Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

Draft PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Seresto (Foresto) collar for cats
Seresto (Foresto) collar for dogs ≤ 8 kg
Seresto (Foresto) collar for cats and dogs ≤ 8 kg
Seresto (Foresto) collar for dogs > 8 kg

Date: 29 February 2016

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/143/001-004/DC
Name, strength and pharmaceutical form	Seresto (Foresto) collar for cats Seresto (Foresto) collar for dogs ≤ 8 kg Seresto (Foresto) collar for cats and dogs ≤ 8 kg Seresto (Foresto) collar for dogs > 8 kg, 4.50 g + 2.03 g collar
Applicant	Bayer Vital GmbH, Tiergesundheit 51368 Leverkusen, Germany
Active substance(s)	Imidacloprid, Flumethrin
ATC Vetcode	QP53AC55
Target species	Dog, cat
Indication for use	***Cats:*** For the treatment and prevention of flea (*Ctenocephalides felis*) infestation for 7 to 8 months. Protects the animal's immediate surroundings against flea larvae development for 10 weeks. Seresto can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). The product has persistent acaricidal (killing) efficacy (*Ixodes ricinus, Rhipicephalus turanicus)* and repellent (anti-feeding) efficacy against tick infestations (*Ixodes ricinus)* for 8 months. It is effective against larvae, nymphs and adult ticks. Ticks already on the cat prior to treatment may not be killed within 48 hours after collar application and may remain attached and visible. Therefore removal of ticks already on the cat at the time of application is recommended. The prevention of infestations with new ticks starts within two days after application of the collar. Ideally, the collar should be applied before the beginning of the flea or tick season.

	Dogs: For the treatment (*Ctenocephalides felis*) and prevention of flea (*Ctenocephalides felis, C. canis*) infestation for 7 to 8 months. Protects the animal's immediate surroundings against flea larvae development for 8 months. Seresto can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). The product has persistent acaricidal (killing) efficacy against tick infestations (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus)* and repellent (anti-feeding) efficacy against tick infestations (*Ixodes ricinus, Rhipicephalus sanguineus)* for 8 months. It is effective against larvae, nymphs and adult ticks. Ticks already on the dog prior to treatment may not be killed within 48 hours after collar application and may remain attached and visible. Therefore removal of ticks already on the dog at the time of application is recommended. The prevention of infestations with new ticks starts within two days after application of the collar. The product provides indirect protection against the transmission of the pathogens *Babesia canis vogeli* and *Ehrlichia canis* from the tick vector *Rhipicephalus sanguineus*, thereby reducing the risk of canine babesiosis and canine ehrlichiosis for 7 months. For treatment of biting/chewing lice (*Trichodectes canis*) infestation. Ideally, the collar should be applied before the beginning of the flea or tick season.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicinal Agencies website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13b of Directive 2001/82/EC as amended.
Date of completion of the original Decentralised procedure	27.07.2011
Date product first authorised in the Reference Member State (MRP only)	N.A.
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DK, EE, FI, FR, EL, HU, IS, IE, IT, LV, LT, LU, NL, NO, PL, PT, RO, SK, SI, ES, SE, 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; local and systemic side effects observed in the target animals 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

One **38 cm collar** (12.5 g) contains 1.25 g imidacloprid and 0.56 g flumethrin as active substances and the excipients titanium dioxide (E 171), iron oxide black (E172), dibutyladipate, propylene glycol dicaprylocaprate, epoxidised soybean oil, stearic acid and polyvinyl chloride.

One **70 cm collar** (45 g) contains 4.5 g imidacloprid and 2.03 g flumethrin as active substances and the excipients titanium dioxide (E 171), iron oxide black (E172), dibutyladipate, propylene glycol dicaprylocaprate, epoxidised soybean oil, stearic acid and polyvinyl chloride.

One collar is packed into a PETP/PE bag and a box. The particulars of the container and controls performed are provided and conform to the regulation.

