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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for BROADLINE (EMEA/V/C/002700/0000)

International non-proprietary name: Fipronil / (S)-methoprene / praziquantel / eprinomectin

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant MERIAL submitted on 24 September 2012 an application for marketing authorisation to the European Medicines Agency (the Agency) for Broadline, through the centralised procedure falling within Article 3(2) of Regulation (EC) No 726/2004 (new active substance (new combination of existing active substances)).

Eligibility to the centralised procedure was agreed upon by the CVMP on 9 February 2012 as Broadline contains a new fixed combination of four existing active substances which was not authorised as a veterinary medicinal product in the Community on the date of entry into force of the above Regulation. The rapporteur appointed was B. Urbain and co-rapporteur C. Muñoz Madero.

The applicant applied for the following indication: "For cats with, or at risk from mixed infestations by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time".

The target species are cats. The route of administration is spot-on use. Broadline contains fipronil, (S)-methoprene, praziquantel and eprinomectin. Eprinomectin is a new substance in cats. The product is presented in single-dose applicators of two different strengths (to facilitate the treatment of different weight cats). The single dose applicators are then packed into polyethylene trays which are then packed inside cardboard cartons.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC, as amended.

The CVMP adopted an opinion and CVMP assessment report on 10 October 2013.

On 4 December 2013, the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC, as amended. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the European Union (EU) or in a third country.

Manufacturing authorisations and inspection status

A declaration of compliance of the manufacture of the active substances with EU good manufacturing practice (GMP) requirements for starting materials has been provided from the Qualified person of the site of batch release.

The manufacturing and batch release of the finished product is by MERIAL SAS, France.

GMP certificates for the sites are available. Inspections of the active substance manufacturing sites, final product manufacturing sites and batch release sites were not considered necessary.

Overall conclusions on administrative particulars

The GMP statuses of both the active substance and dosage form manufacturing sites have been satisfactorily established.

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

Part 2 - Quality

Composition

Broadline is a spot-on solution combining two ectoparasiticides (fipronil 83 mg/ml and (S)-methoprene 100 mg/ml) and two endoparasiticides (praziquantel 83 mg/ml and eprinomectin 4 mg/ml). Two different single-dose strengths are proposed: 0.3 ml and 0.9 ml. Both volumes are filled in the same spot-on applicator system.(A filling overage of 0.0615 ml per spot-on applicator is included compensating for the residual volume in the spot-on applicators after expression of the container content. In this way the delivery of the claimed dose is ensured. There are no other overages.

The active substances are solubilised in a non-aqueous solvent mixture. The main solvent is dimethyl isosorbide. The co-solvent is glycerol formal, stabilised, which contains disodium edetate, n-propyl gallate and thiodipropionic acid. Butylhydroxytoluene (BHT) is included as an antioxidant.

Container

The primary packaging material, for both presentations, is a 1 ml single-dose spot-on applicator. Each spot-on applicator comprises of a clear cyclic olefin copolymer syringe-shaped barrel (siliconised), a polypropylene plunger rod with plunger (siliconised) and a bromobutyl rubber tip cap.

Secondary packaging consists of individual polyethylene trays (to hold the spot-on applicators in place) with plastic lids to reduce children from accessing the product. The plastic trays are then packed into cardboard cartons. Pack sizes of 1, 3, 4 and 6 (this for the higher strength only) spot-on applicators are proposed.

Development pharmaceutics

A spot-on solution for topical administration of the product was proposed as administration is technically simple and is less stressful to cats.

Solubility has been tested in approximately 30 organic solvents. Several solvents were identified as providing adequate solubility for the necessary concentrations of the four active substances. The choice and amounts of excipients has been adequately justified.

The formulation is hygroscopic, and therefore water absorption needs to be restricted to prevent precipitation and/or degradation of the active substances. Two types of spot-on applicators were tested with the formulation. The one chosen demonstrated less water absorption by the formulation when stored at higher temperatures and humidities.

In view of the nature of the organic solvent system for the finished product, further data on the extractables from the primary packaging materials was requested and has been provided. The levels of leachables remain within acceptably low ranges. Absorption exhibited by the (S)-methoprene into the rubber components of the packaging has been sufficiently documented and considered acceptable. Based on the presented data and considering the nature of the finished product, a widening of the assay shelf-life requirement (compared to that used at time of release) was accepted for the (S)-methoprene. No further actions were deemed necessary.

Significant photolability was observed for (S)-methoprene and eprinomectin when exposed to light. The choice of the cardboard carton used for secondary packaging was shown to provide sufficient protection to the product against photodegradation.

Method of manufacture

The manufacturing process is considered to be a standard process. Manufacture of the bulk solution and its filling into spot-on applicators is a relatively simple and straightforward process. For commercial scale production of the product, the defined operating parameters are based on the parameters applied for the batches described in the development section.

In-process controls on the bulk solution include the appropriate physical and chemical aspects to be checked before proceeding to the filling process. Microbiological properties will be documented during process validation on production scale batches, for which the protocol is provided.

The analytical results for three commercial scale batches suggest that the production process is robust. Prospective validation of the manufacturing process will be performed post-authorisation at the proposed manufacturing site on three production scale batches of the finished product. The validation protocol has been presented and was deemed acceptable.

Control of starting materials

Active substance

Praziquantel is described in the European Pharmacopoeia (Ph. Eur.) and is covered by a certificate of suitability. The certificate of suitability does not include a re-test date. Stability data according to current VICH guidance were submitted in support of a re-test period of 60 months with no particular storage conditions, and this is justified.

Fipronil is not the subject of a monograph in either the Ph. Eur. or any other pharmacopoeia of the EU. The data for this active substance are included in full detail within the dossier. Redefinition of the starting materials was considered satisfactory. The retest period of 36 months, without any particular storage conditions, is supported by data.

(S)-Methoprene is not the subject of a monograph in either the European Pharmacopoeia (Ph. Eur.) or any other pharmacopoeia of the EU. The data for this active substance are presented in the form of an ASMF. (S)-Methoprene is already used as active ingredient in a centrally authorised veterinary medicinal product from the same applicant (EMEA/V/C/002002). The version of the ASMF was the same as that used in the previous application, no new assessment has therefore been performed. However, the specification was slightly adapted by the finished product manufacturer. The retest period of 3 years with no particular storage recommendations is justified.

