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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report of an application for the granting of a community marketing authorisation for

CERTIFECT (EMEA/V/C/002002)

Introduction

An application for the granting of a community marketing authorisation of CERTIFECT has been submitted to the Agency on 2 March 2010 by MERIAL in accordance with Regulation (EC) No. 726/2004 of the Council and the European Parliament.

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 biting lice. The route of administration is topical spot-on use. The target species is dogs. The Committee confirmed that the product would be eligible under Article 3 of Regulation (EC) No 726/2004 as it contains a new combination of active substance which has not been authorised in the Community for use in a medicinal product intended for use in animals.

Part 1 - Administrative particulars

The pharmacovigilance system is in place and has been assessed as satisfactory.

Part 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 deck 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

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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 the product already marketed by the applicant, MERIAL, containing fipronil and (S)-methoprene (10% w/v / 9% w/v) (FRONTLINE COMBO) as active substances and butylhydroxyanisole and butylhydroxytoluene as antioxidants. Polysorbate 80 and povidone were used as crystallisation inhibitors. Ethanol and diethylene glycol monoethyl ether were retained as solvents.

Amitraz solution (solution B) is the new part corresponding to amitraz mixed with a solvent, octyl acetate. No preservative was included in the composition.

Container

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

This double deck pipette consists of a heat-formed shell of polypropylene/co-extruded polyethylene-ethylvinyl alcohol-polyethylene laminate incorporating a purple dye on both external sides of the pipette that is sealed to a central backing between both cavities composed of co-extruded polyethylene-ethylvinyl alcohol-polyethylene/aluminium foil and a coextruded polyethylene-ethylvinyl alcohol-polyethylene laminate.

The secondary packaging consists of an opaque blister package made up of a plasticised aluminium formed shell of polyethylene, polyamide/aluminium foil/polyamide/polyethylene sealed to a backing of polyethylene/aluminium/polyamide.

Each blister card contains three individually packaged pipettes.

The inner sealing layer from both primary and secondary packaging comes into contact with the two solutions and is made up of polyethylene.

In part IIC of the dossier, sufficient data about the primary and secondary packaging were provided. The retained controls include at least a control of appearance and an infrared identification test. This is 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 satisfactorily opened.

Development pharmaceutics

The initial goal was to develop a topical formulation containing fipronil and amitraz in a common solvent system. Chemical incompatibility between amitraz and fipronil and the components of the fipronil/(S)-methoprene solution was revealed. Several studies to find a common solvent system were performed without success.

The applicant decided to develop 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 regarding 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, the objective was to find a solvent to dissolve this active substance and keep it stable. The addition of pH modifiers, the presence of nitrogen, the tests of several class 3 solvents, the addition of odour enhancers or chemical scavengers, the use of a physical drying agent and the addition of sodium carbonate were successively tested. The use of a physical drying agent (molecular sieves treatment) was preferred and justified to stabilise amitraz.

The applicant assessed the impact of both different types of molecular sieve and different durations of the treatment on several parameters: amitraz assay, formamidine level, water content and acid value. The results showed an improvement in amitraz solution stability and no evolution of acid value and water content. Optimisation of the manufacturing process of amitraz solution was also developed. The main goals were:

- to establish an optimum mixing time for complete amitraz dissolution,
- to assess the quantity of molecular sieves required to meet acceptable acid value and water content when sieves are added directly into the processing tank,
- to assess filter compatibility and efficiency with the formulated product.

The choice of the recommended parameters on addition of amitraz, mixing, quantity and molecular sieves, duration of treatment, filter size, filter membrane and pore size and filtration pressure were explained and justified.

The formulation composition is associated with a specific manufacturing process including molecular sieves (type 13X, 10Å pore size, 4-8 mesh). The choice of the formulation of amitraz solution was satisfactorily justified regarding the chosen solvent system and molecular sieves.

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, including a leak test on each pipette size, and absence of cross-contamination between pipettes were also demonstrated. Various secondary packagings were also 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 remain within the dose limits retained in the finished product specification (100-115% of each nominal volume).

Method of manufacture

Both solutions are manufactured separately by mixing all formulation ingredients and then filling them into the double deck pipettes which are then packaged into the secondary package (blister). The manufacturing formula provided for both solutions are satisfactory. The product is manufactured, packaged, labelled and tested on a GMP site at MERIAL, 4, Chemin du Calquet in Toulouse, France.

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 filing into double deck pipettes.

The amitraz solution is treated before filtration with molecular sieves to ensure the stability of the solution. Details on this manufacture including mixing times and speed mixing were given.