The choice of the formulation is 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 products have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances imidacloprid and flumethrin are established substances not described in the European Pharmacopoeia. Both 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 materials. Batch analytical data demonstrating compliance with the specifications 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 these products.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specifications control the relevant parameters for the pharmaceutical form. The tests in the specifications, 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 specifications.

G. Stability

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

Stability data on the finished products have been provided in accordance with applicable European guidelines, demonstrating the stability of the products throughout their shelf life when stored under the approved conditions.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant conducted studies with the active ingredients of the collar and provided bibliographic data. It was shown that imidacloprid modifies cholinergic synaptic transmission in insects through binding to post-synaptic nicotinic acetylcholine receptors in the central nervous system which results in sustained

depolarisation and paralysis. Flumethrin specifically binds to sodium channels of neural cell membranes of ectoparasites thereby inducing a delay in repolarisation. These effects lead to death of the parasites.

Both active ingredients are slowly and continuously released from the collar towards the animal and reach insecticidal/acaricidal concentrations on the animal's body surface during the entire efficacy period. Imidacloprid was transiently found in low concentrations in plasma from cats and dogs wearing the collar while flumethrin was not detectable.

Toxicological Studies

- Single Dose Toxicity

Acute toxicity studies with imidacloprid were performed in rats and mice. After oral dosing in mice the no observed adverse effect level (NOAEL) was 10 mg/kg body weight (bw) based on motor and locomotor activity. In rats the NOAEL was 10 mg/kg bw following intraperitoneal dosing. Dermal toxicity of imidacloprid was low, the no observed effect level (NOEL) was 5000 mg/kg bw in rats.

The acute oral toxicity of flumethrin in rats was characterised by a NOAEL of 1 mg/kg bw based on reduced motility, staggering, and spastic gait. The lowest lethal dose was 25 mg/kg bw. The two isomers of flumethrin, trans-Z1 and trans-Z2 flumethrin, had different toxic potency as indicated by LD_{50} values of trans-Z1 flumethrin of > 5000 mg/kg bw in male rats and > 500 mg/kg bw in female rats and of trans-Z2 flumethrin of 10 to 50 mg/kg bw in male and female rats.

Acute dermal toxicity at doses of 500 and 1000 mg/kg bw in male rats produced clinical signs such as reduced activity, emaciation, hunched posture, lateral recumbency, nasal discharge, piloerection, polyuria, salivation, stained fur, sensitivity to touch or sound and dermal erythema.

No additive or synergistic effects of a combination of imidacloprid and flumethrin became evident in an acute oral toxicity study in rats.

- Repeated Dose Toxicity

Imidacloprid was administered in the diet for 52 weeks to dogs and revealed a low potential for toxic effects. The NOEL was 500 ppm corresponding to 15 mg/kg bw.

In a 13-week feeding study with flumethrin in dogs, reduced food consumption, vomiting, and slight reduction in body weight were observed from 200 ppm on.

- Reproductive Toxicity, including Teratogenicity:

The effects of imidacloprid on reproduction were investigated in a multigeneration study in rats. Flumethrin was tested in a multigeneration study and in two-generation studies in rats. The results of these studies did not reveal adverse effects of imidacloprid or flumethrin on fertility or reproduction.

Embryo-fetal development studies were performed in rats and rabbits. Neither imidacloprid nor flumethrin induced teratogenic or fetotoxic effects.

No studies on the combination were performed. The safety of the product has not been established in pregnant and lactating target animals, therefore use of the collar is not recommended during pregnancy and lactation.

- Mutagenicity

Imidacloprid and flumethrin were investigated for mutagenic potential in standard in vitro and in vivo test systems such as Salmonella microsome assay (Ames test), hypoxanthine-guanine-phosphoribosyl-transferase assay (HGPRT assay), rat primary hepatocyte unscheduled DNA synthesis assay (UDS assay), mouse bone marrow micronucleus induction test, and hamster bone marrow chromosome aberration assay. Both compounds were considered to possess no mutagenic activity.

