August 2011
EMA/532709/2010
Veterinary Medicines and Product Data Management

Scientific Discussion

CERTIFECT (EMEA/V/C/002002)

This module reflects the initial scientific discussion for the approval of CERTIFECT (as published in August 2011). For information on changes after this date please refer to module 8 of the EPAR (steps taken after authorisation).

1. Summary of the dossier

CERTIFECT contains the adulticidal antiparasitic active ingredients, fipronil and amitraz, in combination with an ovicidal and larvicidal active ingredient, (S)-methoprene, and is presented in packs containing blister cards of dual cavity pipettes. It is indicated to be used against infestations with ticks, alone or in association with fleas and/or chewing (biting) lice. The route of administration is topical spot-on use. The target species is dogs. CERTIFECT is eligible for assessment under the centralised procedure under Article 3 of Regulation (EC) No 726/2004 as it contains a new combination of active substances which has not been authorised in the Community for use in a medicinal product intended for use in animals.

2. Quality

Composition

CERTIFECT spot-on solution for dogs is a combination product containing in one half of the pipette the fipronil/(S)-methoprene solution and in the other half of the pipette amitraz solution, in a dual cavity (chamber) pipette, designed as a topically applied treatment to control fleas and ticks on dogs. The product is prepared as a ready to use liquid in single use dual pipettes in four different fill volumes (1.07 ml, 2.14 ml, 4.28 ml and 6.42 ml) to cover the recommended minimum dose of 6.7 mg/kg bodyweight (bw) for fipronil, 6 mg/kg bw for (S)-methoprene and 8 mg/kg bw for amitraz to dogs, by topical application to the skin.

Fipronil/(S)-methoprene solution (solution A) corresponds to a product already licensed and marketed in the EU (by the applicant, MERIAL) containing fipronil and (S)-methoprene (10% w/v / 9% w/v) as active substances, and including butylhydroxyanisole and butylhydroxytoluene as antioxidants. Polysorbate 80 and povidone are included as crystallisation inhibitors. Ethanol and diethylene glycol monoethyl ether are included as solvents.

Amitraz solution (solution B) consists of the active substance amitraz in a solvent, octyl acetate. No preservative is included in the composition.

Container

The primary package consists of a dual cavity pipette. The four pipette sizes have the same external size except for the formed cavity, which increases with the volume.

The composition of the double cavity pipette and the secondary packaging were described in detail. Each blister card contains three individually packaged pipettes.

In part IIC of the dossier, sufficient data about the primary and secondary packaging were provided. The retained controls were satisfactory.

A precaution "*Cut off pipette tip with a pair of scissors*" was added in SPC section "*4.9 Amounts to be administered and administration route*" to ensure that the pipette is opened satisfactorily.

Development pharmaceutics

The applicant developed separately the amitraz and fipronil/(S)-methoprene solutions, but in the same packaging to allow the simultaneous application of both solutions. This point is justified in respect of the compatibility studies. The product consists of two solutions: one containing fipronil and (S)-methoprene as active substances and the other containing amitraz as active substance. The data provided for the fipronil/(S)-methoprene solution development corresponded to those provided in the fipronil/(S)-methoprene solutions for cats/dogs already marketed by MERIAL. No new studies were presented. The choice of each excipient in the formulation was justified.

An important part of the pharmaceutical development corresponds to the development of the amitraz solution. Due to the sensitivity and instability of amitraz an important aspect was to stabilise amitraz. Optimisation of the manufacturing process of amitraz solution was also developed and the choice of the recommended parameters was explained and justified.

The packaging was chosen to ensure chemical and physical compatibility with both solutions, to protect fipronil/(S)-methoprene solution against oxidation, to exclude oxygen from diethylene glycol monoethyl ether, to maintain container-closure integrity, to exclude moisture from amitraz and also to provide child resistant packaging. An additional factor was simplicity for the user, presenting the solutions in an easy to squeeze and easy to apply presentation. Container-closure integrity testing of the dual pipettes and absence of cross-contamination between pipettes were also demonstrated. Various secondary packagings were tested to reduce amitraz hydrolysis as much as possible, protect from moisture and achieve a satisfactory level of child resistance of the packaging. The choice of the secondary packaging was considered to be adequately justified.

Reproducibility of the dose was studied and all values remained within the dose limits retained in the finished product specification.

Method of manufacture

Both solutions are manufactured separately by mixing all formulation ingredients and then filling them into the double cavity pipettes which are then packaged into the secondary package (blister). The manufacturing formulae provided for both solutions are satisfactory. Flow charts of the manufacturing processes are clearly presented in the dossier. The principle of manufacture of each solution consists of the preparation of the solution (dissolution of the active substance and the excipients), filtration and then filling into double cavity pipettes. The amitraz solution is treated before filtration to ensure the stability of the solution. Details on this manufacture were given.

The packaging of both solutions consists of the forming of the double cavity pipettes followed by filling with amitraz solution and then with fipronil/(S)-methoprene solution.

The in-process controls were described and completed by the controls performed during the primary packaging and during the secondary packaging step. The tests were satisfactorily described.

