FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
La Haute Marche
Javené BP 90203
35302 FOUGERES cedex
FRANCE

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Frontline Tri-Act spot-on solution for dogs 2-5 kg
Frontline Tri-Act spot-on solution for dogs 5-10 kg
Frontline Tri-Act spot-on solution for dogs 10-20 kg
Frontline Tri-Act spot-on solution for dogs 20-40 kg
Frontline Tri-Act spot-on solution for dogs 40-60 kg

Date: 28/07/2014

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0266/001-005/DC
Name, strength and pharmaceutical form	Frontline Tri-Act spot-on solution for dogs 2-5 kg Frontline Tri-Act spot-on solution for dogs 5-10 kg Frontline Tri-Act spot-on solution for dogs 10-20 kg Frontline Tri-Act spot-on solution for dogs 20-40 kg Frontline Tri-Act spot-on solution for dogs 40-60 kg
Applicant	MERIAL – 29 AVENUE TONY GARNIER – 69007 LYON
Active substance(s)	FIPRONIL and PERMETHRIN
ATC Vetcode	QP53AX65 (fipronil, combination).
Target species	Dogs
Indication for use	For the treatment and prevention of flea and/or tick infestations where repellent (anti-feeding) activity is necessary against sandflies, biting flies and/or mosquitoes. For the treatment and prevention of *Ctenocephalides felis* flea infestations and prevention of *Ctenocephalides canis* flea infestations. The product kills existing *C.felis* fleas within 24 hours. One treatment prevents new flea infestations for 4 weeks. The product can be used as part of a treatment strategy for flea allergy dermatitis where this has been previously diagnosed by a veterinarian. The product has a repellent efficacy against ticks (*Dermacentor reticulatus*) from 7 days and up to week 4 after treatment.. Nevertheless, single ticks may attach and detach within the first 24 hours after infestation. The product has immediate acaricidal efficacy against *Rhipicephalus sanguineus* and *Ixodes ricinus*, but if ticks are present when the product is applied, all ticks may not be killed within 48 hours after treatment. The product has persistent acaricidal efficacy against ticks (*Ixodes ricinus, Dermacentor reticulatus, Rhipicephalus sanguineus*) for 4 weeks. The product has a repellent efficacy (anti- feeding) for 3 weeks against sandflies (*Phlebotomus perniciosus*) and for 4 weeks against mosquitoes *(Culex pipiens*). The product has a persistent insecticidal efficacy for 3 weeks against sandflies (*Phlebotomus perniciosus).* The product repels and kills stable flies (*Stomoxys calcitrans*) for five weeks.

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	Fixed combination application in accordance with Article 13 (b) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	22 May 2014
Concerned Member States for original procedure	AT – BE – BG – CY – CZ – DE – DK – EL – ES – FI – HR - HU – IE – IT – LU – MT – NL – NO – PL – PT – RO – SE – SI – SK – UK

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 6.760% (w/v) fipronil and 50,48% (w/v) permethrin as active substances and excipients butylhydroxytoluene, N-methylpyrrolidone and triglycerides medium chain.

The primary packaging is a single-dose pipette with an extended neck to dispense the product and consists of a heat-formed film of polyethylene-ethylvinyl alcohol-polyethylene/polypropylene. The secondary packaging consists of a plastic/aluminium blister with a plastic/aluminium backing. 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 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 substances are permethrin and fipronil, established active substances. The active substances are manufactured in accordance with the principles of good manufacturing practice.
The active substance specifications are 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 applicant has provided bibliographical data about pharmacological features of fipronil and permethrin.

Fipronil is an insecticide and acaricide belonging to the phenylpyrazole family. Fipronil and its metabolite fipronil sulfone act at ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA) as well as desensitising (D) and non-desensitising (N) channels gated by glutamate (Glu, unique invertebrate ligand-gated chloride channels), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of arthropods.

Permethrin belongs to the Type I class of pyrethroids, which are acaricides and insecticides with repellent activity. 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 hyper-excitability and death of the parasite.

The pharmacokinetic profiles of fipronil and permethrin in combination were studied after topical application in dogs by measuring plasma and hair concentrations for 58 days following treatment. Both permethrin and fipronil, together with its major metabolite, fipronil sulfone, are well- distributed on the haircoat of a dog

during the first day after application. The concentrations of fipronil, fipronil sulfone and permethrin in the hair coat decrease with time and are detectable for at least 58 days after dosing.
Fipronil and permethrin act topically upon contact with external parasites and the low systemic absorption of fipronil and permethrin is not relevant for the clinical efficacy.

Toxicological Studies

The applicant has provided relevant bibliographical data to characterise acute and chronic toxicity, reproductive toxicity and mutagenicity / carcinogenicity for each of the active ingredients of the product.

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 was required.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Tolerance in the Target Species of Animals

The applicant has conducted two controlled target animal tolerance studies using multiples of the recommended dose in adult dogs and to 8-week-old puppies.
A third study was performed in order to assess the oral toxicity of the formulation after ingestion of a full commercial unit. Transient hypersalivation and emesis may be observed until 4 hours after the exposure.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

IV.B Clinical Studies

No clinical or tolerance interactions have been observed in proper clinical and tolerance studies. The combination is shown to be well tolerated with slight adverse effects already known for the individual substances. The efficacy of the combination has also been demonstrated in compliance with the guidelines. The justification of the combination is mainly based on the enlargement of the spectrum.

The applicant has conducted:

- 6 dose confirmation studies to support the treatment and prevention claim against *Ctenocephalides felis* and *Ctenocephalides canis* flea infestations.
- 6 dose confirmation studies to support the repellency claim against *Dermacentor reticulatus*, the acaricidal efficacy against *Rhipicephalus sanguineus* and *Ixodes ricinus* and the persistent acaricidal efficacy against ticks (*Ixodes ricinus, Dermacentor reticulatus, Rhipicephalus sanguineus*).
- A field study supporting tick and flea claims.
- 3 dose confirmation studies to support the repellent efficacy against sandflies (*Phlebotomus perniciosus*) and against mosquitoes (*Culex pipiens*).
- One dose confirmation study to support the claim against stable flies (*Stomoxys calcitrans*).

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.