FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
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DECENTRALISED PROCEDURE (FORMERLY, UK AS RMS)

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Duoflect spot-on solution for cats 0.5-5 kg
Duoflect spot-on solution for dogs 2-10 kg and cats > 5kg
Duoflect spot-on solution for dogs 10-20 kg
Duoflect spot-on solution for dogs 20-40 kg
Duoflect spot-on solution for dogs 40-60 kg

DATE: 24 JULY 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure numbers	New product n° FR/V/0345/001 (old procedure number UK/V/0489/001/DC) New product n° FR/V/0345/002 (old procedure number UK/V/0489/002/DC) New product n° FR/V/0345/003 (old procedure number UK/V/0489/003/DC) New product n° FR/V/0345/004 (old procedure number UK/V0489/004/DC) New product n° FR/V/0345/005 (old procedure number UK/V0489/005/DC) Change of RMS: 28 March 2018
Name, strength and pharmaceutical form	DUOFLECT SPOT-ON SOLUTION FOR CATS 0.5-5 KG; DUOFLECT SPOT-ON SOLUTION FOR DOGS 2-10 KG AND CATS >5 KG; DUOFLECT SPOT-ON SOLUTION FOR DOGS 10-20 KG; DUOFLECT SPOT-ON SOLUTION FOR DOGS 20-40 KG; DUOFLECT SPOT-ON SOLUTION FOR DOGS 40-60 KG
Applicant	CEVA SANTE ANIMALE 10 AVENUE DE LA BALLASTIERE 33500 LIBOURNE France
Active substance(s)	Fipronil (S)-methoprene
ATC Vetcode	QP53AX65
Target species	Dogs, Cats

Indication for use	Dogs Treatment and prevention of flea and/or tick infestations. - Treatment and prevention of flea infestations (*Ctenocephalides spp*). Immediate insecticidal efficacy against new infestations with adult fleas persists for 9 weeks. Prevention of the multiplication of fleas by inhibiting the hatching of flea eggs (ovicidal activity) and the development of flea eggs into adult fleas for 8 weeks after application. - Treatment and prevention of tick infestation (*Dermacentor reticulatus*, *Rhipicephalus sanguineus*). The product has immediate and persistent acaricidal efficacy for 6 weeks after application. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) in dogs. Cats Treatment and prevention of flea and/or tick infestations. - Treatment and prevention of flea infestations (*Ctenocephalides spp*). Immediate insecticidal efficacy against new infestations with adult fleas persists for 8 weeks. Prevention of the multiplication of fleas by inhibiting the hatching of flea eggs (ovicidal activity) and the development of flea eggs into adult fleas persists for 6 weeks after application - Treatment and prevention of tick infestation (*Rhipicephalus turanicus*). The product has immediate and persistent acaricidal efficacy for 5 weeks after application. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

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 original decentralised procedure	29th January 2014. National phase (FR): 24th February 2014
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States for original procedure	Belgium, France, Germany, Italy, Luxembourg, Spain. UK added via RMS change. DK, FI, HU, NO, PL, RO, SI, HR, SE added following repeat use procedure ended on 03 July 2019 (FR/V/0345/001-005/E/001)

I. SCIENTIFIC OVERVIEW

These products are intended for the treatment of flea and/or tick infestations. In dogs, there is immediate insecticidal activity against new infestations of adult fleas (*Ctenocephalides* spp) persisting for 9 weeks, and prevention of the multiplication of fleas and development of adults from flea eggs for 8 weeks after application. The products for dogs also treat and prevent tick infestation (*Dermacentor reticulatus*, *Rhipicephalus sanguineus*) for 6 weeks post-application.

In cats, there is immediate insecticidal activity against new infestations of adult fleas (*Ctenocephalides* spp) persisting for 8 weeks and prevention of the multiplication of fleas and development of adults from flea eggs for 6 weeks after application. The products for cats also treat and prevent tick infestation (*Rhipicephalus turanicus*) for 5 weeks post-application. The products may be used to treat Flea Allergy Dermatitis (FAD) in both dogs and cats.

The products are 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 products 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.[1] 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. Composition

The products contain fipronil and (S)-methoprene.