Validation of the manufacturing process

The manufacture of the fipronil/(S)-methoprene solution was satisfactorily validated for the range of batch sizes. The manufacture of the amitraz solution was performed on pilot batches and was completed on larger consecutive batches. Validation data show that the process is reproducible and that the capacity of the filter is adequate.

The maximal storage time of fipronil/(S)-methoprene solution was specified. The maximal storage time of amitraz solution before filling was also specified and validated. Considering among other factors, the low delivered volumes and the safety margin, new limits were proposed for the delivered volumes established for each size of pipette and were considered acceptable.

Control of starting materials

Active substances

Fipronil and (S)-methoprene are controlled according to in-house monographs. Scientific data are presented under a separate Drug Master File (DMF) for each of these active substances.

Fipronil is adequately controlled, its synthetic route is sufficiently detailed and the methods and their validation are satisfactorily described. Specifications retained for the primary packaging of fipronil were provided. Batches were tested in stability according to VICH requirements. The proposed retest period was justified. The absence of impact of aged fipronil active substance on its dissolution and solubility in the manufacture of fipronil/(S)-methoprene solution was demonstrated.

An (S)-methoprene DMF was provided. (S)-Methoprene is satisfactorily controlled and its synthesis is sufficiently described. Sufficient details are given on the methods and their validation. Details of stability studies were provided. Industrial batches were tested according to VICH requirements. It was confirmed that the specifications retained at release apply until use.

According to stability data, both of the retest periods proposed can be accepted.

Amitraz is controlled according to the British Pharmacopoeia (BP) veterinary monograph. Scientific data were provided on the testing for release of the active substance. The synthetic route is well described. The specifications proposed for starting materials and reagents are considered satisfactory. The validations of methods used to control the active substance and the residual solvents were completed. Specifications retained for the primary packaging of amitraz were provided. Stress studies showed that amitraz is photostable. Batches were tested according to VICH requirements under controlled humidities and a range of temperatures. The proposed retest periods were satisfactorily justified.

Excipients

Excipients used in the manufacture of the fipronil/(S)-methoprene solution are considered quite standard for use in a spot-on and their quality specifications comply with the corresponding European Pharmacopoeia (Ph. Eur.) monographs. Sufficient data were provided.

The solvent used in the manufacture of amitraz solution is octyl acetate. Data on this excipient are sufficient. The value retained for the acid value was confirmed.

A certificate of analysis was presented for each excipient.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Based on the data provided for the active substances and the excipients, there is no risk for transmission of animal spongiform encephalopathy agents.

Control tests during production

See section Method of Manufacture.

Control tests on the finished product

A table of release specifications was established for each solution with a description of control tests applied. For the release specifications of the fipronil/(S)-methoprene solution, the limits for related substances (fipronil sulfone, a metabolite of fipronil, and the cis-isomer of (S)-methoprene) are justified and consistent with those in the fipronil/(S)-methoprene spot-on product already authorised in the EU. A tighter limit for water content is justified and in accordance with batch data.

The release specifications of the amitraz solution were updated satisfactorily in compliance with the BP monograph on amitraz for impurities. The higher limits retained for the delivered volume were tightened for small, medium and large pipettes of amitraz solution in accordance with batch data. This is satisfactory. Updated release specifications including the requests were presented for both solutions.

All of the methods used to control the finished product were sufficiently described. The equivalency between the Ph. Eur. method for acid value and the method retained in the dossier was demonstrated. The validation of the method used to control the active substances, fipronil and (S)-methoprene, and their impurities was completed. Validation of the methods used to control microbial quality and acid value is satisfactory.

Data from batches in compliance with the release specifications were presented.

Stability

Stability data, from a number of batches of different pipette sizes stored at long term, intermediate and accelerated conditions, were submitted.

In the shelf-life specification for the fipronil/(S)-methoprene solution, the lower limits for active substance content, and the limit for water content, were specified. Higher limits for the delivered volumes of the small and medium pipettes were proposed and considered acceptable. The widening of the antioxidant content limits was also considered justified.

In the shelf-life specification for the amitraz solution, the maximum limit for impurities was tightened in accordance with the BP limits.

All the presented stability results comply with the proposed specifications after 9 months storage at each of the tested conditions (long term, intermediate and accelerated conditions).

New stability studies were initiated with the new packaging. The results of these demonstrate a shelf-life of 18 months is justified. Results from a photostability study (with conditions in accordance with VICH guidance) show that the product should be protected from light, so the precaution "*Store in the original package*" is retained in the SPC and justified. A freeze-thaw cycling stability study was presented and the results demonstrate the precaution "*Do not freeze*" is not necessary in the SPC.

Overall conclusions on quality

CERTIFECT is a fixed combination spot-on containing fipronil, (S)-methoprene, and amitraz in a dual cavity pipette. The dual cavity pipette contains fipronil and (S)-methoprene together on one side and amitraz on the other. In order to assure proper opening of the pipette, the user is advised to use scissors to cut off the pipette tip. Proper opening of the dual cavity pipette is deemed important to ensure that the contents are delivered as foreseen. The delivered dose has been shown to be reproducible in appropriate testing where all values remained within the dose limits retained in the finished product specifications.

