IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Damtix 500 mg/100 mg spot-on solution for dogs over 4 kg up to 10 kg

PRODUCT SUMMARY

EU Procedure number	IE/V/0663/002/DC
Name, strength and pharmaceutical form	Damtix 500 mg/100 mg spot-on solution for dogs over 4 kg up to 10 kg
Active substance(s)	Permethrin (40:60), imidacloprid
Applicant	Krka, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia
Legal basis of application	Application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of procedure	09/02/2022
Target species	Dogs
Indication for use	For the treatment and prevention of flea (*Ctenocephalides felis*) infestation. Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD) where this has been previously diagnosed by a veterinary surgeon. The product has persistent acaricidal efficacy against tick infestations (*Rhipicephalus sanguineus* and *Ixodes ricinus* for four weeks, and *Dermacentor reticulatus* for three weeks) and persistent repellent efficacy (*Ixodes ricinus*) for three weeks. Ticks already on the dog may not be killed within two days after treatment and may remain attached and visible. Therefore the removal of ticks already on the dog at the time of treatment is recommended, in order to prevent them from attaching and having a blood meal. One treatment provides repellent (anti-feeding) activity against the sand fly *Phlebotomus perniciosus* for three weeks and against the mosquito *Aedes aegypti* from 7 days up to 14 days after treatment. Reduction of the risk of infection with *Leishmania infantum* via transmission by sandflies (*Phlebotomus perniciosus*) for up to 3 weeks. The effect is indirect due to product's activity against the vector.
ATC vet code	QP53AC54
Concerned Member States	DE, FI, FR, EL, ES, IT, PT

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the Health Products Regulatory Authority (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

This was a generic 'hybrid' application submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended, assessed via a dose confirmation study, as *in vivo* bioequivalence for spot-on products cannot be demonstrated by bioavailability studies. The reference product was Advantix Spot-on Solution for Dogs, marketed in the UK since December 2003. The product is intended for use in dogs, for the treatment and prevention of flea infestation by *Ctenocephalides felis*, and against tick infestations by *Rhipicephalus sanguineus, Ixodes ricinus* and *Dermacentor reticulatus*.
The product can be used as a repellent against *Ixodes ricinus* for three weeks, against the mosquito *Aedes aegypti* from 7 days up to 14 days post treatment and against the sand fly *Phlebotomus perniciosus* for three weeks. Due to the product's activity against *P. perniciosus* the product can be used for the reduction of the risk of infection with *Leishmania infantum* via transmission by *P. perniciosus* for up to 3 weeks
The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any 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

A. Qualitative and Quantitative Particulars

The product contains 500 mg of permethrin (40:60) and 100 mg of imidacloprid as active substances. The excipients are butylhydroxytoluene (E321), triglycerides, medium chain, N-methylpyrrolidone, citric acid (E330) and dimethyl sulfoxide.
The container closure system consists of a white polypropylene pipette closed with a polyethylene (HDPE) cap. Each pipette is packaged in a polyethylene terephthalate/aluminium/low density polyethylene bag.
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 at a licensed manufacturing site.
Process validation data for the manufacturing process has been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance permethrin (40:60) complies with an in-house specification. The active substance imidacloprid is an established substance described in the European Pharmacopoeia.
Both active substances are manufactured in accordance with the principles of good manufacturing practice. The active substance specifications provided for both active substances are considered adequate to control the quality of the material.
Batch analytical data demonstrating compliance with these specifications have been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies
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 (pharmaceuticals)

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 has 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 substances permethrin (40:60) and imidacloprid have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substances when stored under the approved conditions.

Stability data on the finished product has 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 was an application for a generic hybrid product, according to Article 13 (3), for which *in vivo* bioequivalence with a reference product could not be demonstrated. The results of pharmacological and toxicological tests from published literature were provided.
Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users and the environment.

III. SAFETY ASSESSMENT

Pharmacological Studies

Pharmacodynamics

Permethrin preferentially binds to the sodium channels within the cells of cold-blooded insects, causing a nerve block and eventual death. The active substance does not have the same effect in mammals, which have a different receptor subtype. The mode of action of imidacloprid is mediated via post-synaptic nicotinic acetylcholine receptors. An agonistic effect is caused via selective binding at insect receptor binding sites, as opposed to mammalian sites.

Pharmacokinetics

Permethrin is partially absorbed from the intestinal tract and is poorly distributed among internal organs, but is seen at higher concentrations in fat. The active substance is rapidly metabolised and excreted via the urine and faeces.
Imidacloprid is rapidly and completely absorbed. In dogs, the active substance can be found in the skin epidermis, hair follicles and sebaceous glands up to 4 weeks after administration as a transferable residue. Elimination of the active substance occurs via the urine and faeces.