Fiprospot Duo spot-on solution for cats 1-5 kg: one 0.4 ml pipette contains 68 mg fipronil and 34 mg (S)-methoprene.
Fiprospot Duo spot-on solution for dogs 2-10 kg and cats > 5kg: One 0.7 ml pipette contains 121 mg fipronil and 60 mg (S)-methoprene.
Fiprospot Duo spot-on solution for dogs 10-20 kg: One 1.4 ml pipette contains 240 mg fipronil and 120 mg (S)-methoprene
Fiprospot Duo spot-on solution for dogs 20-40 kg: One 2.8 ml pipette contains 480 mg fipronil and 240 mg (S)-methoprene.
Fiprospot Duo spot-on solution for dogs 40-60 kg: One 4.2 ml pipette contains 720 mg fipronil and 360 mg (S)-methoprene.

The container/closure system consists of:

Front foil:	Polypropylene / polyethylene terephthalate
Lidding foil:	Polyester /aluminium / polyester / polyethylene terephthalate

Pipettes are packed in child resistant blisters. Packs containing 1, 3, 6, 12, 24, 60 or 120 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.

B. Method of Preparation of the Product

The products are 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. The manufacturing process is a mixing and filtering procedure, followed by shipping of bulk product for filling into pipettes.

[1] Summary of Product Characteristics.

C. Control of Starting Materials

The active substances are fipronil and (S)-methoprene active substances not described in the European Pharmacopoeia (Ph. Eur). These established active substances are manufactured in accordance with the principles of good manufacturing practice.
Each active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided. Relevant ASMF were submitted.

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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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. Tests include those for appearance, identity and content of active substances, impurities, water content, preservative content, uniformity of dosage units and microbiological purity.

G. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.
Fipronil

Three production batches were stored in commercial packaging at 25ºC/60% RH and 40ºC/75% RH. Data for 36 months at 25ºC/60% RH and 6 months at

40ºC/75% RH demonstrated that the active substance is stable under these conditions. A retest period of 3 years is acceptable.

(S)-methoprene

Commercially prepared batches of the active substance were stored under nitrogen in light-resistant containers at 25ºC/60% RH and at 40ºC/75% RH. Active substance stored at 25ºC/60% RH was tested at 0, 3, 6, 12, 18 and 24 months. Active substance stored at 40ºC/75% RH was tested at 0, 1, 3 and 6 months. Retest time was established as being 2 years when stored at 2-8ºC.

Stability tests on the finished product were provided for product stored in commercial packaging for up to 24 months at 25ºC/60% RH and at up to 6 months at 40ºC/75% RH. A shelf-life of 3 years was established.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

The applicant provided bibliographical data in support of the toxicological aspects of the two active substances, and also provided studies on the irritation and dermal sensitisation of the products. A user risk assessment (URA and environmental risk assessment (ERA) were also provided.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

Fipronil

In the target organisms, fipronil antagonises the gamma aminobutyric acid (GABA) channels resulting in the blocking of the pre-synaptic transfer of chloride ions across the cell membrane. This results in uncontrolled activity of the nervous system, a manifestation of the insecticidal and acaricidal activity of fipronil. Fipronil additionally binds glutamate activated chloride channels not found in mammals.

(S)-methoprene

This active substance is an analogue of the juvenile hormone of insects. Addition of (S)-methoprene therefore causes abnormalities to occur during the developmental stages of the target organisms, it additionally, has negative effects on the reproductive capacity of adult insects.

Pharmacokinetics

Fipronil

Dermal absorption studies were provided for humans, rats and rabbits. At 200 mg/ml, dermal penetration was seen to a greater extent in rabbits and rats, but at 0.2 mg/ml dermal penetration was similar between human, rabbits and rats. In a rat dermal study using ^{14}C-fipronil, the quantity of active substance absorbed was less than 1% of the dose applied. In a single oral dose study in rats using radio-labelled fipronil, the active substance was found to be widely distributed. Faeces appeared to be the main route of excretion.

Sulfone, amide and reduction products are common metabolites of fipronil metabolism, and fipronil is commonly found within the hair and hair follicles of treated animals.

(S)-methoprene

A single radio-labelled dose of 25 mg/kg was administered orally to rats in one study. Peak concentration occurred after approximately 6 hours, which was followed by a slow decline with a 48 hour half-life. Distribution in rats was found to be in the liver, kidney and lungs, with peak concentration seen at 6-12 hours after dosing. Less of the active substance was seen in fat and muscle. A further study on the metabolism of (S)-methoprene mammals, showed that much is oxidised. The active substance is in general excreted biphasically, with a rapid first phase, followed by a slower second phase.

Suitable data were submitted on the use of the combination of the active substances.

Toxicological Studies

The applicant provided bibliographical data.