The method of manufacture of CERTIFECT is satisfactorily described and considered appropriate for a spot-on solution. The in-process controls were described. The process of manufacture is considered as being fully validated.

Starting materials, including active substances and excipients, have been described adequately, and, from the assessment, there is no risk for transmission of animal spongiform encephalopathy agents foreseen. All of the methods used to control the finished product were sufficiently described and validated. According to the stability test results, the shelf-life of the finished product is 18 months when stored in the original package.

The quality of CERTIFECT spot-on solution can thus be considered as fully demonstrated and in line with current standards including EMEA/CVMP/QWP/544461/2007 “Quality aspects of single dose veterinary spot-on products.”

3. Safety

Safety documentation

The hazard assessment for CERTIFECT takes into account the toxicological data of the three individual active substances, as well as the new toxicological data of the final formulated product provided in the file.

The main toxicological reference values, obtained in acute and chronic toxicity studies, were retained from agency reviews. In addition, new studies performed with CERTIFECT final formulation allowed to define, for oral administration, an oral LD50 and a No Observed Mortality Level (>1g/kg) and, for dermal administration, a dermal LD50 and a No Observed Mortality level (>5g/kg). The final formulation of CERTIFECT (fipronil plus (S)-methoprene combined with amitraz) should be considered as a slightly irritating formulation to the skin and as a moderately irritating formulation to the eyes. The final formulation elicited a delayed contact hypersensitivity response.

As regards excipients used in the product, in 1997, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) put octyl acetate in the functional class of flavouring agent and indicated that when used at current levels of intake as a flavouring agent, there were no safety concerns. Octyl acetate is used as a solvent in the amitraz solution and specific studies have been conducted using the final formulation of CERTIFECT including octyl acetate. These studies show an acceptable safety profile for both dogs and users. In light of the fact that CERTIFECT is indicated for use in dogs, no further data are necessary to conclude on the acceptable safety profile of this excipient.

In accordance with Annex I of Directive 2009/9/EC, the absence of a repeat-dose toxicity study in non-food producing animals is justified since it is replaced by a study conducted in the target animal (tolerance studies).

For tolerance studies, new studies have been performed with CERTIFECT in dogs (and one in cats) to evaluate the safety profile. Pharmacovigilance data on the fipronil/(S)-methoprene spot-on product for dogs, which is already authorised in the EU, were also presented. The overall conclusion showed that even if there are some transient changes, it can be considered that the topical application of the final formulation is well tolerated in dogs at up to 5 times the therapeutic doses when administered 6 times at two week intervals, in puppies 7-8 weeks of age up to 5 times the therapeutic doses administered topically once and in bitches up to 3 times the therapeutic doses at intervals of 28 days or less before breeding and throughout breeding, pregnancy and lactation until weaning.

Another study, performed in order to mimic exposure due to grooming or licking, showed that the oral administration of the product is well tolerated at levels up to 0.2 x the therapeutic dose.

In cats, the topical administration of fipronil combined with amitraz is well tolerated at a dose of 10 mg/kg bodyweight per active substance. Doses of 30 and 50 mg/kg bodyweight of the combination induced side effects (known as amitraz toxicity in cats) which generally resolved within two days after treatment.

The omission of reproductive, genotoxicity and carcinogenicity studies is justified by the demonstration of the non-interaction and the use of well-established substances.

User safety

The user risk assessment has been performed in a detailed manner and it is concluded that this assessment is satisfactory. In accordance with the EMA Revised guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/2003 Rev.1, Table 1) the applicant has considered a number of tasks and situations that may lead to exposure to CERTIFECT by the user.

During the pre-application phase of the product, the results of the margins of exposure (MOE) obtained with each active substance were in line with results of the MOE obtained with the formulated product. In one scenario, the presence of a potentially unacceptable risk was identified. Children in the household of the user may accidentally come into contact with a significant amount of the product. If a child was exposed through the oral and/or dermal routes, they may show amitraz-mediated neurological side effects, including dizziness and lethargy, however these effects are reversible. Furthermore, the child resistant packaging is considered sufficiently difficult for children to open, and therefore to mitigate the risk for children from accidental exposure to the contents of a full pipette (that is, before application of the product to the animal).

During the application phase of the product, the results showed the absence of any unacceptable risk, and took into account that level of exposure corresponding to a worst case scenario. The delayed-type sensitising potential is taken into account for CERTIFECT (topically applied) in the product information where it is recommended that gloves should be worn by the person applying the product.

During the post-application exposure, the results obtained can lead to the conclusion that there is no unacceptable risk for the user or for children in the household of the users. It is nevertheless noted that the calculated MOE for fipronil showed, after short term exposure, values that are not so far from 100 (= 133 for short-term oral exposure). In addition, given that acute neurological effects in children due to amitraz are also a potential risk after application, risk mitigation advice that children should not come into contact with recently treated animals is considered necessary, and such advice is included in the SPC and product literature accordingly.

