Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ectoline 67 mg Spot-On Solution for Small Dogs
Ectoline 134 mg Spot-On Solution for Medium Dogs
Ectoline 268 mg Spot-On Solution for Large Dogs
Ectoline 402 mg Spot-On Solution for Very Large Dogs

PuAR correct as of 08/10/2018 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0310/001/DC UK/V/0310/002/DC UK/V/0310/003/DC UK/V/0310/004/DC
Name, strength and pharmaceutical form	Ectoline 67 mg Spot-On Solution for Small Dogs Ectoline 134 mg Spot-On Solution for Medium Dogs Ectoline 268 mg Spot-On Solution for Large Dogs Ectoline 402 mg Spot-On Solution for Very Large Dogs
Applicant	Alfamed S.A.S.
Active substance(s)	Fipronil
ATC Vetcode	QP53AX15
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides* spp.) and tick (*Dermacentor reticulatus*) infestations. Insecticidal efficacy against new infestations with adult fleas persists for up to 8 weeks. The product has a persistent acaricidal efficacy for up to 4 weeks against ticks (*Rhipicephalus sanguineus*, *Ixodes ricinus*, *Dermacentor reticulatus*). If ticks of some species (*Rhipicephalus sanguineus* and *Ixodes ricinus*) 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.

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

Legal basis of original application	Application in accordance with Article 13.3 of Directive 2001/82/EC as amended by Directive 2004/28/EC
Date of completion of the original decentralised procedure	17 April 2009
Concerned Member States for original procedure	France Germany Italy Portugal Spain Concerned Member States added during Repeat Use procedure:- Denmark Finland Poland

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[1]. The product is safe for the user, the consumer of foodstuffs from treated animals 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.

These products were previously authorised under the name Alfamed 67 mg spot-on solution for small dogs, Alfamed 134 mg spot-on solution for medium dogs, Alfamed 268 mg spot-on solution for large dogs and Alfamed 402 mg spot-on solution for very large dogs but variation to change the name of the product was approved in August 2009 and the names were changed to 4Fleas fipronil 67 mg spot-on solution for small dogs, 4Fleas fipronil 134 mg spot-on solution for

[1] SPC – Summary of Product Characteristics.

medium dogs, 4Fleas fipronil 268 mg spot-on solution for large dogs and 4Fleas fipronil 402 mg spot-on solution for very large dogs respectively.[2]

II. QUALITY ASPECTS

A. Composition

Ectoline 67 mg spot on solution for small dogs

The product contains 67 mg/pipette fipronil as active substance and butylhydroxyanisole, butylhydroxytoluene, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system is either thermoformed pipettes or polypropylene pipettes. Thermoformed pipette is a white or transparent multi-layer plastic single-dose pipette containing an extractible volume of 0.67 ml. The internal layers in contact with the product are made of polyacrylonitrile-methacrylate. The white external complex is composed of polypropylene / cyclic olefine copolymer / polypropylene. The polypropylene pipette is a white polypropylene single-dose pipette containing an extractible volume of 0.67 ml packaged in uncoloured plastic blister composed of polypropylene / cyclic olefine copolymer / polypropylene closed by heat sealing with a thermosealable lacquered aluminium foil and placed in a carton box or blister card.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

Ectoline 134 mg spot on solution for medium dogs

The product contains 134 mg/pipette fipronil as active substance and butylhydroxyanisole, butylhydroxytoluene, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system is either thermoformed pipettes or polypropylene pipettes. Thermoformed pipette is a multi-layer plastic single-dose pipette containing an extractible volume of 1.34 ml. The internal layers in contact with the product are made of polyacrylonitrile-methacrylate. The white external complex is composed of polypropylene / cyclic olefine copolymer /

[2] Note: the names of the products have now changed to Ectoline 67 mg Spot-On Solution for Small Dogs, Ectoline 134 mg Spot-On Solution for Medium Dogs, Ectoline 268 mg Spot-On Solution for Large Dogs and Ectoline 402 mg Spot-On Solution for Very Large Dogs, via a variation procedure, 10th March 2011.

polypropylene. The polypropylene pipette is a white polypropylene single-dose pipette containing an extractible volume of 1.34 ml packaged in uncoloured plastic blister composed of polypropylene / cyclic olefine copolymer / polypropylene closed by heat sealing with a thermosealable lacquered aluminium foil and placed in a carton box or blister card.

Ectoline 268 mg spot on solution for large dogs

The product contains 268 mg/pipette fipronil as active substance and butylhydroxyanisole, butylhydroxytoluene, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system is either thermoformed pipettes or polypropylene pipettes. Thermoformed pipette is a multi-layer plastic single-dose pipette containing an extractible volume of 2.68 ml. The internal layers in contact with the product are made of polyacrylonitrile-methacrylate. The white external complex is composed of polypropylene / cyclic olefine copolymer / polypropylene. The polypropylene pipette is a white polypropylene single-dose pipette containing an extractible volume of 2.68 ml packaged in uncoloured plastic blister composed of polypropylene / cyclic olefine copolymer / polypropylene closed by heat sealing with a thermosealable lacquered aluminium foil and placed in a carton box or blister card.

Ectoline 402 mg spot on solution for very large dogs

The product contains 402 mg/pipette fipronil as active substance and butylhydroxyanisole, butylhydroxytoluene, benzyl alcohol and diethyl glycol monoethyl ether as excipients.

