Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Refordog 40 mg/200 mg Spot-on Solution for Dogs over 1.5 kg up to 4 kg
Refordog 100 mg/500 mg Spot-on Solution for Dogs over 4 kg up to 10 kg
Refordog 250 mg/1250 mg Spot-on Solution for Dogs over 10 kg up to 25 kg
Refordog 400 mg/2000 mg Spot-on Solution for Dogs over 25 kg up to 40 kg
Refordog 600 mg /3000 mg Spot-on Solution for Dogs over 40 kg up to 60 kg

Date Created: January 2025

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Refordog 40 mg/200 mg Spot-on Solution for Dogs over 1.5 kg up to 4 kg
Applicant	Vetpharma Animal Health, S.L Les Corts, 23, 08028 Barcelona, 08028, Spain
Active substance	Imidacloprid Permethrin (Cis:Trans 40:60)
ATC Vetcode	QP53AC54
Target species	Dogs
Indication for use	For dogs with, or at risk from mixed infestations by fleas, biting lice, ticks, sand flies, mosquitos and stable flies. The veterinary medicinal product is only indicated when use against all the following parasite species is required at the same time. For the treatment and prevention of flea (Ctenocephalides canis, Ctenocephalides felis) infestation and for the treatment of biting lice (Trichodectes canis). Fleas on dogs are killed within one day following treatment. One treatment prevents further flea infestation for four weeks. The veterinary medicinal product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). The veterinary medicinal product has persistent acaricidal and repellent efficacy against tick infestations (Rhipicephalus sanguineus and Ixodes ricinus for four weeks, and Dermacentor reticulatus for three weeks). By repelling and killing the tick vector Rhipicephalus sanguineus, the veterinary medicinal product reduces the likelihood of transmission of the pathogen Ehrlichia canis,

	thereby reducing the risk of canine ehrlichiosis. The reduction in risk has been shown in studies to commence from 3 days following application of the veterinary medicinal product and to persist for 4 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 sand flies (Phlebotomus papatasi for two weeks and Phlebotomus perniciosus for three weeks), against mosquitoes (Aedes aegypti for two weeks and Culex pipiens for four weeks) and against stable flies (Stomoxys calcitrans) for four weeks. 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 the veterinary medicinal product's activity against the vector.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 8 of VMRs 2013 (Schedule 1, Para 10) as amended.
Date of conclusion of the procedure	04/10/24

I. SCIENTIFIC OVERVIEW

These are 'hybrid' applications because the products are for topical use, and therefore bioequivalence cannot be established through bioavailability studies. The reference product is Advantix Spot-on solution for dogs which has been authorised in the UK since 2003.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains Imidacloprid and Permethrin, the excipients Triglycerides, medium-chain, Butylated Hydroxytoluene, Citric Acid Monohydrate and N Methyl Pyrrolidone.

The spot on formula consists of white laminated polypropylene and aluminium of single dose 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured in accordance with the relevant regulatory guidelines.

II.C. Control of Starting Materials

The active substance is Imidacloprid and Permethrin, an established active substance described in the European Pharmacopoeia. 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.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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 sites have been provided demonstrating compliance with the specification. Control tests on the finished product are those suitable for this pharmaceutical form.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable regulatory 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 regulatory guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 18 months.
There are no special storage requirements for this veterinary medicine.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

This veterinary medicinal product is an ectoparasiticide for topical use containing Imidacloprid and Permethrin. This combination acts as an insecticide, acaricide and as a repellent.

Imidacloprid is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it can be classified as a chloronicotinyl nitroguanidine. Imidacloprid is effective against adult fleas and larval flea stages. In addition to the adulticide flea efficacy of imidacloprid, a larvicidal flea efficacy in the surroundings of the treated pet has been demonstrated. Larval stages in the dog`s immediate surroundings are killed following contact with a treated animal. It has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) in insects. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death of the parasite.

Permethrin belongs to the type I class of pyrethroid acaricides and insecticides and also acts as repellent. Pyrethroids affect the voltage-gated sodium channels in vertebrates and non-vertebrates. Pyrethroids are so called “open channel blockers” affecting the sodium channel by slowing both the activation and the inactivation properties thus leading to hyperexcitability and death of the parasite.

In the combination of both substances, it has been shown Imidacloprid functions as the activator of arthropod ganglion and therefore increases the efficacy of permethrin.

The veterinary medicinal product provides repellent activity (anti-feeding activity) against *Phlebotomus perniciosus* (> 80% for 3 weeks), mosquitoes and ticks. Field data from an endemic area showed that the product indirectly reduces the risk of transmission of Leishmania infantum from infected sandflies (*Phlebotomus perniciosus*) for up to 3 weeks, thereby reducing the risk of canine leishmaniosis in treated dogs.

Resistance to permethrin may develop and it is known that resistance manifests in single or multiple mutations of its primary target site, the voltage-gated sodium channels (VGSC), commonly referred to as knockdown resistance (kdr- or skdr-mutation). Other mechanisms of resistance development include cuticle thickening and metabolic resistance via over expression of metabolizing P450 mono-oxygenases, esterases, and glutathione-S-transferases.

Toxicological Studies

Not applicable due to the legal basis of this application.

User Safety

A user risk assessment was provided in compliance with the relevant guidelines.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- This veterinary medicinal product contains butylhydroxytoluene which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes.
- The predominant clinical symptoms that in extremely rare case may be shown are transient sensory irritations of the skin like tingling, burning sensation or numbness.
- Avoid contact between the veterinary medicinal product and skin, eyes or mouth.
- Do not eat, drink or smoke during application. Do not ingest.
- Wash hands thoroughly after use.
- 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.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- People with known hypersensitivity to permethrin should avoid contact with the veterinary medicinal product.
- If the veterinary medicinal product gets accidentally into the eyes, they should be thoroughly flushed with water. If skin or if eye irritation persists, obtain medical attention immediately and show the package insert to the physician.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Treated dogs must not be handled especially by children for at least 12 hours after application of the veterinary medicinal product. It is therefore recommended to treat the dogs e.g. in the evening. Recently treated dogs should not be allowed to sleep together with their owner, especially children.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Tolerance in the Target Species

Tolerance studies were not required because bioequivalence was established.

IV.II. Clinical Documentation

Not required due to the legal basis of the 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 of the product(s) is favourable.

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.

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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.

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