In conclusion, the result for when the product has been applied to the animal justified the need for a risk management measure regarding children. As part of this risk management measure, it is advised in the product information to treat animals during the day and that those recently treated dogs should

not sleep with their owners, especially children. In addition, gloves are recommended for the user to avoid direct contact with the product and minimise the potential risk of sensitisation.

The agreed risk management measures allow to reach an acceptable risk level for all different exposure scenarios by means of the addition of appropriate warnings in the SPC, the presence of instructions in the product as well as on the secondary packaging (blister pack).

Environmental risk assessment

The environmental risk assessment concluded at Phase I in accordance with Guideline CVMP/VICH/592/98. As regards this guideline, for companion animals, no phase II assessment is necessary to conclude the environmental impact assessment. The active ingredients of CERTIFECT being ecto-parasiticides, in order to minimise the environmental impact as much as possible, a safety phrase has been included in the product information: “Dogs should be prevented from accessing streams and rivers for 48 hours following treatment.” As regards ecotoxicity, with the proposed warnings, the use of the product in dogs can be considered safe for the environment.

Residues documentation

Not applicable.

Overall conclusions on safety

The applicant has provided the main toxicological reference values, obtained in acute and chronic toxicity studies, for the well known active substances. In addition, new studies performed with CERTIFECT’s final formulation allowed to define reference values for oral and dermal administrations. Results show that CERTIFECT should be considered as slightly irritating to skin and as moderately irritating to eyes, and that it elicited a delayed contact hypersensitivity response.

The assessment of tolerance studies is repeated under Part 4 Efficacy and, as it concerns the target species, is summarised there.

From the user safety assessment, it can be concluded that the margin of safety for the user is acceptable. However, children that accidentally come into contact with the product may be exposed at a high enough level to lead to reversible neurological signs like dizziness and lethargy. The risk of this happening before application is low as the child resistant packaging is considered to be adequate in limiting accidental exposure by children. As children may well come into contact with the treated animal, risk mitigation is necessary to limit exposure after administration. The product information therefore includes ample warnings that children should not come into contact with recently treated dogs.

In addition, the delayed-type sensitising potential is taken into account for CERTIFECT, which is topically applied, in the product information, and it is recommended that gloves should be worn by the person applying the product.

The environmental risk assessment shows that the assessment can stop at Phase I, as per VICH guideline GL6 (CVMP/VICH/592/1998), because the product is for use in companion animals (dogs) only. As the active substances are ecto-parasiticides, it is nevertheless deemed necessary to assure safe exposure of the active substances within the environment that treated animals should be prevented from accessing streams and rivers for 48 hours following treatment.

Overall the safety of the product was assessed as being satisfactory, with warnings, where appropriate, being included in the SPC and product information.

4. Efficacy

Pharmacodynamics

The mode of action of the three actives, fipronil, (S)-methoprene and amitraz, of the combination product CERTIFECT was well-documented. Fipronil acts 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. (S)-methoprene is an insect growth regulator (IGR), especially a juvenile hormone mimic. Amitraz acts by the perturbation of octopamine-mediated processes through interaction with octopamine sensitive receptors in the insect nervous system.

In vitro studies showed the synergistic activity of amitraz and fipronil on *Rhipicephalus sanguineus* ticks as well as an increase in the speed of action. In an *in vivo* non-GCP study in dogs, it was demonstrated that the effect duration for ticks (*Rhipicephalus sanguineus*) was prolonged when fipronil and amitraz were applied in combination, as compared to the administration of fipronil alone. To further support the claimed early onset of effect, three *in vivo* studies were presented where the potential for preventing attachment of ticks and the detachment of ticks infesting beagle dogs were explored. As compared to a placebo group and at measurements made 24 hours after tick exposure, CERTIFECT treatment prevented the attachment of ≥87% of the ticks during 4 weeks after treatment. Furthermore, more than 90% detachment was noted 24 hours after treatment. These studies suggested a rapid onset of activity although a repellent effect was not noted. As no comparison to a fipronil plus (S)-methoprene product was made, the additional value of amitraz could not be determined on the basis of the pharmacodynamic studies.

Development of resistance

Flea and tick resistance to amitraz and fipronil exists. Based on available data the level of resistance seems low for the moment, although mechanisms of resistance are still not fully understood.

Pharmacokinetics

The pharmacokinetic profile and interaction potential of fipronil, (S)-methoprene and amitraz were determined, as well as the hair coat distribution of the three drugs, following topical application of a combination spot-on product containing fipronil and (S)-methoprene authorised in the EU, and amitraz, as paired formulations in the target species. No significant statistical pharmacokinetic interaction was observed. Quantifiable levels on hair coat were observed until 42-58 days following the application.

Dose determination/justification

The doses of fipronil and of (S)-methoprene are considered to be well-established as the combination of the two active ingredients is registered since 2003 in Europe. A dose determination study was conducted to select the optimum dose of amitraz to add to the current combination. Doses of 4 mg/kg bw, 8 mg/kg bw and 16 mg/kg bw of amitraz were assessed. The results of the study support the selection of the dose of ≥8 mg/kg bw against *Rhipicephalus sanguineus* tick infection. It was not clearly established that this species is dose limiting for amitraz and thus if extrapolation could be made to all species included in the claim. However, the strain of *Rhipicephalus sanguineus* used in the dose selection study possesses a particularly low sensitivity to fipronil and was therefore selected by the applicant as representing a worst case challenge. Moreover, *Rhipicephalus sanguineus* is the only tick species that is found around the world and represents the most common tick species.