Eprinomectin is also not the subject of a monograph in either the Ph. Eur. or any other pharmacopoeia of the EU. The information on eprinomectin is also included in full detail within the dossier. The specification is based on the United States (US) pharmacopoeia monograph. The limits for impurities have been set to acceptable levels and the proposed specification is considered acceptable. The re-test period is 36 months if stored below 8 °C, and this has been justified.

Excipients

None of the two solvents, glycerol formal (stabilised) and dimethyl isosorbide are described in the Ph. Eur. or any pharmacopoeia of the EU.

Glycerol formal (stabilised) is already used in two injectable veterinary medicinal products produced by MERIAL and authorised for use within the EU. This excipient contains disodium edetate, n-propyl gallate and thiodipropionic acid as chelating and anti-oxidant agents. Glycerol formal (stabilised) and the stabilising agents are covered by acceptable specifications.

Dimethyl isosorbide is already used in a human medicinal product authorised for use within the EU (Brevoxyl). It is included in the US Food and Drug Administration (FDA) list of inactive ingredients for approved drug products.

Butylhydroxytoluene is the subject of a Ph. Eur. monograph.

A certificate of analysis is presented for each excipient.

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

The CVMP concluded that the risk of transmitting spongiform encephalopathies through this product has been considered in compliance with the current regulatory texts.

None of the starting materials or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3).

Control tests during production

There are no intermediate products during manufacture. The production process is covered by an appropriate list of in-process controls which are regarded as relevant to ensure a consistent quality.

Control tests on the finished product

The specifications for release are suitable to control the quality of the finished product and include the relevant physical, chemical and microbiological tests for this type of product. The methods for density, clarity and colour of solution, uniformity of dosage units and microbiological contamination are performed in accordance with the Ph. Eur.

All analytical methods used to control the finished product were sufficiently described and have been appropriately validated for the intended purposes and in accordance with VICH guidelines.

Batch analytical data in compliance with these release specifications were presented.

Stability

In the shelf life specifications, widening of the limits is proposed for water content, (S)-methoprene assay, BHT assay and for the degradation products fipronil sulfone, (S)-methoprene cis isomer and for the total of (S)-methoprene degradation products. This was justified by stability data. (S)-Methoprene was seen to be partially absorbed by the rubber components of the packaging material. The phenomenon has been sufficiently documented by the applicant by demonstrating that the losses were physical only and that an under assay limit of 90.0% during shelf life was feasible.

Stability data on three pilot batches of both strengths stored at long term, intermediate and accelerated conditions were submitted. Also the results of a photostability study according to VICH conditions and of a freeze-thaw cycling study have been presented.

Based on the outcome of these studies, it was agreed on a shelf life of 2 years for the finished product with the storage recommendation ‘Store in the original cardboard boxes in order to protect from light’.

Overall conclusions on quality

Broadline is a spot-on solution for cats combining two ectoparasiticides (fipronil and (S)-methoprene) and two endoparasiticides (praziquantel and eprinomectin) in a single-dose spot-on applicator of 0.3 ml or 0.9 ml.

The manufacturing process and the process controls are well described. Data in support of the registration have demonstrated that the manufacturing process is robust, leading to a finished product in compliance with the quality specifications. The validation protocol for the prospective validation that will be performed post-authorisation was accepted.

All starting materials, active ingredients as well as excipients, are adequately described and are covered by appropriate specifications. Control methods are described and validated, where relevant and stability data are presented for the active ingredients in order to support the re-test periods.

Suitable specifications for the finished product have been elaborated for release testing as well as for testing during shelf life. Control methods are sufficiently described and validated.

In accordance with the provided stability data, the shelf life for the finished product is 2 years, when stored in the original cardboard boxes in order to protect from light.

The quality of Broadline spot-on solution is therefore considered demonstrated and in-line with current standards, including EMEA/CVMP/QWP/544461/2007 'Quality Aspects of Single-dose Veterinary Spot-on Products.'

Recommendations for future quality development

Not applicable.

Part 3 – Safety

Safety documentation

Pharmacodynamics

Data were provided to outline the pharmacodynamic actions of the active substances. The known mechanisms of action of the substances and the non-interference studies are described under Part 4.

The four substances contained in Broadline (fipronil, (S)-methoprene, eprinomectin and praziquantel) have been shown to act essentially through different mechanisms and molecular targets, and to target different parasite groups, although each of fipronil and eprinomectin present a possible residual activity on the main target receptor of the other. The absence of significant interaction at the pharmacodynamic level is supported by the well-established properties of the active ingredients, and by five new clinical studies investigating the possible interactions at the level of clinical efficacy in the target species.

Pharmacokinetics (PK)

The pharmacokinetic properties of the substances, individually and in the combination, are described using literature data and a series of own PK studies. The latter allowed to establish PK profiles in plasma and on the hair coat; overall no statistically significant difference was detected when comparing the active ingredients used separately and in combination, indicating the absence of significant PK interactions. This is described in more detail under Part 4.

Toxicological studies

As all the individual active substances are already used in authorized veterinary medicinal products, their established toxicological profiles are presented in a summarized form only, essentially with reference to authority reviews. Those authority reviews consist in JMPR or JECFA reports (for fipronil, (S)-methoprene and eprinomectin), in a US EPA (Environmental Protection Agency) report for (S)-methoprene, and in EMA MRL summary reports for eprinomectin (EMEA/MRL/520/98, EMEA/MRL/114/96) and praziquantel (EMEA/MRL/141/96).

For the individual substances, the lowest acute oral LD_{50} values obtained are 95 mg/kg in mouse for fipronil, >5,000 mg/kg in rat for (S)-methoprene, 55 mg/kg in rat for eprinomectin and 2,249 mg/kg in rat for praziquantel. Acute dermal LD_{50} are available for fipronil and (S)-methoprene; the lowest values are of 354 mg/kg in rabbit and >2,000 mg/kg in rat, respectively.