- Single Dose Toxicity

Fipronil was found to be acutely toxic to rats and mice following oral administration, and was slightly toxic to rabbits via the dermal route. In general, (s)-methoprene is considered less toxic than fipronil.

- Repeated Dose Toxicity

Fipronil

Studies were provided for repeat dose studies. In rats, dietary doses were given at 0, 0.07, 0.33, 1.93, or 19.87 mg/kg/day to males and 0, 0.07, 0.37, 2.28 and 24.03 mg/kg/day to females. In this study, the NOEL[2] was established at 0.33 mg/kg/day for males and 0.37 mg/kg/day for females. An oral study in dogs given doses at 0, 0.5, 2.0 and 10 mg/kg/day provided NOEL of 2 mg/kg/day for males and 0.5 mg/kg/day for females. In a further study, gelatine capsules given to dogs at 0, 0.2, 2 or 5 mg/kg/day product a NOEL of 0.2 mg/kg/day in both males and females. Neurotoxic effects were noted. Please also refer to carcinogenicity below.

(S)-methoprene

Racemic methoprene was administered to male and female dogs at doses of 6.2, 12 and 120 mg/kg/day for 90 days. No deaths occurred, but an increase in liver weight was noted. A NOEL of 8.6 mg/kg/day was confirmed.

[2] NOEL – No observed effect level.

Reproductive Toxicity, including Teratogenicity

Fipronil

In one study, rates were administered fipronil in the diet at 0, 0.25, 2.5 and 26 mg/kg/day (male rats), and 0, 0.27, 2.7 and 28 mg/kg/day (female rats). At amounts greater than 2.5 mg/kg/day, systemic effects were seen in the parental animals. Litters of treated parental animals showed adverse effects when given the fipronil-containing diet, and a reduction in fertility was also noted The NOAEL for parental toxicity was 0.25 mg/kg/day while for reproductive toxicity, it was observed to be 2.5 mg/kg/day.

A study in rats in which fipronil was administered to the cervical region of female rats at doses of 70, 140 and 280 mg/kg day showed that progesterone levels were increased and oestrodial levels were reduced. This altered the ovulating cycle of the rats. Fipronil reduced the pregnancy index in the highest dose group during mating studies, although other factors such as body weight, weaning weight, implantation and the number of resorptions were not affected.

In addition to further data provided for embryotoxic studies, it was established that fipronil has an effect on reproduction in laboratory animals. Suitable warnings appear in the SPC for use of the product in dogs and cats, i.e. use of the product during pregnancy and lactation is recommended only after the benefit/risk assessment by the responsible veterinarian. A further study in rabbits, administered fipronil at 0, 0.1, 0.2, 0.5 and 1 mg/kg/day demonstrated no treatment-related effect, and established the NOAEL[3] at 1 mg/kg/day.

(S)-methoprene

In one study, rats were fed 0, 25 and 75 mg/kg/day racemic methoprene prior to mating. Pups from ensuing litters were utilised in follow-on mating studies. Evidence from the studies suggested that the NOAEL was 33 mg/kg/day, (29mg/kg/day when corrected for purity). A further study suggested a NOEAL for embryotoxicity of 570 mg/kg/day, (the highest dose tested).

In rabbits, a development study using racemic methoprene showed reduced body weight and increase frequency of abortions and the highest dose used, 2000 mg/kg/day. The NOAEL for both maternal and foetal toxicity was established as being 200 mg/kg/day.

Mutagenicity

Published data were provided showing that the two active substances showed negative for genotoxic tests.

[3] NOAEL – No observed adverse effect level.

Carcinogenicity (if necessary)

Fipronil

Fipronil was added to the diet of mice for 78 weeks at doses 0, 0.1, 0.5, 10, 30 or 60 parts per million. An adverse effect possibly due to an increase in liver weights was seen in the highest dose group only. A NOAEL was established at the equivalent of 0.055 mg/kg/day.

In a further combined carcinogenicity/toxicity study, rats were dosed in the diet with fipronil at 0, 0.019, 0.059, 1.27 or 12.68 mg/kg/day and at 0, 0.025, 0.078, 1.61, or 16.75 mg/kg/day for females. High mortality rates prevented the conclusion of the study with chemical changes and organ alterations noted at the two highest dose rates. Benign and malignant changes occurred in the thyroid glands of both sexes. The NOEL for clinical signs (neurotoxicity) and alterations in haematology/clinical chemistry and thyroid hormones was established for males at 0.019 mg/kg/day and for females at 0.025 mg/kg/day.