Target animal tolerance

For tolerance studies, new studies have been performed with CERTIFECT in dogs (and in cats) to evaluate the safety profile. Pharmacovigilance data on the fipronil/(S)-methoprene spot-on product for dogs, which is already authorised in the EU, were presented. The overall conclusion showed that even if there are some transient changes, it can be considered that the topical application of the final formulation is well tolerated in dogs at up to five times the therapeutic dose when administered six times at two week intervals, in puppies of 7-8 weeks of age at up to five times the therapeutic dose administered topically once and in bitches at up to three times the therapeutic dose at intervals of 28 days or less before breeding and throughout breeding, pregnancy and lactation until weaning.

Another study, performed in order to mimic exposure due to grooming or licking showed that the oral administration of the product is well tolerated at 0.1 x the therapeutic dose whereas adverse events were quite commonly noted at 0.2 x the therapeutic dose. It is reasonable to believe that the oral uptake through grooming or licking would be at a maximum of 0.1 x the recommended dose and thus safety is acceptable in this respect.

The omission of reproductive, genotoxicity and carcinogenicity studies is justified by the demonstration of the non-interaction and the use of well-established substances. Nevertheless, for information, the data obtained from agency reviews were presented.

Dose confirmation

Many dose confirmation studies were conducted around the world on ticks, fleas, lice and sarcoptic mange mites. The effects of water and/or shampoo have also been evaluated in several specific studies.

The studies were performed according to the 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 (EMEA/CVMP/EWP/005/2000-Rev.2). The design of the studies was a classic one; treated group compared to untreated group, groups of at least 6 animals, infestation with an adequate number of parasites, weekly control by counting the parasite, and calculation of efficacy.

Dose confirmation studies were conducted on the European tick species *Ixodes ricinus*, *Dermacentor reticulatus*, *Rhipicephalus sanguineus* and *Ixodes hexagonus* and the non-European species *Ixodes scapularis*, *Amblyomma americanum*, *Amblyomma maculatum*, *Haemaphysalis elliptica* and *Haemaphysalis longicornis*.

With regard to the European species, elimination of existing tick infestation within 48 hours was demonstrated for all species. The persistent acaricidal activity (≥90% reduction) was 5 weeks for *Rhipicephalus sanguineus*, *Dermacentor reticulatus* and *Ixodes ricinus*. Furthermore, *Ixodes ricinus* appeared to be the dose-limiting species. For *Ixodes hexagonus* activity persisted for only 9 days. Based on the 48 hours count, these data support a 5 weeks efficacy claim except for *Ixodes hexagonus,* which was deleted from the product information.

With regard to the non-European species, elimination of existing tick infestation within 48 hours was demonstrated for *Ixodes scapularis*, *Amblyomma americanum*, *Amblyomma maculatum* and *Haemaphysalis elliptica*, but elimination of *Haemaphysalis longicornis* was demonstrated at a low infestation rate, which was not considered to be strongly indicative of efficacy. Five-week-long effect duration was demonstrated for the following non-European ticks: *Ixodes scapularis*, *Amblyomma maculatum*, *Amblyomma americanum* and *Haemaphysalis elliptica*. Regarding efficacy at 24 hours count, ≥ 90% reduction was noted for up to 5 weeks. The available data for *Haemaphysalis longicornis* suggest that duration of effect is of the order of several weeks, and therefore this non-European tick species could also be retained.

Fleas are killed by CERTIFECT within 24 hours. In order to justify the efficacy duration, the applicant combined all individual data derived from a number of dose confirmation studies already provided and an additional study that was ongoing at time of submission. The pooling of data is acceptable since both the general protocol of the studies was standardised and the majority of individual studies provided persistent adulticidal activity against *Ctenocephalides felis* for at least 4 weeks. The results based on the pooled data showed that a ≥95% efficacy was obtained for 5 weeks (36-37 days) at 24 hour count. However, to reflect the variable outcome in the different dose confirmation studies for fleas (3-7 weeks), it is considered appropriate to set the effect duration to "up to 5 weeks".

No dose confirmation study was provided to support efficacy against lice (*Trichodectes canis*). However the CVMP considers the lice indication as a minor use. It is thus acceptable to extrapolate the proven efficacy of fipronil against lice infestation to the current product as it is not expected that amitraz will change the efficacy against lice.

No new data were provided to show that the product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). Nevertheless, this claim is acceptable on the basis of previous data provided to support that claim for the fipronil spot-on product authorised in the EU, and the similarity demonstrated between the current product and the fipronil spot-on product authorised in the EU.

