FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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NATIONALE PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

CANIGUARD LINE ON CHIEN A LA PERMETHRINE

Date: 13/09/2012

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	CANIGUARD LINE ON CHIEN A LA PERMETHRINE
Applicant	BEAPHAR ZONE INDUSTRIELLE SECTEUR D RUE DES ELECTRICIENS 06700 ST LAURENT DU VAR
Active substance(s)	PERMETHRINE
ATC Vetcode	QP53AC04
Target species	Dogs
Indication for use	Treatment of flea (*Ctenocephalides felis*) in dogs. Insecticidal efficacy against new infestations with adult fleas persists during 4 weeks. The new fleas are killed in the 48 hours following the infestation. The product has not demonstrated an immediate acaracidal activity against ticks but own an acaricidal efficacy against new infestation for 6 weeks against ticks (*Rhipicephalus sanguineus*). If ticks of this species 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.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of completion of the national procedure	19/06/2012

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.
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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 0.4 g/ml permethrin 40/60 as active substance and the following excipients: butylhydroxyanisole, butylhydroxytoluene and diethylene glycol monoethyl ether.

The container/closure system is a pipette of 2 or 4 ml in PEHD. The particulars of the containers and controls performed are provided and conform to the regulation.

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 licensed manufacturing sites.

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 permethrine, an established active substance. 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.

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

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The mechanism of action of permethrin was well documented. It acts by inhibiting nerve signals via sodium channel blockage in target microorganisms. Due to its physicochemical properties permethrin is able to cross the insect's cuticle and cause knockdown of the parasite on the animal.

A pharmacokinetic study was provided with the final formulation and showed a very low dermal absorption of the product.

Toxicological Studies

The applicant has provided own studies and bibliographical toxicological data.

Whatever the route of administration, the permethrin toxicity after single administration in rat is low.

The permethrin toxicity after repeated oral administration is also very low. Repeated dose trials identified the nervous system and the liver as the main target organs for permethrin systemic toxicity. The lowest NOAEL after oral administration is 5 mg/kg/d in rats and dogs. After dermal application, the lowest NOAEL is 1000 mg/kg/d in rabbits.

In addition, permethrin does not show any reproductive, teratogenic and embrytoxic effects.

Permethrin is not considered to be mutagenic (EMEA/MRL/843/02-FINAL, September 2002). This conclusion is also confirmed by the WHO (WHO, 1990).
The carcinogenic potential of permethrin is not a cause for concern (EMEA/MRL/843/02-FINAL, September 2002). The FAO-WHO evaluations analysed several studies in rat and mouse and concluded that the carcinogenic potential of permethrin is very low. It is limited to the female mouse and is probably due to an epigenetic phenomenon (IPCS Inchem, 1999).

Concerning skin sensitisation and skin and eyes irritation, studies provided with the final formulation showed that permethrin does not induce skin sensitisation. The product was classified as slightly irritant to skin and moderately irritant to eyes.

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 are adequate to ensure safety to users of the product.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

The product is not expected to pose a risk for the environment when used as recommended.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

A tolerance study has been carried out in dogs. The applied doses were once, twice and five times the recommended dose. Adverse effects observed were rare and are correctly reported in section 4.6 and 4.10 of the SPC.

IV.B Clinical Studies

A dose determination, a dose confirmation and a field trial study enrolling more than 200 dogs were provided.

They support the formulation containing 400 mg de perméthrine par ml and demonstrate the efficacy of the product in treatment of flea (*Ctenocephalides felis*) in dogs. It also showed that the insecticidal efficacy against new infestations with adult fleas persists during 4 weeks. The new fleas are killed within 48 hours following the infestation.

The product has not demonstrated an immediate acaracidal activity against ticks but own an acaricidal efficacy against new infestation for 6 weeks against ticks (*Rhipicephalus sanguineus*). If ticks of this species 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.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.