(S)-methoprene

Racemic methoprene was given in the diet to mice at concentrations of 38, 150 and 380 mg/kg/day. The notable adverse effect was on changes to the liver which led to the establishment of a NOAEL equivalent to 130 mg/kg/day when corrected for purity.

Other Studies

Fipronil

Fipronil was administered orally to rats at doses of 0, 0.5, 5 and 50 mg/kg. Clinical toxicity was only observed at the highest dose, with neurotoxic signs seen only in male mice and convulsions seen in both species. A NOAEL of 0.5 mg/kg was established. A further study using a spot-on solution was performed in rats, with the active substance applied at 1, 2 and 4 times recommended dose; equivalent to 70, 140 and 280 mg/kg. Some behavioural abnormalities were observed, related particularly to the highest dose.

In a developmental neurotoxicity study in rats, fipronil was administered at 0.05, 0.90 and 15 mg/kg/day. The maternal NOEL was 0.90 mg/kg/day. The NOEL for developmental toxicity was established as 0.05 mg/kg/day, based on a reduction in pup weights and an increase in preputial separation in males.

Studies on thyroid function, which may be altered by fipronil, indicated that biliary clearance of the hormone was affected. This may cause an increase in thyroid-stimulating hormone.

(S-methoprene)

(S)-methoprene was shown to have no androgenic, oestrogenic, glucocorticoid or anabolic activity.

Combined product

In a variety of studies, the combined product was shown not to be an irritant or sensitiser to skin. Fipronil desulfinyl, the significant metabolite of fipronil seen after photodegradation, was also not observed to cause irritation or sensitisation problems. An investigation to determine the level of active substances on gloves after petting dogs showed that levels were highest 12 hours after administration for all compounds and declined over the course of the treatment to 0.5% by 7 days.

Observations in Humans

Published data on the adverse effects of fipronil in humans suggests that acute exposure causes no long-term harm and is self-limiting. Adverse reactions include vomiting, drowsiness headache, vertigo and sweating. There were no data relating to the absorption of (S)-methoprene by humans.

User Safety

The applicant has provided a user risk assessment in compliance with the relevant guideline in force at time of initial application, which discussed possible routes of exposure.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- This product can cause eye irritation.
- Avoid contact of the product with skin, eyes or mouth. People with known hypersensitivity to any of the ingredients should not treat their animal with this product.
- Treated animals should not be handled or played with for at least 12-hours after treatment. Animals should be treated in the evening in order to minimise contact with the treated animal. On the day of treatment, treated animals should not be permitted to sleep with their owner, especially children.
- Do not eat, drink or smoke while handling the product.

- Wash hands thoroughly after use.
- In case of accidental spillage on skin, wash off immediately with soap and water.
- If the product accidentally gets into the eyes, they should be thoroughly flushed with water.
- If the product is accidentally swallowed, seek medical advice immediately and show the package leaflet to the physician.

Environmental Risk Assessment

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline. The product is not to be used in food-producing animals, and the product is not considered to cause a threat to the environment when used as recommended. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed, with a direction that recently treated dogs should not enter watercourses.

III.B Residues documentation

Not applicable.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Refer to Section III, Safety Testing, Pharmacological Studies. Suitable data were provided.

Fipronil - Mode of action
The mode of action has been supported by bibliographical references. The principal drug target for fipronil is the GABA gated chloride channel. Binding results in GABA antagonism leading to neurotoxicity and death in invertebrates. Fipronil can result in neurotoxicity in mammals at high doses however; insects are significantly more sensitive to the toxic effects. Fipronil has been demonstrated to have an adulticidal effect in fleas and ticks.

S-methoprene - Mode of action
The mode of action of S-methoprene has been supported by bibliographical references. S-methoprene is an insect growth regulator (IGR) with ovicidal and larvicidal activity. Specifically it is defined as a juvenile hormone analogue and its principal target is the insect neuroendocrine system where it exerts a regulatory effect at the level of gene expression. Studies have demonstrated the inhibitory effects of S-methoprene on insect development, with the key periods of sensitivity being early embryonic development and metamorphosis. S-methoprene has both an ovicidal and larvicidal effect on fleas when used topically to treat cats and dogs.

Fixed combination of fipronil/(s)-methoprene
The insecticidal and acaricidal effects of fipronil can be demonstrated alongside the IGR effects of S-methoprene in the same animal after topical application.