A number of placebo controlled studies to support efficacy against mite infestation (*Sarcoptes scabiei* var *canis*) were included. Dogs were either naturally infested or infestations were induced and efficacy evaluated repeatedly up to 56 days. The outcome was not adequate to support efficacy against mite infestation and the claim was thus not retained.

Field trials

A number of field trials conducted with the final combination in several geographical areas have been provided by the applicant. Among these, field studies were performed against fleas and ticks, for the prevention of Ehrlichiosis and for the prevention of babesiosis.

The tick and flea field studies provided compared the efficacy of CERTIFECT with the fipronil/(S)-methoprene spot-on product already authorised in the EU, in a non-inferiority design. Non-inferiority of CERTIFECT in comparison to the fipronil/(S)-methoprene spot-on product already authorised in the EU, was demonstrated for both fleas and ticks and this study confirmed the duration of persistent efficacy against ticks as 5 weeks. The persistent adulticidal activity against *Ctenocephalides felis* fleas of up to 5 weeks was established based on dose confirmation studies was confirmed by the results of the field study where an 8 week duration was observed.

No lice field studies were conducted with the final product. However, lice field trials performed using fipronil alone and/or fipronil+(S)-methoprene were previously assessed for the registration of the respective products. As no negative interaction due to amitraz is expected and as treatment of lice infestation could be considered as a minor use, it is not considered that a further field study with the new product is necessary.

No mange field studies were conducted with the final product. Due to insufficient supporting data, this parasite was not retained in the list of claimed indications.

Other studies

The influence of water immersion or shampooing performed at least 10 days after treatment has been studied in various studies including different tick species. According to some of the studies, a single shampoo applied 17 days after treatment did not affect effect duration, whereas in another study

reduced effect duration (3 weeks) was noted after a single shampoo treatment. Similarly, a reduced effect duration was noted when shampooing was performed weekly. Weekly water immersion reduced effect duration regarding ticks in one of the studies, whereas in another study effect duration appeared unaffected. Although the effect of water immersion during the first 10 days after treatment has not been studied, it is regarded as acceptable to only advise the user to avoid water contact for the dog during the first 48 hours which would allow the administration spot to dry. This is in line with the recommendations for the fipronil/(S)-methoprene spot-on product already authorised in the EU, and for amitraz containing products, and no difference with regard to water stability as compared to previously authorised products is expected. The wording included in section 4.5 of the SPC is considered to reflect the outcome of the different studies in an appropriate manner.

Laboratory studies have been performed in dogs to evaluate the ability of the product to prevent the transmission of *Babesia canis*, *Ehrlichia canis*, *Borrelia burgdorferi, Anaplasma phagocytophilum* and *Borrelia afzelii* from infected ticks.

Dogs were allocated to two treatments groups (group 1: untreated and group 2: combination product) and were exposed to ticks that had been confirmed as harbouring disease agents. Post-challenge dogs were observed clinically and biological samples were carried out to diagnose the disease transmission in the two groups.

The challenge studies failed because of inability to demonstrate transmission respectively of *Ehrlichia canis* and *Borrelia afzelii* in any of the study animals, including untreated controls. Another study explored the preventive potential of CERTIFECT regarding transmission of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* via *Ixodes scapularis*. Dogs were infested with ticks confirmed to carry *Borrelia burgdorferi* and *Anaplasma phagocytophilum* after different intervals of CERTIFECT treatment (14 to 28 days). Other dogs were kept as controls. Transmission of *Borrelia* was not noted in any CERTIFECT treated animal, by any of the methods used. In the control group, transmission of *Borrelia* was confirmed by at least one of the methods. Quite a few (23%) ticks were confirmed to be infected with *Anaplasma phagocytophilum*. Nevertheless, it was noted that 75% of untreated animals sero-converted by day 63 whereas no CERTIFECT treated dog sero-converted. No other diagnostic measures were applied and clinical signs were apparently not noted in any dog. Thus, a preventive effect was demonstrated but the study was small which means that the assessment of risk was connected to some uncertainty. Due to this it would not be acceptable to claim more than a reduction of the risk for transmission of these diseases by ticks. Another study was carried out to demonstrate the preventive efficacy of the product against the transmission of canine babesiosis. A number of dogs were kept as controls whereas 4 additional groups were formed each containing dogs that were exposed to *Babesia* infected ticks 7, 14, 21 and 28 days after CERTIFECT treatment. All control dogs sero-converted and developed clinical signs typical for canine babesiosis and they were positive on blood smears. In the CERTIFECT treated animals no typical clinical signs were noted and sero-conversion was prevented in 85% of animals. In the CERTIFECT treated animals that sero-converted the titres were quite low (1:80 and 1:160) as compared to the untreated animals (1:160-1:2560). The applicant clarified through provision of relevant information that the cut-off for sero-conversion is 1:80. The study suggests that CERTIFECT treatment reduces but does not totally exclude the risk for transmission of *Babesia canis* from infected ticks.