Toxicological Studies
The applicant provided bibliographical data.

- Single Dose Toxicity

In animal studies using permethrin, it was noted that the LD50 is much higher where the cis:trans ratio is greater for the cis isomer. The vehicle of administration also had impact. The proposed products are designed to give optimal efficacy at the recommended dose. Imidacloprid is of low toxicity when applied dermally to mammals.

- Repeated Dose Toxicity

Permethrin
An oral NOEL of 5 mg/kg bw/day was seen in a 52 week study in dogs, and at 1000 mg/kg/day in rabbits. Significant adverse effects noted were increased liver weight, due to microsomal enzyme induction and neurotoxicity. The SPC states an accepted single dose of 50 mg/kg.

Imidacloprid
In repeated dose studies using imidacloprid, liver changes and reduced weight gain were the most significant adverse reactions observed. For dogs, the lowest NOAEL which was based on immunotoxicity studies was 5 mg/kg bw/day. The SPC states an accepted single dose of 10 mg/kg.

- Reproductive Toxicity, including Teratogenicity

From bibliographical data provided, permethrin is not considered to be toxic with regard to reproduction. Imidacloprid is not considered toxic with regard to embryotoxicity or teratogenicity, with some effects seen only at doses above maternal toxicity.

- Mutagenicity

The mutagenicity of permethrin was assessed using a battery of relevant tests. Only an in vitro test for chromosomal damage gave a positive result, but in isolation, this result was not considered significant in relation to use of the products.
Imidacloprid was tested using a battery of in vitro tests. A slight increase in chromosomal aberration rate was noted, but this was not seen as significant. All in vivo chromosomal tests were negative.

- Carcinogenicity

No NOAEL that could be translated to humans was identified from rodent studies for permethrin. No carcinogenic effects were noted for imidacloprid in mice or rats in long-term dietary administration.

Studies of Other Effects
Repeat dose neurotoxicity studies in the dog and rat did not identify a NOEL for permethrin. A NOAEL of 25 mg/kg was proposed for use in acute oral exposure scenarios. The active substance is mildly irritating to the eyes and skin, but was not a skin sensitiser when tested by the Magnusson/Kligman method.
From relevant studies, a NOAEL of 5 mg/kg was determined as being the most relevant for acute scenarios of the user risk assessment for imidacloprid. In suitable studies imidacloprid was identified as not being a skin or eye irritant, and is not expected to be a skin sensitiser.

Observations in Humans
For permethrin, toxicity data is limited to dermal exposure. Reversible paraesthesia and mild irritation have been reported at the site of contact up to 12 hours after exposure. Mild contact dermatitis has been noted for imidacloprid.

User Safety
A user risk assessment was provided in compliance with the relevant guideline.
NOAEL were suitably calculated for the worst case scenario, namely, interaction with the active substances and children.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:

- Avoid contact between the product and skin, eyes or mouth.
- Do not eat, drink or smoke during application.
- Wash hands thoroughly after use.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- People with known skin sensitivity may be particularly sensitive to this product.
- The predominant clinical symptoms that in extremely rare cases may be shown are transient sensory irritations of the skin like tingling, burning sensation or numbness.
- If the product gets accidentally into the eyes, they should be thoroughly flushed with water. If skin or if eye irritation persists, seek medical advice immediately and show the package leaflet or the label to the physician.
- Do not ingest. In case of accidental ingestion seek medical advice immediately and show the package leaflet or the label to the physician.
- Treated dogs should not be handled especially by children until the application site is dry. This may be ensured by treating the dogs in the evening. Recently treated dogs should not be allowed to sleep together with their owner, especially children.
- In order to prevent children from getting access to pipettes, keep the pipette in the original packaging until ready for use and dispose of used pipettes immediately.

Environmental Safety
A Phase 1 environmental study was appropriately submitted in line with relevant guidelines. The product will be given to individual non-food producing companion animals. The SPC and product literature carry suitable warnings.

IV. CLINICAL ASSESSMENT

IV.I. Pre-Clinical Studies

Pharmacology
The efficacy of the product, as cited with regard to the indication in the SPC, was demonstrated via pivotal dose confirmation studies.

Tolerance in the Target Species

The applicant provided an animal oral toxicity study, and a target animal safety study conducted in accordance with the relevant guidelines, as well as providing published literature in support of this section. The adverse events noted in the oral toxicity study included vomiting, tremors and incoordination, but overall ingestion of 1x dose was well tolerated. In the target animal tolerance study a dose of up to 5x recommended dose was well tolerated. The main effects observed were local skin reactions, including erythema, oedema and alopecia, in addition to scaling and spiking of the hair which were seen in the 1x group. The product literature accurately reflects the type and incidence of adverse effects which might be expected to be seen.