The lowest oral repeated dose NOAELs are 0.019 mg/kg/day in rat (> 1 year) for fipronil, 8.6 mg/kg/day in dog (90 days) for (S)-methoprene, 0.8 mg/kg/day in dog (90 days) for eprinomectin, and 33 mg/kg/day in rat (30 days) for praziquantel. Twenty one-days dermal NOAELs in rabbit are available for fipronil, (S)-methoprene and praziquantel, and are of 5 mg/kg/day, 100 mg/kg/day and 167 mg/kg/day, respectively.

As regards reproductive and developmental toxicity, the lowest recorded oral NOAELs are 0.9 mg/kg/day in rat for fipronil, 29 mg/kg/day in rat for (S)-methoprene, 1.2 mg/kg/day in rabbit for eprinomectin and 300 mg/kg/day in mouse and rabbit for praziquantel.

The mutagenicity tests were negative for all substances.

Fipronil is a mild skin and eye irritant, and eprinomectin is slightly irritating to the eye, while (S)-methoprene and praziquantel are not classified as irritating. None of the compounds is a skin sensitizer.

In addition, for the individual substances, two acute oral toxicological studies (in accordance with good laboratory practice (GLP)) were provided as for the user safety assessment (see also below). The first of those studies follows Organisation for Economic Co-operation and Development (OECD) Test Method 401; it uses single oral doses of fipronil in groups of 20 rats. The resulting NOAEL relates on neurological signs and is of 2.5 mg/kg. In the second study, groups of 10 rats received single oral doses of eprinomectin, and a NOAEL of 8 mg/kg was drawn, also associated to neurological signs.

The three excipients are well-known in the EU in pharmaceutical and cosmetic products.

Glycerol formal and BHT are present in approved veterinary medicinal products. Glycerol formal and dimethyl isosorbide are solvents; glycerol formal is classified as an allowed substance with no MRL required, and dimethyl isosorbide is included on the FDA list of inactive ingredients for approved drug products. BHT is a fat anti-oxidant and a EU approved food additive (E321). Three further compounds, propyl gallate, disodium edetate and thiodipropionic acid, are present in very small amounts as stabilizers (anti-oxidants) of glycerol formal; the two first are EU approved food additives (E310 and E385, respectively), and the last is included in the FDA Generally Recognized As Safe (GRAS) list of food additives.

For the combination, the toxicological data provided specifically consists in the following new GLP studies, conducted with the finished product: (i) An acute oral toxicity (LD_{50}) in rats, (ii) An acute dermal toxicity (LD_{50}) in rats, (iii) a skin irritation study in rabbits, (iv) an eye irritation study in rabbits and (v) a skin sensitization (delayed contact hypersensitivity) study in guinea pigs.

The acute oral toxicity study was conducted in accordance with OECD guideline 420 and EEC method B.1 bis; it gives an oral LD_{50} value of > 351 mg/kg, corresponding to roughly 1x the maximum recommended dose. Five rats received a dose of 351 mg/kg and 5 rats, the dose of 117 mg/kg. One of the rats dosed at 351 mg/kg died after presenting abnormal gait and stance; this death is explained by a physical trauma.

The acute dermal toxicity study was conducted in accordance with OECD guideline 402 and EEC method B.3; the dermal LD_{50} value is of > 2,000 mg/kg which corresponds to approximately 5x the maximum recommended dose. In that study, one group of 10 rats received a single topical dose of 2,000 mg/kg. Abnormal gait and stance were observed in all animals for 1 to 3 days, but this can be explained by the removal of the restrictive gauze wrapping.

The skin irritation study was conducted in line with OECD GL 404, using 3 rabbits, and concluded that the product is not irritating to the skin.

The eye irritation study was in accordance with EEC method B.5 and involved 3 rabbits; the product was classified as slightly irritating to the eye. Finally, in the delayed contact hypersensitivity study, carried out in accordance with OECD guideline 406 on 20 guinea pigs, it appeared that the product is not a dermal sensitizer.

No specific repeated-dose toxicity study of the combination was provided and therefore no subacute/chronic oral toxicity endpoints were generated for the combination. However this is adequately covered by the target species tolerance studies (see related section) as allowed in the case of companion animal products by Annex I of Directive 2001/82/EC.

No data as to reproductive and developmental toxicity are provided for the combination. This was justified by the absence of selective developmental or reproductive toxicity of the individual active ingredients, the absence of significant interactions at the pharmacokinetic and clinical efficacy level and the absence of increased neurotoxicity as appears from the toxicological or tolerance studies. As regards the target species, this is acceptable since adequate warnings are included in section 4.7 of the summary of product characteristics (SPC). Also, this was deemed acceptable in the framework of user safety, since adequate risk mitigation measures were included in the SPC and the product packaging is sufficiently child-resistant.

The absence of mutagenicity/genotoxicity and carcinogenicity data specific to the combination is considered acceptable in the case of a product intended to treat companion animals, and because such aspect of toxicity generally relate essentially to the properties of the individual substances.

As a special toxicity study, a combination of fipronil, (S)-methoprene and eprinomectin was used to explore the effects of eprinomectin in six Collie dogs stated to be ivermectin-sensitive (non-GLP study). Severe, fatal toxicosis occurred with the dermal dose of 50 mg/kg eprinomectin (33x the maximum recommended dose in cat) whereas a dose of 12.5 mg/kg (8x the maximum dose) only induced mild clinical signs. The risk for co-housed dogs is thus considered very low; nevertheless, as a precaution a relating warning was included in section 4.5 of the SPC.

In conclusion, the established toxicological profile for the individual active substances is presented essentially with reference to authority reviews. In addition for the individual substances, two acute oral toxicological studies in rat (GLP) were provided as for the user safety assessment. They conclude to an acute oral NOAEL of 2.5 mg/kg for fipronil and an acute oral NOAEL of 8 mg/kg for eprinomectin, both relating to neurological signs. The three excipients are well-known in the EU in pharmaceutical and cosmetic products, and no concerns relating to those substances were identified.