In a small field trial including dogs treated monthly with CERTIFECT 8 times, and control dogs which were exposed to naturally infected ticks harbouring *Babesia canis,* no sign of infection (PCR and indirect fluorescence) was noted in CERTIFECT treated animals whereas the disease was confirmed in 20-40% of control dogs. The low level of infection in the control dogs suggests a low exposure to challenge and thus the study provides only limited support for a reduced risk for transmission of *Babesia canis* via ticks. However another field study was performed including beagle dogs divided into an untreated group and a group treated monthly with CERTIFECT in total 5 times and

they were continuously exposed to ticks naturally infected with *Ehrlichia canis*. During the study it was confirmed that the infected ticks were present in the area, although the infection rate appeared highly variable.

To conclude on the evaluable laboratory and field studies submitted to support the claim for a preventive effect of CERTIFECT against four specific tick-borne diseases, the estimate of protective potential is uncertain as the studies were small. Complete protection against transmission of the four claimed organisms was not demonstrated, however, a reduced risk for disease transmission and subsequent development of disease was agreed.

Overall conclusion on efficacy

CERTIFECT is a fixed combination of well-known active substances (amitraz, fipronil and (S)-methoprene).

Well-conducted and controlled clinical trials demonstrated that the product is efficacious in the treatment of ticks and fleas. The efficacy in the treatment of lice infestations is also accepted on the basis of cross-reference to data submitted for the authorisation in the EU of a fipronil and (S)-methoprene containing spot-on product.

Topical application of CERTIFECT is well tolerated in dogs at multiple times the therapeutic dose, both in puppies of 7-8 weeks of age and in bitches. Grooming and licking and subsequent ingestion of the product by the treated dog have been investigated and are not usually expected to lead to any significant adverse events.

Due to an apparent synergistic effect between fipronil and amitraz, a faster onset of effect and an added persistent effect on tick prevention is noted. However, the prolongation of the effect as compared to the fipronil/(S)-methoprene spot-on product already authorised in the EU is limited. Regarding the effect against fleas the effect duration supported by data is up to 5 weeks. The efficacy in reducing the risk of transmission of tick-borne diseases has been documented through laboratory and field studies. In the laboratory studies, a number of diagnostic means were used (including PCR and ELISA testing) to measure a reduction in the risk of transmission of diseases due to *Babesia canis*, *Borrelia burgdorferi*, and *Anaplasma phagocytophilum*, from infected ticks. In the field studies, *Babesia canis* and *Ehrlichia canis* were studied as well as the clinical manifestation of disease in sick animals. Disease transmission was not complete and therefore prevention of disease cannot be claimed. However, the studies taken together perform a coherent whole which demonstrate that through an indirect effect of CERTIFECT on ticks, the risk of transmission of disease is reduced.

The benefit of the product is to treat and prevent infestations with ticks and fleas, to treat chewing lice infestation, to prevent environmental flea contamination and to aid in the treatment of flea allergy dermatitis (FAD). These claims are similar to the two-component (fipronil/(S)-methoprene) spot-on product already authorised in the EU,. The justification of adding amitraz in the combination is based on the fact that a quicker onset of activity and a one week longer duration of effect against ticks are demonstrated, as well as the claim for reducing the risk for transmission of certain tick-borne diseases. CERTIFECT has also a documented effect against some additional tick strains, but since they are of non-European origin any additional benefits of the product in this respect are regarded as being very limited.

As regards the overall efficacy of the product, sufficient data have been provided to support the following claim:

"Treatment and prevention of infestations in dogs by ticks (*Ixodes ricinus, Dermacentor reticulatus, Rhipicephalus sanguineus, Ixodes scapularis, Dermacentor variabilis, Haemaphysalis elliptica,*

Haemaphysalis longicornis, Amblyomma americanum and *Amblyomma maculatum)* and fleas *(Ctenocephalides felis* and *Ctenocephalides canis).* Treatment of infestations by chewing lice (*Trichodectes canis*). Prevention of environmental flea contamination by inhibiting the development of all flea immature stages. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). Elimination of fleas and ticks within 24 hours. One treatment prevents further infestations for 5 weeks by ticks and for up to 5 weeks by fleas.

The treatment indirectly reduces the risk of transmission of tick-borne pathogens from infected ticks for 4 weeks."

5. Benefit risk assessment

Introduction

CERTIFECT is a full application for a new combination product containing three active substances: amitraz, fipronil and (S)-methoprene. The application is supported by a full dossier.

The product is indicated for use in dogs for the treatment and prevention of infestations in dogs by ticks (*Ixodes ricinus*, *Dermacentor reticulatus*, *Rhipicephalus sanguineus*, *Ixodes scapularis*, *Dermacentor variabilis*, *Haemaphysalis elliptica*, *Haemaphysalis longicornis*, *Amblyomma americanum* and *Amblyomma maculatum*) and fleas (*Ctenocephalides felis* and *Ctenocephalides canis*). It is also indicated for the treatment of infestations by chewing lice (*Trichodectes canis*), and also for the prevention of environmental flea contamination by inhibiting the development of all flea immature stages. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). The elimination of fleas and ticks occurs within 24 hours, and one treatment prevents further infestations for 5 weeks by ticks, and for up to 5 weeks by fleas.