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

The in-process controls include control of the density and delivered volumes of both solutions and control of acid value and water content for amitraz solution. This list of in-process controls was completed by the controls performed during the primary packaging (delivered volumes, vacuum pressure test, vacuum oven test and visual aspect) and during the secondary packaging step (visual aspect). The tests judged as being critical, vacuum pressure test and vacuum oven test are satisfactorily described.

Validation of the manufacturing process

The manufacture of the fipronil/(S)-methoprene solution was satisfactorily validated for the range of 40-2400 litres batch size. The manufacture of the amitraz solution was performed on pilot batches (60 litres) and was completed on three consecutive 600 litre 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 (12 weeks) 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.

BASF Agro BV holds a European DMF on fipronil.

Fipronil is adequately controlled, its synthetic route is sufficiently detailed and the methods and their validation are satisfactorily described. The absence of control of optical rotation or isomer ratios determination in the routine tests was justified. Discrepancies about the address of the synthesis were clarified. Specifications retained for the primary packaging of fipronil were provided. Three batches were tested in stability according to VICH requirements. The proposed retest period of 2 years 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.

Wellmark International holds a DMF for (S)-methoprene.

An updated version of the (S)-methoprene DMF was provided, during the response to the list of questions, including a clear separation of the open and restricted parts. Discrepancies about the address of the synthesis were clarified. (S)-methoprene is satisfactorily controlled and its synthesis is sufficiently described. The test for residual solvents is the only test not performed by MERIAL upon receipt. Sufficient details are given on the methods and their validation. An important number of stability studies were included in the applicant's part of the (S)-methoprene DMF. Only the Wellmark International Stability Commitment Reports for 2001 production campaign were detailed in the assessment report. Nineteen 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 retest periods proposed by MERIAL (3 years) and by BASF (2 years) can be granted.

Amitraz is controlled according to the British Pharmacopoeia (BP) veterinary monograph. In addition acetone insolubles, acid value and residual solvents are tested for release of the active substance.

Scientific data were provided. 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. The use of the HPLC method to control amitraz rather than the use of the BP method was justified. Specifications retained for the primary packaging of amitraz were provided. Stress studies showed that amitraz is photostable. Three batches were tested according to VICH requirements at 5°C, 25°C, 30°C and 40°C under controlled humidity. Both proposed retest periods: 18 months with the storage precaution "Store in a refrigerator (2-8°C)" or 12 months with the storage precaution "Do not store above 25°C" 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 monographs (Ph.Eur.). 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 is 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. Each solution is controlled for appearance, delivered volume, uniformity of dosage units, clarity, colour, relative density, identification and assay of active substance, assay of impurities, antioxidants contents (only for fipronil/ (S)-methoprene solution), water and acid value (only for amitraz solution). A skip testing was also retained for microbial contamination.

For both solutions, the percent expression of active substance content was supplemented by an expression in terms of the quantity by mass of the active substance in a container of average delivered mass or volume in accordance with Guideline EMEA/CVMP/QWP/544461/2007 "Quality aspects of single dose veterinary spot-on products".

For the release specifications of the fipronil/(S)-methoprene solution, limits retained for related substances have already been granted in the marketed product FRONTLINE COMBO (for fipronil sulfone which is a metabolite of fipronil, and the cis-isomer of (S)-methoprene). A new tightened limit for water content was proposed and is 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 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 for specificity, accuracy and precision at low levels. The non-use of the correction factor for fipronil sulfone was satisfactorily justified. Validation of the methods used to control microbial quality and acid value is satisfactory.

Data of three batches in compliance with the release specifications were presented. Due to storage times applied during the manufacture, the applicant confirms that the date of production will be taken as the start of the shelf-life if batches are released more than 30 days from the production date.

Stability

Three batches, each packaged in the different pipette sizes, were placed on stability. The proposed matrixing plan is accepted. These batches were placed on stability at 25°C/60% RH[1], 30°C/65% RH and 40°C/75% RH and VICH light and temperature cycling conditions.

In the shelf-life specifications of fipronil/(S)-methoprene solution, the lower limit of active substance contents was tightened to 95% and the limit for water content to not more than 1%. New acceptable higher limits for delivered volumes of small and medium pipettes were proposed. The widening of antioxidants contents was justified.

In the shelf-life specifications of amitraz solution, the maximum limits for impurities were tightened in accordance with the BP limits.

No control of water tightness of the pipettes was included in the release and shelf-life specifications. However, vacuum tests were added to the in-process controls. This point is considered satisfactory. The procedures are the same as those employed at release. In order to solve the problems of leakage, a new packaging was proposed, corresponding to a new sealing design of the pipette, which is the addition of calcium oxide (desiccant) in the inside layer of a co-extruded polyethylene copolymer.