For the combination, the toxicological data provided specifically consists in the following new GLP studies, conducted with the finished product: (i) An acute oral toxicity (LD_{50}) in rats, (ii) An acute dermal toxicity (LD_{50}) in rats, (iii) a skin irritation study in rabbits, (iv) an eye irritation study in rabbits and (v) a skin sensitization (delayed contact hypersensitivity) study in guinea pigs. The acute oral toxicity study gives an oral LD_{50} value of > 351 mg/kg, corresponding to roughly 1x the maximum recommended dose. The dermal LD_{50} value is of > 2,000 mg/kg, which corresponds to approximately 5x the maximum recommended dose. It was concluded that the product is not irritating to the skin, is slightly irritating to the eye, and is not a dermal sensitizer.

No subacute/chronic oral toxicity endpoints were generated for the combination; however this is adequately covered by the target species tolerance studies as allowed by Annex I of Directive 2001/82/EC in the case of companion animals.

No data as to reproductive and developmental toxicity are provided for the combination. This was justified by the absence of selective developmental or reproductive toxicity of the individual active ingredients and the absence of significant interactions.

The absence of mutagenicity/genotoxicity and carcinogenicity data specific to the combination is considered acceptable in the case of a product intended to treat companion animals, and since the individual substances were shown not to be mutagenic.

The effects of eprinomectin as combined with fipronil and (S)-methoprene were explored in ivermectin-sensitive Collie dogs. Fatal toxicosis occurred at about 33x the maximum recommended dose in cat, whereas a 8x dose only induced mild clinical signs. Despite the risk to in-contact dogs appears very low, a precautionary warning was included in section 4.5 of the SPC.

Tolerance in the target species of animal

Since eprinomectin is a new substance in cat, its individual tolerance profile in that species was investigated in two non-GLP studies, where increasing levels of eprinomectin from highest recommended dose (HRD) were combined with lower levels of the other substances (maximum of 1.66x HRD), and administered topically in the same solvent system as the final formulation. A neurological assessment was specifically carried out, the following parameters being assessed: coordination, mental status (depression), salivation, and pupillary reflex.

The study designs of the GLP-studies investigating the combination can be summarized as follows:

Study	**Dose levels**	**Route**	**Treatment regimen**	**Age of the cats**	**Health status**
No 1, not final formulation, GLP	1x, 3x, 5x	Topical	3x at 14 days	Kittens (7–9 w)	Healthy
No 2, pivotal, GLP	1x, 3x, 5x	Topical	6x at 28 days	Kittens (7–9 w)	Healthy
No 3, GLP	1x, 3x	Topical	3x at 28 days	adults	Heartworm infestation
No 4, GLP	1x	Oral	Once	adults	Healthy

In the first study, both the topical and the oral route were tested. Three groups of 6 cats were treated by the dermal route with eprinomectin levels of 4, 5.33 or 6.6 x the maximum recommended therapeutic dose (RTD), administered 3 times at 14 days intervals. One further group of 6 cats was treated orally with consecutive, escalating doses of 0.2, 0.66 and 1.33x the maximum RTD, the three doses being separated by a 14 days interval. The levels of the active ingredients other than eprinomectin varied with the substance and the route, but were of maximum 0.64x the intended maximum therapeutic dose (RTD).

The second study involved the dermal route only, with eprinomectin levels of 1, 3 and 5x the intended RTD, corresponding to levels of the other substances of 0.32x to 1.66x RTD; the doses were administered to groups of 8 cats, three times at 14 days intervals.

In the above two studies investigating mainly the tolerance of eprinomectin, transient pupil dilatation was observed in most animals, generally mild and resolving within 1 to 3 days. Also, one instance of mild incoordination, one instance of mild depression and one instance of mild salivation were observed each in 1 out of 6 cats treated at 4x or 5.33x HRD topically, and increased salivation was observed in 2 out of 8 animals receiving 3x the HRD topically.

Tolerance of the candidate combination was then investigated in four studies testing increasing doses in adult cats and kittens, using the dermal and the oral route, and involving healthy cats or cats experimentally infested with adult heartworms. Each dose group comprised 8 to 12 cats.

In the first of these studies, an abnormal pupillary reflex was observed in 1/8 cat from the 3x group and 4/8 cats from the 5x group, as well as one instance of vomiting and one instance of mild depression in the 3x group; in all treated groups, several instances of licking/scratching directly after administration were noted. In the second study, considered as pivotal, one cat from the 5x group showed transient neurologic signs (ataxia, disorientation, apathy) and pupil dilatation with response to light, with complete recovery the day after. A series of other mild or moderate transient pupil dilatation instances were also observed, as well as few instances of transient salivation or itching following administration. In the third study, using cats infested with heartworms, no adverse reactions were observed. In all the cats dosed orally, salivation and mouth licking was observed, for a few hours at the most, and in few cases, vomiting or regurgitation were recorded.

Concerning the consequences of the observed instances of mydriasis this would not constitute a concern for safety, since the impairment of the pupillary reflex is a well-known potential side effect of avermectins and in these studies was always transient and in most cases mild and possibly physiological and/or attributable to stress. However, pupil dilatation is mentioned in the SPC as a potential neurological adverse reaction.

The other observed signs, i.e., vomiting, salivation, and neurological signs such as ataxia and apathy, are also adequately reflected in the SPC, sections 4.6 and 4.10.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1). Three types of scenarios are considered.

The first scenario considers accidental oral or dermal contamination of a child having access to a product applicator during the pre-application (storage) phase. The risk was initially assessed by comparing for the formulated product the exposure to one entire large size applicator in a 15 kg child, to the LD_{50} values derived from the rat dermal and oral acute toxicity studies specific to the combination product, leading to margins of exposure (MOEs) of 28 and 4, respectively, without taking into account any uncertainty factor (UF).

Oral and a dermal LOEL derived from the tolerance studies were then used in cats as alternative toxicity endpoints, as these would relate to mild effects recognized as insignificant in view of the rare occurrence of the scenario. Using the highest doses received in the cat tolerance studies, considered as well tolerated doses that correspond to 2,194 mg/kg of the final product for the dermal route and 439 mg/kg for the oral route, the resulting MOEs are similar to the previous approach, i.e. 31 for the dermal route and 6 for the oral route.

By applying the usual UF of 100 the risk quotients (RQs) would be below 1 and risk management measures are necessary to prevent access from children to the product. Prevention of child access to the product is managed by that the product is contained in applicators that are further packed in trays and cardboard boxes. Trays are lidded with plastic lids that prevent children from easy access to the product. Moreover the likelihood of exposure to the product during storage is very low.

