



Veterinary
Medicines
Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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DECENTRALISED PROCEDURE

**PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY
MEDICINAL PRODUCT**

Fyperix 50 mg Spot-On Solution for Cats

**PuAR correct as of 09/03/2018 when RMS was transferred
to DE. Please contact the RMS for future updates**

MODULE 1

PRODUCT SUMMARY

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| EU Procedure number | UK/V/0395/001/DC |
| Name, strength and pharmaceutical form | Fyperix 50 mg Spot-On Solution for Cats |
| Applicant | KRKA, d.d., Novo mesto Šmarješka cesta 6 8501 Novo mesto Slovenia |
| Active substance | Fipronil |
| ATC Vetcode | QP53AX15 |
| Target species | Cats |
| Indication for use | <p>Treatment of fleas (<i>Ctenocephalides</i> spp.) and tick (<i>Ixodes ricinus</i>) infestations in cats.</p> <p>The product has a persistent insecticidal efficacy for up to 4 weeks against fleas (<i>Ctenocephalides</i> spp.) and acaricidal efficacy for up to 4 weeks against <i>Ixodes ricinus</i> and for up to 1 week against <i>Dermacentor reticulatus</i> and <i>Rhipicephalus sanguineus</i>. If ticks of some species (<i>Dermacentor reticulatus</i> and <i>Rhipicephalus sanguineus</i>) 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.</p> <p>The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD), where this has been previously diagnosed by a veterinary surgeon.</p> |

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

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| Legal basis of original application | Generic 'hybrid' application in accordance with Article 13 (3) of Directive 2001/82/EC as amended. |
| Date of completion of the original decentralised procedure | 21 st March 2012. |
| Date product first authorised in the Reference Member State (MRP only) | Not applicable. |
| Concerned Member States for original procedure | Denmark, Finland, France, Germany, Italy, The Netherlands, Norway, Portugal, Spain, Sweden. |

I. SCIENTIFIC OVERVIEW

This application was 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 product was developed as a generic of Frontline Spot On Cat 10% w/v Spot on Solution, produced by Merial Animal Health Ltd.

The products are indicated for the treatment of flea (*Ctenocephalides* spp), and tick (*Dermacentor reticulatus* and *Ixodes ricinus*) infestations in cats. The product has a persistent insecticidal efficacy for up to 4 weeks against fleas (*Ctenocephalides* spp.) and acaricidal efficacy for up to 4 weeks against *Ixodes ricinus* and for up to 1 week against *Dermacentor reticulatus* and *Rhipicephalus sanguineus*. If ticks of some species (*Dermacentor reticulatus* and *Rhipicephalus sanguineus*) 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 the control of Flea Allergy Dermatitis (FAD), where this has been previously diagnosed by a veterinary surgeon.

The active substance, fipronil, is an insecticide and ascaricide of the phenylpyrazole family. The action of fipronil is the inhibition of the GABA¹ 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.

¹ GABA – Gamma-amino butyric acid.

II. QUALITY ASPECTS

A. Composition

The product contains fipronil, and excipients butylhydroxyanisole E320, butylhydroxydroytoluene E321, polysorbate 80, povidone K25 and dimethyl sulfoxide. The container/closure system consists of white polypropylene pipettes closed with either a polyethylene or polyoxymethylene cap. Each 0.5 ml pipette is packed in a polyethylene terephthalate/aluminium/low density polyethylene triplex bag, and a box may contain 1, 3, 6, 10, 20 or 30 pipettes. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservative are 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. 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 fipronil an established active substance described in the European Pharmacopoeia (Ph. Eur). 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. 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.

E. Control on intermediate products

Not applicable

F. 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. This includes relevant general characteristics, identification, quantitative determination and purity tests.

G. 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. A retest period of 3 years was supported for the active substance.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the 30 months stability of the formulation when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the product as packaged for sale: 30 months.
Store in the original container in order to protect from light and moisture.
The product should be maintained at room temperature (above 14°C) for approximately one hour prior to administration.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACOTOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

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.