- Carcinogenicity:

Based on the results of two-year feeding studies in rats no evidence of carcinogenic effects of imidacloprid or flumethrin was found.

Observations in Humans

In healthy male volunteers single or repeated dermal applications of a 1% solution of imidacloprid did not induce local signs of irritation. The same formulation had no sensitizing effects in male volunteers.

User Safety

A comprehensive user risk assessment has been provided by the Applicant.
Small children and toddlers resp. who are in close contact with collar-wearing pets were considered the most susceptible population. They may be exposed dermaly as well as orally (via hand-to-mouth contact) when playing with or stroking animals or in case that they put remnants of the collar into their mouth or lick the collar when it is attached to the pet.
The transfer of imidacloprid and flumethrin to the hand of users who administer collars to pets or who stroke a pet wearing the collar was investigated and the obtained data were used to calculate theoretical dermal and oral exposure rates of adults and children. Based on these theoretical exposure rates and NOAELs from relevant animal toxicity studies, margins of safety were calculated for various exposure scenarios. From the results of these calculations it was concluded that exposure to the ingredients of the collar is not associated with an unacceptable risk for users who administer the collar, as well as animal tenders and children who live in close contact with collar-wearing pets.
Appropriate warnings and precautions are included in the product literature in order 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 further assessment was required because of the insecticidal properties of the active ingredients (ectoparasiticides). A tailored risk assessment was performed by the applicant in order to assess the risk of an increase of the environmental concentration of the active ingredients. The applicant showed that no losses of the active ingredients of the collar itself are expected. Further, the applicant simulated a bathing and rain fall exposure resulting from losses of the active ingredients of the animals' fur. Two toxicity studies on waterflea were provided. The risk for sediment dwelling organisms was discussed. The assessment concluded that no risk for daphnids and sediment dwelling organisms resulted. No Warnings are therefore required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant has conducted *in vitro* studies and provided bibliographical information on the active ingredients of Seresto-collars. From these data imidacloprid was characterised as a so-called neo-nicotinoid that inhibits signal transduction on nicotinic acetylcholine receptors of insects, whereas pyrethroids such as flumethrin were found to bind to voltage-gated sodium channels causing repeated neuron activation. The cooperation of imidacloprid and flumethrin was suggested to cause the death of parasites via permanent depolarization of insect neurons. This hypothesis formed the basis for the combined use of these compounds in Seresto-collars.

In vitro-experiments confirmed a synergistic effect of both compounds on fleas when applied in a 1:1.85 ratio, whereas the efficacy against ticks was apparently based on the mono-substance flumethrin.

Pharmacokinetics
When Seresto-collars were applied to dogs and cats according to the proposed treatment regime, the actives reached parasiticidal concentrations in the hair coat of animals over the claimed 8 months-activity period. A proportion of the actives was absorbed either through the skin or by licking the coat and appeared in serum.

These amounts were not expected to contribute to the parasiticidal efficacy of the collars.

Tolerance in the Target Species of Animals

The Applicant submitted a series of target animal safety studies in puppies and kittens as well as in young adult dogs and cats. Treatment regimes included the application of multiple Seresto-collars. Although concentrations of imidacloprid and flumethrin determined on the hair coat of animals did not parallel the number of collars applied, the target animals had been exposed to concentrations of the actives that exceeded the levels at regular treatment considerably.

Tolerance of dogs and cats towards treatment with Seresto-collars was examined by applying standard clinical and laboratory parameters and by comparing results with those from animals treated with vehicle collars or with no collars at all.

Target animal safety was also examined during the clinical efficacy studies.

Tolerance of dogs and cats even to multiple collars was generally good. There were incidences of vomiting or depression and changes in food-intake associated with the application of collars in cats, and incidences of eye discharge, vomiting and loose stools and changes in food-intake in dogs in some experiments, which were not confirmed in others. Drug-relation of these events particularly in cats could not be ruled out.