The second scenario concerns contamination of the skin or mucosae of the owner during application. The likely exposure is derived from an older study estimating exposure to fipronil during spot-on administration by pet groomers, with dosimeters placed under protective clothing and gloves. Exposure values estimated for each active substance were compared to individual subacute or acute neurotoxicity toxicological endpoints, leading to MOEs ≥ 200,000. Furthermore, contamination during application is limited by standard user safety warnings. This is disputable due mainly to the methodology of the exposure study and as the active substances are considered separately, which is not a worst-case and not in line with the provisions of the CVMP Guideline on

pharmaceutical fixed combination products (EMEA/CVMP/83804/2005). In addition, most toxicological endpoints for individual compounds are not justified by full reports but by reference to FAO/WHO evaluations. Furthermore, a qualitative assessment was made by referring to the skin and eye irritation study and the skin sensitization study, showing that at relevant levels the whole product is only slightly irritating to the eyes, what can be prevented through standard user safety warnings.

An additional calculation was made during assessment of the data provided. The estimated MOE during the application phase, based on the exposure of an adult to a whole large applicator and like for the pre-application phase on the tolerated dermal dose derived from cat tolerance studies, would be 125 for the dermal exposure and 25 for the oral exposure. The dermal exposure during the application phase leads to an acceptable risk. Moreover there is a warning on the SPC to avoid the contact of the applicator content with fingers and to wash off with soap and water in case of exposure. For the oral exposure the RQ is below 1. However total oral exposure to an entire applicator is considered unlikely and partial ingestion would be accidental. Also the SPC contains warnings not to drink or eat during application.

The third scenario relates to the potential risk induced by the handling or stroking of a treated animal by an owner (a child, as a worst case), in the post-application phase. Exposure to each active substance is derived from a new study where dislodgeable amounts were measured on gloves from a handler stroking treated cats each day for one month. The time-averaged values after are then confronted to subacute or chronic toxicological endpoints for individual substances, leading to MOEs for long-term exposure of 211–14,000 for the dermal route and 380–500,000 for the oral route, which are all higher than the conventional UF of 100. A favourable assessment was also performed for short-term exposure using the higher residue levels recorded just after treatment, and furthermore, the risk is mitigated by user warnings limiting contact with recently treated animals. This is considered acceptable, as none of the active substances have shown developmental toxicity, the post-application exposure can be considered as conservative, and the MOEs are largely conservative even considering the sum of oral and dermal exposure.

The Committee concluded that sufficient data on user safety had been provided and that the SPC should include the following warning:

"Handling of treated animals should be limited until the application site is dry and children should not be allowed to play with treated animals during this period. It is therefore recommended that recently treated animals do not sleep with owners, especially children".

Environmental risk assessment

A phase I Environmental Impact Assessment is provided, in accordance with guideline CVMP/VICH/592/1998, and supportive guideline EMEA/CVMP/ERA/418282/2005-Rev.1. According to the phase I decision tree, no phase II assessment is required since the product is intended for the treatment of non-food animals only, and furthermore, the treatment is given on an individual basis; therefore exposure of the environment to the product is considered insignificant.

The risk to the environment is considered negligible when used according to the SPC.

Overall conclusions on the safety documentation

The four individual active components of Broadline (fipronil, (S)-methoprene, eprinomectin and praziquantel) are already used in authorized veterinary medicines, and toxicological profiles of these individual substances are known.

Eprinomectin constitutes a new active substance in cats. Two non-GLP tolerance studies in cat were conducted with increasing eprinomectin levels between 1x HRD and 6.6x HRD via the topical route of administration and associated to low levels of the other substances. The dosing was repeated at 14-day intervals. Results showed

transient pupil dilatation in most animals, usually mild and resolving in 1–3 days. Incoordination, depression and salivation were observed at low frequency at eprinomectin levels above the HRD.

The toxicological data provided for this new combination consist in two acute LD_{50} studies in rats, one dermal and one eye irritation study in rabbits, and one skin sensitization study in guinea pigs. All studies were conducted in accordance with GLP. For acute toxicity in rats the results show an oral LD_{50} value above 351 mg/kg and a dermal LD_{50} value exceeding 2,000 mg/kg, based on the finished product. The product appeared to cause a slight eye irritation in rabbits however no skin irritation or dermal sensitization could be shown in rabbits or guinea pigs, respectively.

Repeated dose toxicity of the combination is covered by three topical tolerance studies involving adult cats and kittens. Target animal safety was investigated at up to 5 times the maximal exposure dose (i.e. up to 15 times the recommended dose) in healthy kittens aged 7 weeks and older treated up to 6 times at four-week intervals. It has also been confirmed in healthy adult cats treated 3 times at two-week intervals with up to 5 times the maximal recommended dose. Results include abnormal pupillary reflex or pupil dilatation, and scratching/licking of the application site, in all treated groups. In the groups exposed to doses above HRD, vomiting, and neurological signs (ataxia, disorientation, apathy) were observed in some animals. Cats infected with adult heartworms tolerated up to 3 times the maximal exposure dose (i.e. up to 9 times the recommended dose), every 4 weeks for 3 treatments, without any adverse effects.

One additional study investigated the tolerance of the product in cats dosed via the oral route; in all groups salivation and mouth licking were observed, and in few cases, vomiting or regurgitation.

Overall, the studies are valid and produce reliable results. The studies show an acceptable tolerance profile, and the observed adverse effects are adequately reflected in the SPC.

The absence of reproductive/developmental toxicity data and of genotoxicity data for the combination was considered acceptable in view of the known properties of the individual ingredients and the absence of significant interactions.

On the basis of a special toxicity study, a low risk for adverse reactions exists in co-housed dogs and therefore a precautionary warning is included in the SPC.

The user risk assessment is considered acceptable and adequate risk management measures are introduced through SPC warnings and the packaging design.

The risk to the environment is considered negligible when used according to the SPC.

The potential risk relating to resistance emergence is addressed below.

Residues documentation

Not applicable.