Pharmacokinetics

Published data were submitted for this section. 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.

Toxicological Studies

- **Single Dose Toxicity**

The acute toxicity of fipronil was studied, with LD₅₀² values reported via the oral route in rats of 97 mg/kg, 95 mg/kg via the oral route in mice and an LC50 of 0.36- 0.42 mg/L in rate after a single inhalation exposure. Adverse effects noted were convulsions, effects on behaviour, and wetness in various body areas. It was discerned that the dermal LD₅₀ when given in distilled water to rats was higher than 2000 mg/kg, and 345 mg/kg when the test material was moistened with corn oil and applied to rabbits. No clinical observations were seen in rats, but they were observed in rabbits, and comprised salivation, tremors, spasms, diarrhoea and emaciation.

- **Repeated Dose Toxicity**

Studies were presented as reviews by the applicant. NOEL³ were derived for oral studies in rats, after a 13 week study of 0.33 mg/kg bodyweight, in dogs 0.5 mg/kg bodyweight, and after year long-trials in dogs of 0.2 mg/kg bodyweight (gelatine capsules), and 0.3 mg/kg bodyweight (in diet). A NOEL of 5 mg/kg bodyweight was seen in rabbits after a 21 day trial on dermal toxicity.

- **Reproductive Toxicity, including Teratogenicity**

Published studies provided data noted that adverse effects occurred above the parental systemic toxicity level in rats in a two-generation study, and when given dermally at 70, 140 or 280 mg/kg bodyweight, there may be adverse effects to the endocrine and reproductive systems in rats. In two further studies analysed, no adverse developmental effects were seen in rabbits or rats.

- **Mutagenicity**

Fipronil and its metabolites were seen to be negative in a range of genotoxicity tests.

- **Carcinogenicity**

No evidence of carcinogenicity was seen in an appropriate mouse study. The NOAEL⁴ was 0.55 mg/kg bodyweight based on systemic effects, liver weights and increased incidence of periacinar microvesicular vacuolation. IN rats, alterations to T-lymphocytes and thyroid-stimulation hormone were observed, along with the development of thyroid tumours. Rats are noted to be more sensitive than humans to thyroid changes. The NOAEL for neurotoxicity was noted as being 0.019 mg/kg bodyweight for fipronil.

² LD₅₀ – Half the lethal dose.

³ NOEL – No observable effect limit.

⁴ NOAEL – No adverse observable effect limit

Other Studies

The applicant provided bibliographical data which showed that:-

Technical grade fipronil was seen not to be a dermal irritant in rabbits. Suitable reviews were provided on metabolites and impurities.

Observations in Humans

The applicant provided bibliographical data information which described the ingestion or inhalation of fipronil in humans. In all cited cases symptoms resolved spontaneously, and consisted of vomiting headache, vertigo, weakness and seizures. In one case, a man died following suspected ingestion of fipronil, but the dose was unknown and another substance may have additionally been involved.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. Warnings and precautions as listed on the product literature (similar to those of the reference product), are adequate to ensure safety to users of the product.

- This product can cause mucous membrane and eye irritation. Therefore, contact between the product and the mouth or eyes should be avoided.
- In the case of accidental eye contact, immediately and thoroughly flush the eyes with water. If eye irritation persists seek medical advice and show the package leaflet or the label to the physician.
- Do not smoke, drink or eat during application.
- Avoid contents coming into contact with the fingers. If this occurs, wash off immediately with soap and water.
- Wash hands after use.
- People with a known hypersensitivity to fipronil or dimethyl sulphoxide or other excipients should avoid contact with the veterinary medicinal product.
- Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children.
- Keep pipettes in original packaging and dispose of used pipettes immediately.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. Warnings and precautions as listed on the product literature are

adequate to ensure safety to the environment when the product is used as directed.

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.
- Fipronil may adversely affect aquatic organisms. Do not contaminate ponds, waterways or ditches with the product or empty container.

IV CLINICAL ASSESSMENT (EFFICACY)

Appropriate safety, pre-clinical tests and clinical trials were required for this 'hybrid' application.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics and pharmacokinetics

Suitable data were provided.