Hair thinning and skin reactions primarily underneath the collars were consistent findings across all experiments in dogs and cats. Re-growth of hair and healing of skin lesions was observed in most animals without removal of collars being necessary. In some animals, however, lesions healed only after collars had been removed. A single case of contact dermatitis probably attributable to collar application was observed in a cat.

In addition to the adverse events already noted during clinical trials, mild behavioural disorders that may include scratching at the application site were observed in both dogs and cats treated in the field after the product has been marketed. Also, in rare cases in cats and in very rare cases in dogs, application site reactions such as dermatitis, inflammation, eczema or lesions were observed and in these instances, collar removal is recommended.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

The Applicant presented literature references according to which pyrethroid-resistance has been reported in tick strains isolated from farm animals overseas.

The mechanism of resistance towards these compounds was attributed to mutations affecting the sodium channel and to increased metabolic degradation of the compounds.
It was suggested that the differences in the targets of imidacloprid (nicotinic acetylcholine receptors) and flumethrin (voltage-gated sodium channels) in insects would complicate the development of resistance.

IV.B Clinical Studies

Laboratory Trials

The applicant has conducted a number of dose determination studies according to both GCP and ectoparasitic guidelines showing that a concentration of 4.5% flumethrin and 10% imidacloprid per Seresto® collar is necessary for a seasonal 7 to 8 months prevention period against tick and flea infestations in cats and dogs.

Ctenocephalides (Ct.) felis in cats and dogs
The applicant has additionally performed dose confirmation studies (5 DCS in cats, 6 DCS in dogs) according to both GCP and ectoparasitic guidelines to confirm the insecticidal efficacy of the Seresto® collar against the adult flea *Ct. felis*. From the study results submitted it can be concluded that the Seresto® collar provided immediate and long term insecticidal efficacy against the cat flea *Ct. felis* for 7-8 months in cats and dogs.

The larvicidal activity of the debris/hair coat obtained from treated cats and dogs during the course of long term studies have also been tested. A larvicidal blanket test revealed efficacy of 10 weeks and 8 months in the surroundings of treated cats and dogs, respectively. The proven long term protection periods are adequately considered in the SPC.

Ctenocephalides (Ct.) canis in dogs
The applicant has conducted both a dose confirmation and a field study to confirm the insecticidal efficacy of the Seresto® collar against the flea species *Ct. canis* in dogs. Insufficient treatment efficacy against *Ct. canis* fleas already on the animals was observed in the laboratory dose confirmation study. In that study only prevention of new flea infestations could be demonstrated for a period of 7 to 8 months.

Flea Allergy Dermatitis (FAD) in cats and dogs
FAD signs completely disappeared after one or two months after treatment as demonstrated in the controlled laboratory and field studies. Additionally, wearing the collar prevents successfully cats and dogs from becoming FAD.

Dose confirmation studies (DCS) in ticks
Additional dose conformation studies (5 in cats, 9 in dogs) have been performed to confirm the acaricidal efficacy of the Seresto® collar against the main cat (*Ixodes (I.)*

ricinus, Rhipicephalus (R.) turanicus) and dog (*R. sanguineus, I. ricinus, Dermacentor [D.] reticulatus*) tick species as well as to generate supportive data of non EU tick species (cats: *Amblyomma [A.] americanum*, dogs: *D. variabilis, I. holocyclus*).

Ixodes ricinus in cats
Two persistent efficacy DCS and one immediate efficacy DCS demonstrated adequate acaricidal (killing) and repellent (anti-feeding) activity against *I. ricinus* over 8 months after application of the collar.

Rhipicephalus turanicus ticks in cats
The acaricidal efficacy of the Seresto® collar against *R. turanicus* in cats was adequately evidenced in one DCS as well as one DDS over a period of 8 months. Repellent activity, however, against *R. turanicus* could not be sufficiently demonstrated.

