigate the formation of resistance.

[5] GLP – Good Laboratory Practice.

Clinical Efficacy

The dose and product size is the same as that of the reference product, therefore there was no requirement for a dose determination study. Data from two dose confirmation studies were submitted for the target species. Both studies were partially blinded, randomised, using dual artificial infestation and negative controls, conducted to GLP/GCP[6] standards.

In the first GLP/GCP compliant, partially blinded, randomised, single site, dose confirmation study, a single application of 10% fipronil topical spot on was compared to untreated controls, in artificially induced tick and flea infestation. The flea species on which the product was tested was *Ctenocephalides felis,* and the tick species on which the product was tested was *Ixodes ricinus*.

A suitable number of young dogs were acclimatised and examined, prior to infestation and subsequent treatment. Counts were performed of fleas and ticks and specific time points. A single topical dose of 10% fipronil was shown to be effective against both species of ticks and fleas at a dose rate of 1.34 ml per dog in the bodyweight range of 10 kg to 20 kg.

A second study analysed the effect of 10% fipronil in the target species on two species of tick, *Dermacentor reticulates* and *Rhipecephalus sanguineus.* The study followed a similar format to that previously described, and 10% fipronil was found to be effective against both tick species.

No clinical field studies were required for these applications, suitable supporting literature was considered appropriate.

CONCLUSIONS ON CLINICAL ASPECTS

The studies submitted showed that the product was effective against the flea and tick species cited in the SPC.

PART V. OVERALL CONCLUSION ON THE PRODUCT

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.

[6] GCP – Good Clinical Practice.

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 Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)