Resistance

No significant resistance data were located for these active substances in a published literature search.

IV.II. Clinical Documentation

Laboratory Trials

The applicant conducted several studies, including a significant dose confirmation study supporting the indication in the SPC. The product contains the same volume and concentration of the active substances as the reference products, and are presented in the same manner. Therefore, efficacy was assessed via dose confirmation studies.

Dose confirmation studies:

Study title	A dose confirmation efficacy study of a single application of an imidacloprid/permethrin spot-on formulation against induced infestations of R. sanguineus and D. reticulatus ticks on dogs
Objectives	Confirmation of the target dose effectiveness of the proposed product against artificially induced tick infestation in dogs.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy dogs of both sexes and aged greater than 6 months, de-wormed and tick-free prior to the start of the study.
Outcomes/endpoints	Calculated using the following formula: Efficacy against ticks (%) = 100 x (mC – mT)/ mC Where mC = Mean number of live ticks on control animals. mT = Mean number of live and killed, engorged ticks on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of pre-administration combined species live attached tick counts and then blocked in pairs. Dogs allocated to group one or two within blocks.
Blinding	Partial blinding.
Method	Fifty unfed ticks of each species applied to each dog on days -6, -2, 7, 14, 21 and 28. Ranking for tick retention on day -4. Tick counts were conducted at 48±2 hours post treatment, or non-treatment. Visual assessment of alloscutum. IVP applied as proposed for use (as per teh SPC). Applied only on day 0.
Statistical method	Differences in tick counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	

Outcomes for endpoints	There was a significant (p<0.001) difference in efficacy between groups on all days, except on day 2.
DISCUSSION	Immediate efficacy was not demonstrated. Persistent efficacy exceeding 95% was demonstrated against both tick species (day 9 to day 30). The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	A dose confirmation efficacy study of a single application of an imidacloprid/permethrin spot-on formulation against induced infestations of I. ricinus ticks on dogs
Objectives	Confirmation of the target dose effectiveness of the proposed product against artificially induced tick infestation in dogs.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy dogs of both sexes, aged greater than 12 months and free of ticks prior to the start of the study.
Outcomes/endpoints	Calculated using the following formula: Efficacy against ticks (%) = 100 x (mC – mT)/ mC Where mC = Mean number of live ticks on control animals. mT = Mean number of live and killed, engorged ticks on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -5 attached tick counts and then blocked in pairs. Dogs allocated to group one or two within blocks.
Blinding	Partial blinding.
Method	Fifty unfed ticks of each species applied to each dog on days -7, -2, 7, 14, 21 and 28. Tick counts were conducted at 48±2 hours post treatment, or non-treatment. Visual assessment of alloscutum. Product administered at four locations between shoulder blades and base of tail. Product administered to provide pre-determined doses including the minimum recommended dose 0.10 mL/kg. Applied only on day 0.
Statistical method	Differences in tick counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant (p<0.0001) difference in efficacy between groups on all days.
DISCUSSION	Immediate efficacy was not demonstrated. Persistent efficacy exceeding 90% was demonstrated from day 9 to day 30. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.
Study title	A study to determine the efficacy of a single application of a flea treatment (imidacloprid/permethrin spot-on), when compared to an untreated control group against artificially

	induced flea infestations (C. felis)
Objectives	Determination of efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy adult dogs of both sexes and flea free prior to the start of the study.
Outcomes/endpoints	Calculated using the following formula: Efficacy against fleas (%) = 100 x (mC – mT)/ mC Where mC = Mean number of live fleas on control animals. mT = Mean number of live fleas on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -5 live attached flea counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 100 unfed fleas applied to each dog over a series of days. Flea counts were conducted 48±2 hours post flea infestation and 24 and 48 hours post IVP administration, (fleas were counted in situ and remaining fleas left on the animal at 24 hour count).
Statistical method	Differences in flea counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.0001$) difference in efficacy between groups on all days.
DISCUSSION	Efficacy against C. felis fleas was demonstrated and treatment claims were granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	A study to determine the efficacy of a single application of a flea treatment (imidacloprid/permethrin spot-on), when compared to an untreated control group against artificially induced flea infestations (C. felis). A study on dogs immersed weekly in water
Objectives	Determination of efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy adult dogs of both sexes and flea free prior to the start of the study.
Outcomes/endpoints	Calculated using the following formula: Efficacy against fleas (%) = 100 x (mC – mT)/ mC