Ixodes ricinus in dogs
Two persistent efficacy DCS and one immediate efficacy DCS were conducted to evaluate the efficacy of the collar against *I. ricinus* ticks. Acaricidal efficacy has been demonstrated at all monthly challenges with *I. ricinus* for the 8 months study period tested.

D. reticulatus in dogs
Adequate persistent efficacy for 6 months could be proven in one DDS against ticks (*R. sanguineus* and *D. reticulatus*) and fleas. In a further DCS the acaricidal efficacy against *D. reticulatus* was detected for 8 months. Immediate efficacy (>90 %) against existing tick infestations, however, could not been demonstrated.

R. sanguineus in dogs
One immediate efficacy DCS as well as four persistent efficacy DCS were conducted to evaluate the efficacy of the collar against *R. sanguineus* ticks in dogs. The results confirmed the persistent acaricidal efficacy against the brown dog tick *R. sanguineus* for up to 8 months.

Non-European ticks species in cats and dogs
Acaricidal activity has been demonstrated in cats against *I. hexagonus* and the non-European tick species *A. americanum* as well as in dogs against *I. hexagonus* and the non-European tick species *I. scapularis (*deer tick*),* the Australian paralysis tick *I. holocyclus* and the American dog tick *D. variabilis*. They are listed in paragraph 5.1 Pharmacodynamic properties of the SPC.

Efficacy against eggs, larvae and nymphs of ticks
It could be demonstrated *in-vitro* that 5 to 10 % of laid eggs from *R. sanguineus* ticks showed a shrivelled, dull and dry appearance when exposed to the sublethal dose of 4 mg flumethrin/L. The appearance of the treated eggs indicated a sterilising effect of flumethrin.

Commentaire [A1]: *D. reticulatus in dogs is missing. One long-term DCS and one long-term DDS were conducted.*

The higher susceptibility of tick larvae and nymphs against imidacloprid/flumethrin was demonstrated *in vitro*, justifying the extension of the claim to nymphs and larvae of ticks.

Repellent efficacy against ticks
Three persistent and two short term efficacy DCS in dogs and cats showed a repellent efficacy of the collar at 6 h after each challenge infestation with *I. ricinus* ticks in both cats and dogs for 8 months. Repellent efficacy against subsequent *R. sanguineus* challenge infestations was also demonstrated in dogs for the 8 months treatment period.

Variable treatment efficacy against ticks already on the animals before applying the Seresto® collar was noted in the studies and only a persistent acaricidal and repellent efficacy claim was demonstrated. The advice to remove ticks already on the dog at the time of application is correctly addressed in the SPC.

Efficacy against *Trichodectes (Tr.) canis* lice in dogs
A DCS was carried out with the collar showing curative efficacy up to D+35 after treatment in dogs. The period covers the entire life cycle of *Tr. canis* from hatching to adults. The claim was supported by a bridging study with an authorized spot on formulation containing imidacloprid. Bridging was justified due to the higher imidacloprid concentrations in the hair coat of collared dogs in comparison to the spot on- treated dogs over time.

The treatment with a Seresto ® collar resulted in complete cure after three months in *Sarcoptes scabiei* pre-infested dogs.

The product literature accurately reflects the demonstrated activity spectrum of the Seresto® collar against fleas, lice, mites and ticks in cats and dogs.

<u>Indirect protection against the transmission of canine vector borne diseases (CVBD)</u>

Ehrlichia canis disease transmission prevention
Indirect protection against the transmission of *Ehrlichia canis* has been demonstrated following challenge infestations of dogs every 14 days with infected *R. sanguineus* ticks in a home environmental tick borne disease transmission study. 100% protection of disease transmission could be proven throughout the entire study period in collared dogs except for D+309. The acaricidal efficacy was always higher than 95%.