Tolerance in the Target Species of Animals

The applicant has conducted target animal tolerance studies using multiples of the recommended dose in the target species. A GLP[4]-compliant study was performed in a suitable number of clinically eligible young cats, (32 kittens: 18 male and 14 female; age: 8 weeks ± 2 days on day 0; weight range: 0.27 kg to 0.97 kg on day 0), using a spot-on product containing 1x, 3x or 5x the maximum recommended dose of the final product, over a period of 7 fortnightly applications. Placebo was used as a negative control. This was a five phase, parallel group,

[4] GLP – Good Laboratory Practice.

randomised, blinded, controlled study. Appropriate observations and clinical measurements were made at suitable time points. Analysis showed that the product was tolerated at x 5 the highest maximum recommended dose level (1.75 ml/kg), for a 12 week period.

A second study evaluated the oral safety of the combined product in adult cats. A 0.35 ml/kg dose was administered to a suitable number of clinically eligible animals, along with a placebo administered at the same dose to additional animals. This was a GLP-compliant study. The study design was parallel grouped, randomised, blinded and controlled. Placebo was used as a negative control. Appropriate observations and clinical measurements were made at suitable time points. No adverse reactions were seen.

A further study was conducted in young dogs. In this study, a suitable number of clinically eligible young dogs, (32 puppies: 12 male and 20 female; age: 8 weeks ± 2 days on day 0; weight range: 1.38 kg to 3.82 kg on day 0), were treated using a spot-on product containing 1x, 3x or 5x the maximum recommended dose of the final product, over a period of 7 fortnightly applications. Placebo was used as a negative control. This was an eight phase, parallel group, randomised, blinded, controlled study. Appropriate observations and clinical measurements were made at suitable time points. Analysis showed that the product was safe for use, no adverse reactions were seen.

A fourth study evaluated the oral safety of the combined product in adult dogs. A 0.36 ml/kg dose was administered to a suitable number of clinically eligible animals, along with a placebo administered at the same dose to additional animals. This was a GLP-compliant study. The study design was parallel group, randomised, blinded and controlled. Placebo was used as a negative control.

Appropriate observations and clinical measurements were made at suitable time points. Salivation was observed in all animals and vomiting was observed in 50% of the animals. The SPC carries suitable warnings demanding the avoidance of oral ingestion of the product. The adverse reactions observed did not have a systemic affect.

Resistance

Bibliographical references were provided in relation to the possible resistance of ticks and fleas to fipronil, not thought to be a major issue in Europe at the current time. No data is available for (S)-methoprene. Adequate warnings and precautions appear on the product literature and in the SPC.

IV.B Clinical Studies

The applicant conducted dose titration and dose confirmation studies, and field clinical trials to demonstrate the efficacy in cats and dogs, according to GCP and the CVMP Guideline EMEA/CVMP/EWP/005/2000 - Rev.2 (Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats).

Efficacy summary for cats:

IGR efficacy against the further development of flea eggs and larvae:

- During a dose titration study, ovicidal and larvicidal efficacy was demonstrated at 6 mg/kg S-methoprene.
- Persistence of IGR (ovicidal activity and prevention of the development of flea eggs to adult fleas) efficacy was shown during two dose confirmation studies until 47 days and 52 days post-treatment respectively.

Adulticidal efficacy against fleas:

- Minimum effective dose 12 mg/kg of fipronil against *Ctenocephalides felis* was shown in a dose titration study.
- Immediate efficacy above 95% was demonstrated during dose titration and dose confirmation studies.
- Persistence of adulticidal efficacy until 44 days and 58 days post-treatment was shown during two dose confirmation studies respectively.
- A field study in representative cats across two geographic regions demonstrated non-inferiority to the reference product Frontline Combo Cat, Merial. These studies were randomised controlled studies over 28 days.

Adulticidal efficacy of fipronil against ticks:

- Minimum effective dose 12 mg/kg of fipronil against *Rhipicephalus turanicus*. was shown in a dose titration study.
- Immediate efficacy against *R. turanicus* was demonstrated during two dose dose confirmation studies. Persistence of efficacy against *R. turanicus* for 30 days and 37 days post-treatment was demonstrated during two dose confirmation studies respectively.

The following indications in cats are supported for the proposed fixed combination:

”Treatment and prevention of flea and/or tick infestations.
The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).
Treatment and prevention of flea infestations (*Ctenocephalides spp*). Immediate insecticidal efficacy against new infestations with adult fleas is seen persisting for 8 weeks. Prevention of the multiplication of fleas by inhibiting the hatching of flea

eggs (ovicidal activity) and the development of flea eggs into adult fleas for 6 weeks after application.