Part 4 – Efficacy

As fipronil, (S)-methoprene and praziquantel are used in authorised veterinary medicinal products for the same therapeutic use, target species, and route of administration as proposed in this fixed combination, it is not necessary to provide detailed pre/clinical data for the individual substances (see also CVMP Guideline on pharmaceutical fixed combination products, EMEA/CVMP/83804/2005).

Pharmacodynamics

Fipronil, (S)-methoprene and praziquantel are used in authorized veterinary medicinal products (VMPs), and their mode and spectrum of action is documented in the public literature. No new studies are provided to that respect. Fipronil, a phenylpyrazole, acts mainly through the blocking of gamma-aminobutyric acid (GABA)-gated chloride ion channels, and shows insecticidal activity against fleas and other insects, and acaricidal activity against some mite species. (S)-Methoprene is an analogue of an insect juvenile hormone, and has a direct and indirect ovicidal action in fleas. Praziquantel is an isoquinoline derivative acting at the level of cell membrane permeability of cestodes and schistosomes, resulting in the killing of the parasites.

Eprinomectin is a new substance in cats; it is, however, authorized in VMPs as a pour-on formulation for cattle, and indicated against a series of nematodes, insects, insect larvae and mites. In the present application its mode of action is essentially described by referring to literature data concerning other avermectins, which act mainly on glutamate-gated chloride channels, leading to the death of the parasites.

The presented literature data also suggest that fipronil and eprinomectin could present a limited activity on glutamate- and GABA-gated chloride ion channels, respectively.

Five non-interference laboratory clinical studies, each using groups of 6 to 10 cats, were provided in order to demonstrate the absence of clinically significant overlap or negative interaction between the activity spectra of the four active substances.

In the first study, which does not use the final formulation product, it is shown that the efficacy against adult fleas (*Ctenocephalides felis*) of a combination containing no praziquantel remains unchanged when compared to the four substances in combination.

Two further studies in accordance with good clinical practice (GCP) showed that eprinomectin alone, as controlled by the candidate combination, has a very poor activity against adult fleas and immature flea stages, and against *Dypilidium caninum*, respectively. In the *D. caninum* trial, the used product was not the final formulation.

In a fourth experiment, not using the final formulation, the addition of eprinomectin and eprinomectin plus praziquantel are shown not to impact the insecticidal or ovicidal activity of fipronil and (S)-methoprene on fleas.

Furthermore, it is confirmed in a fifth, GCP trial that praziquantel, as controlled by the final combination, is not active against *Toxocara cati* and *Ancylostoma tubaeforme*.

The potential activity on ticks and lice of eprinomectin is not described using specific data, but is deemed negligible as regards its use in Broadline, in view of its poor contribution to efficacy against the primary target ectoparasite (fleas).

Justification of the combination

The proposed combination, under the conditions of use as recommended in the SPC, is adequately justified as per the provisions of the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005). Indeed, each of the four substances broadens the activity spectrum of the product to specific groups of parasites, which are considered to be of medical importance and possibly present in cats as concurrent infestations or high risk of infestation.

While fipronil and (S)-methoprene target ectoparasites, primarily fleas and their immature forms, eprinomectin is effective against gastro-intestinal nematodes and heartworm larvae, and praziquantel against tapeworms. The dose of the individual substances was adequately justified, through a series of dose finding studies (see below, dose determination) and taking into account the absence of clinically significant interaction with regard to their activity towards the main target parasites.

To justify the need for such a wide spectrum product, a European epidemiological multicentre, multinational survey was provided. The study was conducted in 2012–2013 involving centres in France, Austria, Hungary, Belgium, Spain, Romania and Italy. For this study 1309 client-owned cats were recruited during routine consultations for parasitological diagnostic through combing, ear examination and coproscopic examination. Results showed that 56% of cats with cestodes were co-infested with at least another parasite and 11.8% of cats with nematodes were also carrying cestodes. Co-infestations of ectoparasites and nematodes were present in 6.4% of the study population whereas ectoparasites and cestodes were observed in 1.2% and nematodes and cestodes in 2.5% of the study population.

Most importantly, considering the proposed indication, 0.69% of the study population was diagnosed as carrying all three target types of parasites (ectoparasites, nematodes and cestodes). This can be considered as the lower limit for the actual target population, which comprises in addition the animals deemed at risk of infestation, through clinical judgement and assessment of the epidemiological risk factors. Indeed, in addition to the fact that prevention against one of the target parasites is necessary in a number of situations (e.g. for ectoparasites), coproscopic examination may also be falsely negative in animals suspected of infestations (e.g., with cestodes or during the pre-patent period). Finally, it is important to acknowledge that the estimated prevalence in the population is likely to have regional differences. The detail of such differences is however at present unknown in the veterinary field.

In order to be clearer as to the definition of the target population, i.e., as to which conditions or types of condition should be targeted specifically and concurrently for a proper use of the product, the wording of sections 4.2 and 4.9 of the SPC was carefully considered. In this sense, the sentence "The product is exclusively indicated where all those three groups are targeted specifically at the same time" is considered crucial for the rational use of this product.

Although on the basis of the provided data, it is expected that the target population for the product will be limited, the combination is considered sufficiently justified, and misuse is prevented through adequate wording of the indications and the instructions for use.

Development of resistance

It is acknowledged that resistance exists as for all antiparasitic substances, but based on literature data, up to now this only concerns single isolated ectoparasite strains and there is currently no report of resistance relevant to the field situation, to any of the concerned substances and in any of the target cat parasites. In the case of praziquantel, resistance has been documented in human parasites. Also, the possibility of cross-resistance of eprinomectin with other macrocyclic lactones should be taken into account as they have a similar mode of action.

However, resistance development in the future could be favoured by misuse or unnecessary use of the product.

Hence, the appropriate use of the product is crucial to ensure that the efficacy is maintained.

Therefore, in order to delay any anticipated development of resistance in the future, the product information should prompt strategical use and define clearly the target population for the product. Apart from a new sentence *"The veterinary medicinal product is exclusively indicated where all those three groups are targeted specifically at the same time."*, sections 4.4 and 4.9 have been modified in order to improve the proper and adequate use of the product, mainly based on the fact that the individual animal is considered and will receive the appropriate medication that will meet their own individual needs.