Babesia canis vogeli disease transmission prevention:
Indirect protection against the transmission of *Babesia canis vogeli* has been proven following challenge infestations of dogs every 14 days with infected *R. sanguineus* ticks in a kennel environmental tick borne disease transmission study. Indirect protection efficacy against transmission of *Babesia canis vogeli* ranged from 92 % to

100 % throughout the study period of 8 months. Indirect protection was further evidenced in a controlled field study in Italy, where no treated dog was found positive in a highly endemic area during the 7 months follow up, while the incidence density rate (IDR) per year for the untreated control was calculated to be 62.85 %.

Leishmania infantum disease transmission prevention
Data from two clinical field studies over a full season in endemic areas in Italy demonstrate 93.4 – 100 % prevention of *Leishmania infantum* transmission *via* sand flies in collar-treated dogs when compared to untreated dogs showing an IDR of 60.7 % and 46.2 %, respectively.

Babesia c. canis disease transmission prevention
100% prevention against the transmission of *Babesia c. canis* via *D. reticulatus* ticks has also been shown in one laboratory study at D+28 after treatment whereas 100 % of the control dogs were infected.

Anaplasma phagocytophilum disease transmission prevention
100% prevention against the transmission of *Anaplasma phagocytophilum* by the vector tick *I. ricinus* has been shown in one laboratory study at 2 months after treatment. In contrast, 50% of the untreated control dogs were tested positive.

Indirect protection against the transmission of feline vector borne diseases (FVBD)

Cytauxzoon felis disease transmission prevention
100% prevention against the transmission of *Cytauxzoon felis* by the vector tick *Amblyomma americanum* has been shown in one laboratory study at single infestation time at one month after treatment. In contrast, 90% of untreated control cats were infected with *Cytauxzoon felis.*

The indirect protection properties of the collar against the transmission of these pathogens are accurately reflected in the SPC.

Field Trials

Two positive controlled field studies involving different North and clinical multicentre and multiregional South European countries were conducted with the final formulation in cats and dogs. Studies have been carried out in comparison to a positive control group (CP) wearing approved collars containing dimpylate.

In cats a total of 256 patients (IVP) belonging to different breeds and husbandries were treated with the collar while 90 animals served as positive controls. In ticks non-inferiority of the IVP compared to the CP at a margin of 15% could be demonstrated. In fleas, both non-inferiority and superiority of the test collar could be shown. There was a distinct reduction in the number of cats suffering on flea allergy dermatitis. On D+28 after treatment none of the 18 FAD cases prior to treatment showed clinical signs of FAD anymore.

In dogs, a total of 286 (IVP) dogs belonging to different breeds and husbandries where treated once with the Seresto® collar while 136 dogs were assigned to the positive control group (CP). Sufficient efficacy against both tick and flea infestation was confirmed over a study period of 8 months. Superiority was demonstrated for the primary endpoints, efficacy in ticks and fleas. There was a pronounced reduction in the number of flea allergy dermatitis patients during the study.

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 Heads of Veterinary Medicinal 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.

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
Change in the shelf-life of the finished product (DE/V/0143/001-004/IB/005)	N/A	12/12/2013

Safety/efficacy changes

Summary of change **(Type; application number)**	**Section updated in Module 3**	**Approval date**
Changes to pharmacovigilance data leading to changes in the SPC and product literature (DE/V/0143/001-004/IB/001)	IV	08/06/2013
Addition of a new therapeutic indication. The change relates to Feline Vector Borne Diseases. (DE/V/0143/001,003/II/002)		14/05/2014

Addition of new therapeutic indications. The changes relate to Canine Vecor Borne Diseases and to the dog flea (Ctenocephalides canis). (DE/V/0143/II/003/G)		14/05/2014
Addition of a new therapeutic indication. The change relates to flumethrin's tick sterilising effects. (DE/V/0143/001-004/II/004)		07/02/2014
Implementation of change(s) requested by the RMS Germany following the assessment of the Periodic Safety Update report (01.08.2013 - 31.01.2014): changes to section 4.6 of the Dog SPCs and to the product literature. (DE/V/0143/002-004/1A/008		20/08/2015