Treatment and prevention of tick infestation (*Rhipicephalus turanicus*). The product has immediate and persistent acaricidal efficacy for 5 weeks after application."

Efficacy Summary for Dogs:

IGR efficacy against the further development of flea eggs and larvae:
- During a dose titration study, ovicidal and larvicidal efficacy was demonstrated at 6 mg/kg S-methoprene.
- Persistence of IGR (ovicidal activity and prevention of the development of flea eggs to adult fleas) efficacy was shown during one dose confirmation study until 61 days and until 8 weeks during a water challenge study.
- Weekly water immersion or a single pre-treatment shampoo in emollient shampoo was not shown to influence the persistence of IGR efficacy until day +62. Weekly shampooing with emollient shampoo or chlorhexidine containing shampoo was shown to reduce the persistence of IGR efficacy to 6 weeks.

Adulticidal efficacy of fipronil against fleas:
- Minimum effective dose 12 mg/kg of fipronil against *Ctenocephalides felis* was shown in the dose titration study.
- Immediate efficacy above 95% was demonstrated during dose titration and dose confirmation studies.
- Persistence of this effect for 65 days post-treatment was demonstrated during the dose titration and one dose confirmation studies.
- Water emersion weekly or a single pre-treatment shampoo in emollient shampoo product was not shown to influence immediate adulticidal efficacy. Weekly shampooing with emollient shampoo or chlorhexidine containing shampoo was shown to reduce the persistence of adulticidal efficacy to three weeks.
- A field study in representative dogs across two geographic regions indicated non-inferiority to the reference product Frontline Combo Dog, Merial. These studies were randomised controlled studies over 28 days.

Acaricidal efficacy of fipronil against ticks:
- Minimum effective dose 12 mg/kg of fipronil against *Rhipicephalus sanguineus* was shown in a dose titration study.
- Immediate efficacy against against *Dermacentor reticulatus* and *Rhipicephalus sanguineus* ticks was demonstrated during two dose confirmation studies.
- Persistence of acaricidal efficacy was demonstrated for 37 days post-treatment against *Rhipicephalus sanguineus* during one dose confirmation study and for 44 days post-treatment during two dose confirmation studies

against *Dermacentor reticulatus* and *Rhipicephalus sanguineus* ticks respectively.

- A field study in representative dogs across two geographic regions demonstrated non-inferiority to the reference product Frontline Combo Dog, Merial. These studies were randomised controlled studies over 28 days.

The following indications are supported in dogs for the proposed fixed combination:

”Treatment and prevention of flea and/or tick infestations. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). Treatment and prevention of flea infestations (*Ctenocephalides spp*). Immediate insecticidal efficacy against new infestations with adult fleas persists for 9 weeks. Prevention of the multiplication of fleas by inhibiting the hatching of flea eggs (ovicidal activity) and the development of flea eggs into adult fleas for 8 weeks after application. Treatment and prevention of tick infestation (*Dermacentor reticulatus, Rhipicephalus sanguineus*). The product has immediate and persistent acaricidal efficacy for 6 weeks after application.”

The followining warning is also added in the SPC:
“The effect of bathing dogs on the duration of product efficacy against fleas has been studied.
Weekly water immersion of dogs following treatment had no effect on the duration of efficacy. Shampooing of dogs with an emollient shampoo 48 hours prior to treatment had no effect on duration of efficacy. Weekly shampooing with an emollient shampoo in dogs may reduce the duration of efficacy to 3 weeks against adult fleas and to 6 weeks against immature stages of fleas. Weekly bathing with a chlorhexidine shampoo may reduce effectiveness against adult fleas to 3 weeks. No data on the effect of bathing/shampooing on the efficacy of the product in cats is available.”

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.

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 veterinary Heads of Agencies website (www.hma.eu).

This section 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.

No significant changes in safety or efficacy data, except extension of the small strength to cats below 1 kg during the renewal procedure (DUOFLECT SPOT-ON SOLUTION FOR CATS ~~1~~ 0.5-5 KG).

The following changes in administrative or quality data were approved:

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change in the invented name UK/V/0489/001-005/IB/003	N/A	02/04/2015
Change in the DDPS - UK/V/xxxx/IA/110/G	N/A	10/08/2016
Change in the DDPS - UK/V/0489/001-005/IA/005/G	N/A	23/08/2017
Modification relating to active substances suppliers FR/V/0345/001-005/IA/001	N/A	13/07/2018
Modification relating to active substances suppliers FR/V/xxxx/WS/034	N/A	20/12/2018