Tolerance in the Target Species of Animals

The applicant conducted a GLP⁵-compliant target animal safety study. A suitable number of young dogs received the product in a partially blinded, parallel grouped, randomised, and negatively controlled study. The animals were divided into groups, and received treatment which consisted of placebo, or the recommended dose, three times the recommended dose, or five times the recommended dose. No adverse reactions to the treatment were observed, in the different groups, or between male and female animals.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted five dose confirmation studies.

Dose confirmation studies:

⁵ GLP – Good Laboratory Practise.

Study 1

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| Study title | Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions. |
| Objectives | To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions. |
| Test site(s) | Laboratory environment. Single centre. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml. |
| Control product/placebo | Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment). |
| Animals | Healthy adult and sub adult cats, 7 animals in each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control product and reference product up to Day 37 for fleas and Day 30 for ticks. |
| Randomisation | Randomised. |
| Blinding | Coded groups. |
| Method | This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas and 50 ticks, at various time points treated according to their respective groups. Flea and tick counts were performed on several occasions up to Day 30/37, as appropriate. |
| Statistical method | Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% ($p < 0.05$). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups. |
| RESULTS | |
| Outcomes for endpoints | <u>Flea Counts</u> <u>Efficacy against <i>C. felis</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>95%), supporting the claim for a 4 week |

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| | <p>persistent effectiveness against <i>C. felis</i>.</p> <p><u>Tick Counts</u></p> <p><u>Efficacy against <i>D. reticulatus</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>90%), providing supporting evidence for a 1 week persistent effectiveness against <i>D. reticulatus</i>.</p> |
| DISCUSSION | The product was shown to be effective against the target parasites. |

Study 2

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| Study title | Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions. |
| Objectives | To evaluate the efficacy of a topically applied spot-on formulation of fipronil against ticks (<i>Dermacentor reticulatus</i>) and the cat flea (<i>Ctenocephalides felis</i>) on cats under laboratory conditions. |
| Test site(s) | Laboratory environment. Single site. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml. |
| Control product/placebo | Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment). |
| Animals | Healthy adult and sub adult cats, 8 animals in each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control and reference product up to Day 23 for fleas and Day 16 for ticks. |
| Randomisation | Randomised. |
| Blinding | Coded groups. |
| Method | This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas and 50 ticks, at various time points and then treated according to their respective groups. Flea and tick counts were performed at several time points up to Day 23/16, as appropriate. |

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| Statistical method | Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% (p<0.05). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups. |
| RESULTS | |
| Outcomes for endpoints | <p><u>Flea Counts</u></p> <p><u>Efficacy against <i>C. felis</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups (>95%), providing supporting evidence for a claim for a 3 week persistent effectiveness against <i>C. felis</i>.</p> <p><u>Tick Counts</u></p> <p><u>Efficacy against <i>D. reticulatus</i></u> There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted. Comparable efficacy was observed for both treatment groups providing supporting evidence for a claim for a 1 week persistent effectiveness.</p> |
| DISCUSSION | The product was shown to be effective against the target parasites. |

Study 3

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| Study title | A controlled, randomised study to evaluate a single application of Fipronil Spot-On for Cats (10% fipronil) as a tick treatment for <i>Ixodes ricinus</i> on cats artificially infested with ticks under laboratory conditions. |
| Objectives | To evaluate a single application of a Fipronil Spot-On Solution (10% fipronil) as a tick treatment for <i>Ixodes ricinus</i> on cats artificially infested under laboratory conditions. |
| Test site(s) | Laboratory environment. Single centre. |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml. |
| Control product/placebo | Control product, Frontline Spot On Cat 10% w/v Spot-On Solution at 0.5 ml. Negative control group (no treatment). |
| Animals | Healthy adult and sub adult cats, 8 animals in each |