All presented stability results comply with the proposed specifications after 9 months of storage in each tested condition. The variability observed on the results of (S)-methoprene content was explained by the reference standard.

New stability studies were initiated with the new packaging. According to these new stability studies, a shelf-life of 18 months can be granted. Results of the photostability study show that the product should be protected from light. The precaution "*Store in the original package*" retained in the SPC is justified. A freeze-thaw cycling study was presented and shows that the precaution "*Do not freeze*" is not necessary in the SPC.

Overall conclusions on quality

Overall the quality of the product was assessed as being satisfactory after responses to the list of questions and list of outstanding issues were received and assessed. Issues related to the choice of secondary packaging, in-process controls, filtration of the finished product, the (S)-methoprene DMF, the control of starting materials for amitraz drug substance, the shelf life specification of amitraz solution, and the lack of a test for water tightness of the pipettes in the release and shelf life specification were resolved. Remaining issues related to the maximal storage of amitraz solution, the equivalency between GC and HPLC methods, the assay of fipronil sulfone, the retest period of amitraz, the new limits of impurities and the new stability studies were also satisfactorily addressed. However, the proposed shelf-life of 2 years cannot be accepted, only a shelf-life of 18 months can be granted

[1] Relative humidity

based upon the available data. As part of the responses to the list of questions and list of outstanding issues, sections 1- 3 and 6 of the SPC were updated appropriately.

CERTIFECT is a fixed combination spot-on containing fipronil, (S)-methoprene, and amitraz in a dual deck pipette. The dual deck 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 deck 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 include control of density and delivered volume of both solutions and control of acid value and water content for the amitraz solution part. 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 the methods used to control the finished product were sufficiently described and validated. As no control of water tightness of the pipette was included in the finished product specifications, vacuum tests were added to the in-process controls. 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.”

Part 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, octyl acetate has not been used as an excipient before in a veterinary medicine. 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 at 77.5% v/v which, at the level of CERTIFECT, results in 29% v/v. Specific studies have been conducted using the final formulation of CERTIFECT including octyl acetate at this level. 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 appear to be necessary for concluding 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 of FRONTLINE COMBO spot on dog 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 for CERTIFECT a number of tasks and situations that may lead to exposure by the user. During the pre-application phase of the product, the results of margin of exposure (MOE) obtained with each active substances were in line with the results of MOE obtained with the formulated product. In one scenario, the presence of a potentially unacceptable risk was identified. Children present in the household of the user may accidentally come into contact with a sufficient amount of product. Children may be exposed through the oral and/or dermal routes and may show amitraz-mediated neurological side-effects. These effects include dizziness and lethargy and are reversible. It is crucial that the packaging is considered sufficiently difficult to open to mitigate the risk for children after an accidental exposure before application. During the application phase, the results showed an absence of unacceptable risk, taking into account that the level of exposure corresponds to a worst case situation. That being said, 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. 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 is a potential risk also after application, the risk mitigation sentence that children should not come into contact with recently treated animals is considered necessary.

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: Within 24 hours after application, dogs are not allowed to access streams and rivers. This safety phrase is based upon the assumption that within 24 hours after application solvents are evaporated and the product is dried upon the hair coat. 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 minimal as the 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 halt in Phase I, as per VICH GL 592/98 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 do not access streams and rivers within 24 hours following administration.

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

Part 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.

Two *in vitro* studies showed synergic activity of amitraz and fipronil on *Rhipicephalus sanguineus* ticks as well as an increase of the speed of action. In an *in vivo* non-GCP study including 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 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 fast onset of activity and disruption of attachment of ticks although a repellent effect was not noted. Furthermore, since no comparison to a fipronil+ methoprene product was made, the additional value of amitraz could not be determined.

Development of resistance

Flea and tick resistance to amitraz and fipronil exist. 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 the combination fipronil + (S)-methoprene (FRONTLINE Plus) + 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. One 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 "BerTek" 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 one in cats) to evaluate the safety profile. Pharmacovigilance data of FRONTLINE COMBO spot on dog 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 (over 40) 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 7 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 (6 of 8) provided persistent adulticidal activity against *Ctenocephalides felis* 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 FRONTLINE Spot-on and the similarity demonstrated between the current product and FRONTLINE Spot-on.