The treatment indirectly reduces the risk of transmission of tick-borne diseases (canine babesiosis, monocytic ehrlichiosis, granulocytic anaplasmosis and borreliosis) from infected ticks for 4 weeks.

Benefit assessment

Direct therapeutic benefit

CERTIFECT is a fixed combination of well-known active substances (amitraz, fipronil, and (S)-methoprene).

Clinical trials demonstrated that the product is efficacious in the treatment of ticks and fleas. The efficacy in the treatment of lice infestations is also accepted on the basis of cross-reference to data submitted during authorisation of a fipronil/(S)-methoprene containing spot-on product already authorised in the EU.

Additional benefits

Due to an apparent synergistic effect between fipronil and amitraz, a faster onset of effect and an added persistent effect on tick prevention is noted. However the prolongation of the effect as compared to the fipronil/(S)-methoprene spot-on product already authorised in the EU is limited. Regarding the effect against fleas the effect duration supported by data is up to 5 weeks. The efficacy in reducing the risk of transmission of tick-borne diseases is documented. CERTIFECT is easy to apply by the owner.

Risk assessment

There is no risk identified for the target animal as CERTIFECT is expected to be well tolerated in dogs, including puppies and bitches. The risk for the user is judged acceptable. However, in particular, children in the household of the user are at risk of developing neurological signs such as dizziness and lethargy if they come into a sufficient amount of product. This risk is addressed, before application of the product, through adequate child resistant packaging, and, after application, by a warning in the product information that children should not be allowed to play with treated animals until the application site is dry. Sensitisation potential of the user has been addressed through the usual warnings (including that gloves should be worn during administration). In addition, the delayed-type sensitising potential is taken into account for CERTIFECT, which is topically applied, in the product information, and it is recommended that gloves should be worn by the person applying the product. The environmental risk assessment halts in Phase I, which is acceptable, as per pertinent guidance, for a product that is used in dogs only. As CERTIFECT contains ecto-parasiticidal active substances, it is recommended in the product information that treated dogs are prevented from accessing streams and rivers for 48 hours following treatment.

Risk management or mitigation measures

Appropriate risk management text is included in the SPC and product information.

The proposed risk management measures (particular warning limiting children from coming into contact with recently treated animals, sensitisation potential in the user addressed through gloves to be worn during administration) allow for an acceptable risk level for all different exposure scenarios with the addition of warnings in the SPC, the presence of instructions in the product as well as a secondary packaging (blister pack).

The packaging keeps the actives separate (amitraz, on one side, and fipronil/(S)-methoprene, on the other) avoiding chemical instability, while they are co-administered and mixed upon the skin and hair of the animal once the spot-on is applied to the animal.

As regards the environmental risk assessment, with the proposed warnings, the use of the product on dogs can be considered as safe for the environment.

Evaluation of the benefit risk balance

The formulation and manufacture of CERTIFECT are well-described and specifications set will ensure that the product that is manufactured will be of consistent quality. The major point to be noted is the chemical incompatibility between fipronil and amitraz, and the galenic solution proposed, which is to set apart, in two different chambers, the two solutions. CERTIFECT is well tolerated by the target animals and presents a low risk for the environment. Appropriate warnings regarding user safety and environmental safety are included in the SPC and the rest of the product information.

The benefit of the product is to treat and prevent infestations with ticks and fleas, to treat chewing lice infestation, to prevent environmental flea contamination and to aid in the treatment of flea allergy dermatitis (FAD). These claims are similar to a two-component (fipronil/(S)-methoprene) product authorised in the EU. The justification of adding amitraz in the combination is based on the fact that a quicker onset of activity and a one week longer duration of effect against ticks are demonstrated, as well as the claim for reducing the risk for transmission of certain tick-borne diseases. CERTIFECT has also a documented effect against some additional tick strains, but since they are of non-European origin any additional benefits of the product in this respect are regarded as being very limited. Furthermore, the improved effect against ticks needs to counterbalance the risk associated with the

handling and administration of amitraz. The latter prerequisite should be fulfilled by compliance with the safety measures described in the product information.

The product has been shown to have an overall positive benefit/risk balance in the approved indication:

"Treatment and prevention of infestations in dogs by ticks (*Ixodes ricinus, Dermacentor reticulatus, Rhipicephalus sanguineus, Ixodes scapularis, Dermacentor variabilis, Haemaphysalis elliptica, Haemaphysalis longicornis, Amblyomma americanum* and *Amblyomma maculatum)* and fleas *(Ctenocephalides felis* and *Ctenocephalides canis).* Treatment of infestations by chewing lice (*Trichodectes canis*). Prevention of environmental flea contamination by inhibiting the development of all flea immature stages. The product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). Elimination of fleas and ticks within 24 hours. One treatment prevents further infestations for 5 weeks by ticks and for up to 5 weeks by fleas.

The treatment indirectly reduces the risk of transmission of tick-borne diseases (canine babesiosis, monocyte ehrlichiosis, granulocytic anaplasmosis and borreliosis) from infected ticks for 4 weeks."

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for CERTIFECT is approvable.

Based on the data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product are considered to be in accordance with Directive 2001/82/EC, as amended.