	Where mC = Mean number of live fleas on control animals. mT = Mean number of live fleas on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of day -4 live attached flea counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 100 unfed fleas applied to each dog over a series of days. Flea counts were conducted 48±2 hours post flea infestation, except on day 2, when counts were performed 48±2 hours post IVP administration.
Statistical method	Differences in flea counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.0001$) difference in efficacy between groups on all days.
DISCUSSION	Efficacy against C. felis fleas was demonstrated and treatment claims were granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications. The SPC carries the following information with regard to animals introduced to water: The product remains effective against fleas if the animal becomes wet. After weekly immersions in water for one minute the period of persistent insecticidal efficacy against fleas was not reduced. However, prolonged, intense exposure to water should be avoided. In cases of frequent and/or prolonged water exposure the persistent efficacy may be reduced. In these cases do not retreat more frequently than once weekly. If a dog requires a shampoo, it should be administered before applying the product or at least 2 weeks after application, to optimise efficacy of the product.

Study title	A study to determine the repellent efficacy of a single application of a spot-on tick treatment when compared to an untreated control group against artificially induced infestations of tick Ixodes ricinus on dogs
Objectives	Determination of repellent efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy adult dogs of both sexes.
Outcomes/endpoints	Calculated using the following formula: Repellent efficacy against ticks (%) = 100 x (mC – mT)/ mC Where mC = Mean number of live free and live attached female ticks on control animals. mT = Mean number of live (free and attached) and dead (free

	and attached) female ticks on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of live attached ticks counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 50 unfed female ticks (±4) applied to each dog over a series of days. Tick counts were conducted 24±1 hour post flea infestation, except on day 2, when counts were performed 48±2 hours post IVP administration.
Statistical method	Differences in tick counts between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.05$) difference in efficacy between groups from Day 8 onwards.
DISCUSSION	Repellent efficacy against I. ricinus ticks was demonstrated and the claim was granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	Repellent (anti-feeding) and adulticidal efficacy of imidacloprid + permethrin spot-on solution for dogs 100 + 500 mg/ml applied to dogs against Aedes aegypti
Objectives	Determination of anti-feeding efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy adult dogs of both sexes.
Outcomes/endpoints	Calculated using the following formula: Repellent efficacy against mosquitoes (%) = 100 x (FC – FT)/ FC Where FC = Mean number of fed (live, moribund and dead) mosquitoes on control animals. FT = Mean number of fed (live, moribund and dead) mosquitoes on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of fed mosquito counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 50 female mosquitoes (±5) applied to each dog over a series of days. Fed mosquito counts were conducted 1 hour post challenge.
Statistical method	Differences between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.05$) difference in efficacy between

	groups on Days 8 and 15.
DISCUSSION	Repellent efficacy against Ae. aegypti mosquitoes was demonstrated and the claim was granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications.

Study title	Efficacy of 10% w/v imidacloprid and 50% w/v permethrin spot-on against sand fly (Phlebotomus perniciosus) challenges on dogs
Objectives	Determination of anti-feeding efficacy when compared to an untreated control group.
Test site(s)	Single site.
Compliance with Regulatory guidelines	Good Clinical Practice.
Test Product	Imidacloprid 100 mg/ml, permethrin 500 mg/ml spot-on solution as investigational veterinary product (IVP).
Control product/placebo	Untreated control group.
Animals	16 healthy adult dogs of both sexes.
Outcomes/endpoints	Calculated using the following formula: Repellent efficacy against sand flies(%) = 100 x (FC – FT)/ FC Where FC = Mean number of fed (live, moribund and dead) sand flies on control animals. FT = Mean number of fed (live, moribund and dead) sand flies on IVP treated animals. Arithmetic and geometric means calculated, but the latter were to provide supportive evidence only.
Randomisation	Separated by sex, ranked within sex in order of fed sand fly counts and then blocked in pairs.
Blinding	Partial blinding.
Method	Approximately 50 sand flies applied to each dog over a series of days. Fed sand fly counts were conducted 60 (±15) min post challenge.
Statistical method	Differences between IVP treated and control group estimated using a mixed model analysis of variance for a repeated measures design, with significance set at the 5% level.
RESULTS	
Outcomes for endpoints	There was a significant ($p<0.05$) difference in efficacy between groups on all days.
DISCUSSION	Repellent efficacy against P. perniciosus mosquitoes was demonstrated and the claim was granted. The product was well tolerated when administered at the recommended dose range. The SPC should be referred to for agreed persistency details and any contraindications. The results allowed to extrapolate the following indication in the SPC: Reduction of the risk of infection with Leishmania infantum via transmission by sandflies (Phlebotomus perniciosus) for up to 3 weeks. The effect is indirect due to product's activity against the vector.

Field Trials

No data were required for this section.

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

Not applicable.