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| | group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas and ticks on cats. Efficacy of the test product was compared to the negative control and reference product up to Day 16. |
| Randomisation | Randomised. |
| Blinding | Coded groups. |
| Method | The study was of a block design. After acclimatisation, animals were infested with approximately 60 ticks at various different time points and then treated according to their respective groups. Tick counts were performed on several occasions up to Day 16. |
| Statistical method | Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% (p<0.05). A Mixed model Analysis of Variance was used, with a 90% reduction in ticks expected from the treatment. |
| RESULTS | |
| Outcomes for endpoints | Tick Counts There was no evidence of a statistically significant difference between the two treated groups. No treatment-related adverse effects were noted, a further test on <i>I. Ricinus</i> was provided (Study 5). |
| DISCUSSION | The product was shown to be effective against the target parasite. |

Study 4

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| Study title | Dose confirmation study to evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against the cat flea <i>Ctenocephalides felis</i> on cats under laboratory conditions. |
| Objectives | To evaluate the efficacy of a topically applied spot-on formulation of Fipronil Spot-On for Cats (10% fipronil) against the cat flea <i>Ctenocephalides felis</i> on cats under laboratory conditions. |
| Test site(s) | Laboratory environment. Single site |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml. |
| Control product/placebo | Negative control group (no treatment). |
| Animals | Healthy adult and sub adult cats, 8 animals in each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against fleas on cats. Efficacy of the test product was compared to the negative control up to Day 37. |

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| Randomisation | Randomised. |
| Blinding | Coded groups. |
| Method | This was a block design study. After acclimatisation, animals were infested with approximately 100 fleas at various different time points, and then treated according to their respective groups. Flea counts were performed at various time points up to Day 37. |
| Statistical method | Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% (p<0.05). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups. |
| RESULTS | |
| Outcomes for endpoints | <u>Flea Counts</u> The results provided support for a claim for immediate efficacy (>95%) and also provided evidence for a claim of persistent efficacy for up to 4 weeks in the SPC. |
| DISCUSSION | The product was shown to be effective against the target species. The SPC carries specific data. |

Study 5

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| Study title | Controlled, randomised study to evaluate the efficacy of a single application of Fipronil Spot-On for Cats (10% fipronil) when compared with an untreated control against artificially induced infestations of ticks (<i>Ixodes ricinus</i>) on cats under laboratory conditions. |
| Objectives | To evaluate the efficacy of a single application of Fipronil Spot-On for Cats (10% fipronil) when compared with an untreated control against artificially induced infestations of ticks (<i>Ixodes ricinus</i>) on cats under laboratory conditions. |
| Test site(s) | Laboratory environment. Single site |
| Compliance with Regulatory guidelines | Good Clinical Practice (GCP) |
| Test Product | Fipronil Spot-On for Cats (10% fipronil), synonymous with the product to be authorised. Product delivered at 0.5 ml. |
| Control product/placebo | Negative control group (no treatment). |
| Animals | Healthy adult and sub adult cats, 8 animals in each group. |
| Outcomes/endpoints | Determine the efficacy of a generic spot-on formulation against ticks on cats. Efficacy of the test product was compared to the negative control up to Day 37. |
| Randomisation | Randomised. |
| Blinding | Coded groups. |
| Method | This was a block design study. After acclimatisation, animals were infested with approximately 60 ticks at various time points, and then treated according to their |

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| | respective groups. Tick counts were performed at various time points up to Day 37. |
| Statistical method | Statistical analysis was performed using appropriate software. All tests were two-sided. Level of significance was set at 5% (p<0.05). Analysis was by geometric or arithmetic means. ANOVA (Analysis of Variance) was used to compare groups. |
| RESULTS | |
| Outcomes for endpoints | The results provided support for a claim for immediate efficacy (>90%) and also provided evidence for a claim of persistent efficacy for up to 4 weeks in the SPC. |
| DISCUSSION | The product was shown to be effective against the target species. The SPC carries specific data. |

The studies conducted supported the claims in the authorised SPC, in compliance with the requirements laid out in the Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats EMEA/CVMP/EWP/005/2000-Rev.2 June2008.

Field Trials

Field studies were not required for this hybrid application.

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.

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 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