Two 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

Seven field trials conducted with the final combination in several geographical areas have been provided by the applicant. Among these seven studies, three field studies (PR&D 0164101, PR&D 0164102 and PR&D 0164103) were performed in EU countries (respectively Albania, Italy and Hungary) against fleas and ticks; two field studies (PR&D 0185001 and PR&D 0185101) were performed in Japan, respectively against fleas and ticks; one study (PR&D 0200201) in Côte d'Ivoire for prevention of Ehrlichiosis and one study (PR&D 0200301) in Hungary for prevention of babesiosis. The Japanese field studies are regarded as informative only.

The ticks and fleas field studies (PR&D 0164101-3) provided compared the efficacy of CERTIFECT with FRONTLINE COMBO in a non-inferiority design where the primary endpoint was adequate response by day 60 according to the investigator's opinion. Non-inferiority of CERTIFECT in comparison to FRONTLINE COMBO was demonstrated for both fleas and ticks. Although the adequacy of the primary endpoint could be questioned, for both products flea count was reduced by >96% at each assessment occasion (Day 2, 7, 14, 21, 28, 35, 42 and 60) and tick count was reduced by >93% until day 35. Thus this study confirms, under southeast European conditions, the duration of persistent efficacy against ticks as 5 weeks. It is noted that the percentage reduction of ticks was quite similar for the two products day 42 and 60, and thus longer effect duration was not indicated for CERTIFECT in comparison to FRONTLINE Plus, the name of FRONTLINE COMBO in the USA. The 3 week persistent

adulticidal activity against *Ctenocephalides felis* fleas established based on dose confirmation studies is 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 support 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 5 well conducted studies including different tick species. According to two of the studies, a single shampoo applied 17 days after treatment did not affect effect duration, whereas in a third 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 FRONTLINE COMBO 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.

Four 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 two challenge studies (PR&D 01959001 and PR&D 0183801) failed because of inability to demonstrate transmission respectively of *Ehrlichia canis* and *Borrelia afzelii* in any of the study animals, including untreated controls. Study PR&D 0188601 explored the preventive potential of CERTIFECT regarding transmission of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* via *Ixodes scapularis*. Thirty-two dogs were infested with ticks confirmed to carry *Borrelia burgdorferi* and *Anaplasma phagocytophilum* after different intervals of CERTIFECT treatment (14 to 28 days). Eight dogs were kept as controls. Transmission of *Borrelia* was not noted in any CERTIFECT treated animal, by any of the methods used (PCR and spirochete culture of tick-infested skin tissue, as well as serology – IDEXX SNAP 4Dx, ELISA and western blot). 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 six out of eight un-treated 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. A fourth study (PR&D 0182801) was carried out to demonstrate the preventive efficacy of the product against the transmission of canine babesiosis. Seven dogs were kept as controls whereas 4 additional groups were formed each containing seven dogs that were exposed to *Babesia* infected ticks 7, 14, 21 and 28 days after CERTIFECT treatment. All seven 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 24 out of 28 animals. In the four 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 10 dogs treated monthly with CERTIFECT 8 times, and 10 control dogs (PRD0200301) 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 2-4 out of 10 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 in the Ivory Coast, including 30 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. In the untreated group 13 dogs were PCR positive and 12 were indirect immunofluorescence test positive for *Ehrlichia canis* during the study and 9 dogs died. In the CERTIFECT group 5 dogs were PCR positive and 2 of these were also IFI positive for *Ehrlichia canis* (Day 113), whereas no dog developed any clinical signs of disease. The high mortality rate is not typical for *Ehrlichia canis* infection but may be due to lack of sufficient supportive care, and potentially due to the fact that the dogs were immunologically naïve to the *Ehrlichia* strain occurring in the area.

To conclude on the four evaluable studies (two laboratory and two field studies) submitted to support the claim for a preventive effect of CERTIFECT against four specific tick-borne diseases, the studies are small implying that the estimate of protective potential is uncertain. Furthermore, a complete protection against transmission of the four claimed organisms was not demonstrated. Nevertheless, 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 during authorisation of a fipronil and methoprene containing product (FRONTLINE COMBO).

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 FRONTLINE Plus 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 2 laboratory studies and 2 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) product FRONTLINE COMBO. 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 is 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."

Part 5 – Benefit risk assessment

Introduction

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

It is indicated for use in dogs.

Benefit assessment

Direct therapeutic benefit

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 during authorisation of a fipronil and methoprene containing product (FRONTLINE COMBO).

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 FRONTLINE Plus 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.

Additional benefits

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 packaging, and, after application, by a warning in the product information that recently treated animals should not come into contact with children. 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 do not access streams and rivers within 24 hours following application.

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 is 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 the two-component (fipronil/(S)-methoprene) product FRONTLINE COMBO. 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 is 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.

Overall the product has been shown to have a 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 pathogens 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.