The container/closure system is either thermoformed pipettes or polypropylene pipettes. Thermoformed pipette is a multi-layer plastic single-dose pipette containing an extractible volume of 4.02 ml. The internal layers in contact with the product are made of polyacrylonitrile-methacrylate or polyethylene-ethylene vinyl alcohol-polyethylene. The white external complex is composed of polypropylene / cyclic olefine copolymer / polypropylene. The polypropylene pipette is a white polypropylene single-dose pipette containing an extractible volume of 4.02 ml packaged in uncoloured plastic blister composed of polypropylene / cyclic olefine copolymer / polypropylene closed by heat sealing with a thermosealable lacquered aluminium foil and placed in a carton box or blister card.

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 which is almost unabsorbed through the skin and the formulation is designed to deposit the active substance easily onto the animal. There are four excipients used in the formulation and each has been used previously in veterinary medicines.

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.

All the excipients used in the final product have monographs in the Ph. Eur. and each comply with the requirements of the current edition of the Ph. Eur.

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 sites have been provided demonstrating compliance with the specification.

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.

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.

H. Genetically Modified Organisms

Not applicable.

J. Other information

Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 36 months.

Special precautions for storage

Store below 30°C.
Store in a dry place.
Store in the original package.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not required.

Toxicological Studies

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not required.

Other Studies

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not required.

User Safety

The applicant has made reference to the user risk assessment submitted in the Expert Report which considered dermal and oral exposure including exposure to children. The user warnings proposed are the same as those for the reference product and are considered satisfactory to address user safety.

Ecotoxicity

The applicant has provided environmental risk assessment in compliance with the relevant guideline which showed that the environmental safety of the product is acceptable.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not provided.

Pharmacokinetics

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not provided.

Tolerance in the Target Species of Animals

The applicant has conducted a target animal tolerance study to evaluate the local and systemic tolerance of the product. The study was conducted on dogs. The dogs were divided into different groups. The study concluded that there were no laboratory or histological changes and no clinical signs associated with the treatment were noted when the product was administered at one, three and five times the expected therapeutic dose for three applications over a period of approximately two and a half months.

Resistance

Since the application is made in accordance with Article 13(3) of Directive 2004/28/EC, on the basis of essential similarity, data on this section of the dossier were not provided.

IV.B Clinical Studies

The applicant has provided four dose confirmation studies; one for fleas *(Ctenocephalides felis)* on dogs, one for each of the following tick species *(Rhipicephalus sanguineus, Dermacentor reticulatus and Ixodes ricinus)* on dogs. The first study was conducted to determine and compare the efficacy of 4Fleas[3] Fipronil spot-on solution with the reference product. The study was conducted on dogs. The study concluded that both the 4Fleas Fipronil spot-on solution and the reference product had a therapeutic efficacy of more than 95% at 48 hours after treatment and this persisted for up to eight weeks, when administered to dogs at the doses stated (0.67 ml for dogs of two to 10 kg bodyweight or 1.34 ml for dogs of more than 10 and up to 20 kg bodyweight).

The second study was conducted to confirm the efficacy of a 4Fleas Fipronil spot-on solution against the tick *Dermacentor reticulatus* on dogs compared to the reference product when applied topically at the rate of 0.067 to 0.335 ml/kg bodyweight. The study was conducted on dogs. It was concluded that both the 4Fleas Fipronil spot-on solution and the reference product had an immediate (therapeutic) efficacy, at 48 hours after treatment, of more than 90% against ticks already on the dogs. This level of efficacy against *Dermacentor reticulatus* persisted for at least four weeks, based on subsequent weekly new tick infestations.

The third study was conducted to determine and compare the efficacy of a 4Fleas Fipronil spot-on solution with the reference product against a French strain of the tick *Rhipicephalus sanguineus*. The study was conducted on dogs. The products were applied at recommended doses. The study demonstrated that the therapeutic efficacy at 48 hours after treatment of both the 4Fleas Fipronil spot-on solution and the reference product was much less than 90% against ticks already on the dogs. However, by one week after treatment and for up to four weeks the persistent efficacy of both the 4Fleas Fipronil spot-on solution and the reference product was more than 90% against subsequent weekly new tick infestations of *Rhipicephalus sanguineus*.

The fourth study was conducted to confirm the efficacy of a 4Fleas Fipronil spot-on solution against the tick *Ixodes ricinus* on dogs compared to the reference product when applied once topically at the recommended dose rate. In the study it was demonstrated that the 4Fleas Fipronil spot-on solution had a therapeutic efficacy at 48 hours after treatment of just under 90% against ticks already on the dog. However, by one week and for at least three weeks after treatment the persistent efficacy of both the 4Fleas Fipronil spot-on solution and the reference product was more than 90% against subsequent weekly new tick infestations of *Ixodes ricinus.*

[3] Note: the names of the products have now changed to Ectoline 67 mg Spot-On Solution for Small Dogs, Ectoline 134 mg Spot-On Solution for Medium Dogs, Ectoline 268 mg Spot-On Solution for Large Dogs and Ectoline 402 mg Spot-On Solution for Very Large Dogs, via a variation procedure, 10th March 2011.

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.

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