Pharmacokinetics

Pharmacokinetics of the active substances, individually or within the combination, is adequately described through literature data and in four pivotal, GLP PK studies. In these studies the final formulation product was investigated in healthy cats (groups of at least 6 individuals were used).

The first of these studies was designed to determine the bioavailability of each active substance. The PK profile of each substance was established by administering the substances individually via the intravenous route and topically as the combination product. Single doses were administered which corresponded to the minimum recommended doses. The average bioavailability was 38% for fipronil, 16% for (S)-methoprene, 45% for praziquantel and 31% for eprinomectin.

In a second study, it was shown that the PK profiles of the substances administered topically individually were similar to the profiles obtained when administering the combination topically as recommended. No statistically significant pharmacokinetic interaction was detected except for one difference concerning the parameter AUC_{last} ($p=0.025$) for eprinomectin. This is considered attributable to a formulation effect altering the absorption rate.

From the data obtained in the two above studies, T_{max} is approximately 8–27 h for fipronil, 6–9 h for (S)-methoprene, 6–7 h for praziquantel and 48–63 h for eprinomectin, with mean C_{max} values of about 45–75 ng/ml, 9–22 ng/ml, 75–157 ng/ml and 16–20 ng/ml, and half-life values of approximately 4.4, 0.29–0.45, 3, and 4.5 days, for fipronil, (S)-methoprene, praziquantel, and eprinomectin, respectively.

The third study also investigated the hair coat distribution of the substances when the proposed product was administered as recommended; a translocation from the application site towards the entire body surface was observed within 1 to 7 days, followed by an exponential decrease. The concentrations decreased from the application site, and the ratios between substances roughly reflected those in the product.

The fourth pivotal study evaluated the dose proportionality (PK linearity) of the active substances, using doses of 0.5x, 1x, 2x and 5x the minimum recommended dose. It was concluded that PK linearity was demonstrated for all substances all over the tested dose range for C_{max} and AUC, except for (S)-methoprene, where linearity at 5x the dose could not be established due to one outlying result, and where only C_{max} was considered due to the low bioavailability.

In several of the laboratory efficacy studies, supportive PK data for eprinomectin were collected.

In addition, two non-GLP studies addressing *in vitro* liver fractions metabolism suggesting a possible inhibition of fipronil metabolism by eprinomectin, but the used concentrations were not relevant to the *in vivo* situation.

Another study was performed to assess *ex vivo* the cat plasma protein binding characteristics of eprinomectin. The binding rate was > 99% in cat, dog and rat plasma, which is also consistent with the results obtained previously in cattle.

From literature data and study data obtained during the development of the products Frontline (fipronil) and Frontline Combo (fipronil and (S)-methoprene) by the same applicant, it appears that fipronil is excreted mainly in the faeces, as unchanged drug and more polar metabolites. The active fipronil metabolite, fipronil sulfone, is produced only at negligible levels in the cat, contrary to the dog. However, fipronil sulfone is detected in low amounts on the cat hair coat, probably as a result of photodegradation.

(S)-Methoprene is metabolized to carbon dioxide and acetate, and exhaled or incorporated into endogenous compounds.

Praziquantel has a moderate tissue distribution, and about 64–84% of praziquantel is bound to plasma proteins. It undergoes hepatic metabolism followed by renal excretion.

Eprinomectin has low clearance from blood, and distributes well into tissues. Its metabolism is limited, and it is mainly excreted unchanged in the faeces.

Dose determination

It has been demonstrated through the company sponsored PK and pharmacodynamics studies that there is no significant interference between the four active substances in the product at the pharmacokinetic level, and no clinically significant interference at the pharmacodynamic level as concerns the main target parasites. Also, no interference at the toxicological level appears from the presented toxicological and tolerance studies.

In line with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), in the absence of pharmacological interactions dose selection for the three substances already authorised in cats (fipronil, (S)-methoprene, and praziquantel) was based on the doses authorised for the individual substances. The dosage of fipronil and (S)-methoprene (10 mg/kg and 12 mg/kg, respectively) was based on the dose established for the Frontline and Frontline Combo products, but in addition, fluctuation of the dose for the more extreme bodyweights is reduced through the existence of two different applicator sizes. Moreover, this dosage is confirmed in one GCP study testing 0x, 0.5x, 1x and 2x the recommended dose in a total of 24 cats experimentally infected by *C. felis*. One further non-GCP study shows that efficacy is not impacted by volume variations, through the use of 0, 0.10 and 0.15 ml/kg in 24 cats experimentally infected by *C. felis*.

Eprinomectin and praziquantel have been shown to have no impact on the insecticidal/ovicidal activity of the combination, through three clinical non-interference studies (see Pharmacodynamics).

A starting dose range for praziquantel was selected on the basis of approved doses for already authorized similar products (8 to 12 mg/kg). The proposed dose (10 mg/kg) was then determined on the basis of 2 non-GCP dose-finding studies using natural *D. caninum* infestation models. In those studies involved groups of 8–10 cats received doses of 0, 6, 8 or 10 mg/kg praziquantel.

The dosage of eprinomectin (0.5 mg/kg), which is a new active substance in cats, has been tested in 6 clinical dose-determination studies each involving 24 to 40 cats experimentally infested with *T. cati* and/or *A. tubaeforme*. Overall in those studies, doses of 0.1, 0.2, 0.25, 0.35, 0.4, 0.5 and 1 mg/kg were administered. *T. cati* was confirmed to be the dose-limiting gastro-intestinal nematode. However, an optimal dose could not be identified clearly among several of the tested levels. Therefore one of the two *D. caninum* dose finding studies, where *T. cati* was recovered incidentally, with associated results slightly under the acceptance threshold (87%) for an eprinomectin dose of 0.5 mg/kg, was used to justify that no lower dose could be retained. Two dose-determination studies were also conducted with *Dirofilaria immitis*, but no conclusion could be drawn due to an unsuccessful challenge.

Dose confirmation

The following minimum recommended doses were chosen for the fixed combination product for confirmation in dose confirmation studies: fipronil 10 mg/kg, (S)-methoprene 12 mg/kg, praziquantel 10 mg/kg and eprinomectin 0.5 mg/kg.

Ectoparasites

Dose confirmation studies on ectoparasites -ticks and fleas- were conducted in accordance with CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000–Rev.2). The efficacy per cent for adult fleas and ticks were originally calculated using geometric means however results based on arithmetic means were also provided. In spite of the recommendations of the Questions and Answers on the CVMP guideline on the "Testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats" (EMA/CVMP/EWP/82829/2009-Rev.1), justifications were put forward by the

applicant to support the appropriateness of considering geometric means. However, in line with the aforementioned guideline the efficacy assessment by CVMP was based on the arithmetic means.

Fleas

Beside the four laboratory efficacy studies involving adult and/or immature fleas and already presented among the non-interference and the dose determination studies, four pivotal dose-confirmation studies are provided to show efficacy against fleas (*C. felis*). Two of them address the insect growth regulator (IGR) effect (as the per cent emergence of adults from eggs, in comparison to controls), together with the adulticidal effect; notably, a specific model of infestation was used including gravid fleas from donor cats, allowing to collect more eggs from the treated cats and therefore, avoiding to relate only on late time points for the IGR effect assessment.

In total, the adulticidal flea efficacy of the combination was confirmed in 8 laboratory studies (2 non-GCP and 6 GCP), showing over 95% persistent efficacy until Day 22 to Day 43, based on arithmetic means.

The IGR efficacy was confirmed in 5 studies in total (1 non GCP and 4 GCP), showing persistent efficacy until Day 37 up to Day 54, based on arithmetic means.

Those laboratory studies involved groups of 6 to 8 cats. The flea species used for the experimental infection was *C. felis*.

In one of the non-interference studies, IGR efficacy was below the 90% acceptance threshold at all-time points. That discordant result was explained by a treatment failure in one cat, possibly due to inappropriate product application.

Accordingly, claimed activity duration towards adult fleas of one month has been mentioned in section 4.2 of the SPC. The duration accepted for the IGR effect is also of one month, since the two studies conducted with the specific model, considered as the most reliable, gave efficacy duration of 37 days.

The claim as to flea allergy dermatitis (FAD) is based only on its acceptance for Frontline Combo, a product from the same applicant containing fipronil and (S)-methoprene.

Ticks

Efficacy against ticks in laboratory conditions is supported by five dose confirmation studies involving *Ixodes ricinus*. Four of those studies were conducted in accordance with GCP and investigated the final formulation. The fifth study was non-GCP and did not investigate the final formulation. The trials involve groups of 6–10 cats.

Variable durations of efficacy of 9 to 37 days result from those studies, and the pooled data show efficacy > 90% against *I. ricinus* until Day 14 only.

However, 98% efficacy was achieved after 3 weeks in 3 out of 5 studies investigating efficacy against *I. ricinus* in the laboratory environment, and in one other study the challenge was not valid. Also, the difficulty in obtaining consistent results in cat tick laboratory studies is recognized.

In addition, two GCP studies testing efficacy towards *I. scapularis*, an exotic species, were provided. These studies involve groups of 10 cats and demonstrate acceptable efficacy up to Day 23–30, except at Day 2 for one of the studies. *I. scapularis* has however been removed from the indications since it is not relevant to the EU field situation.

In view of these results and those of the field studies performed in the EU and in Japan for ticks (see below), a claim for persistent efficacy against ticks of 3 weeks is deemed acceptable.

Lice

In support of the claim against the chewing lice *Felicola subrostratus*, no studies were provided, but reference was made to two laboratory and two field trials conducted by the applicant with Frontline and Frontline Combo, containing fipronil.

In the absence of any product-specific data demonstrating clinical equivalence, the claim was deemed not acceptable and was removed from the SPC.

Endoparasites

Efficacy against helminths is demonstrated in accordance with VICH GL 7 on general requirements for efficacy of anthelmintics, and VICH GL 20 on specific recommendations for feline concerning efficacy of anthelmintics.

Gastro-intestinal nematodes

Efficacy against adult *T. cati* and *A. tubaeforme*, is supported by 6 specific laboratory dose confirmation studies using natural or induced infestations, adding to one already presented non-interference and one dose determination study, and to incidental, supportive results from five trials targeting primarily other worm species. Studies using naturally infested cats were conducted in Albania. Among the specific dose confirmation studies, three address efficacy against *A. tubaeforme* and *T. cati* larval stages; also, in some studies efficacy figures as to L4 are derived but are associated to low worm numbers or inadequate count timing. Those laboratory studies involved groups of 6 to 12 cats.

The main design characteristics and results of those trials can be summarized as follows. Results in brackets relate to incidental findings and/or results not in line with the reference guideline; unless specifically mentioned, the figures relate to adult worms.

GCP compliance	Study type, infestation type	Main target	*T. cati*	*A. tubaeforme*
yes	Dose determination, Induced	*T. cati*	**100%** (L4: 100%)	/
yes	Non-interference, Induced	*T. cati, A. tubaeforme*	**99.4%** (L4: 97.7%)	(100%) (L4: 100%)
yes	Dose confirmation, Natural	*T. cati*	**98.6%**	(100%)
yes	Dose confirmation, Natural	*A. tubaeforme*	(92.4%)	**99.0%**
yes	Dose confirmation, Induced	*T. cati* L3 and L4, *A. tubaeforme* adults and L4	**100% L3/L4 100% L4**	**100% 100% L4**
yes	Dose confirmation, Induced	*T. cati* L3 and L4, *A. tubaeforme* adults and L4	**0% L3/L4 83.2% L4**	**99.8% 87% L4**
yes	Dose confirmation, Induced	*T. cati, A. tubaeforme* + L4	*No adequate challenge*	**100% 100% L4**
yes	Dose confirmation, Induced	T. cati + L3 and L4	**100% L3/L4 100% L4**	/
yes	Dose confirmation, Natural	*A.braziliense*	(100%)	(100%)

yes	Dose confirmation, Natural	*T. taeniaeformis*	/	(100%)
yes	Dose confirmation, Natural	*T. taeniaeformis*	(100%)	(81%)
yes	Dose confirmation, Natural	*D. caninum*	(100%)	(100%)
yes	Dose confirmation, Natural	*D. caninum*	(100%)	(100%)

For both *T. cati* and *A. tubaeforme,* efficacy on the adult stage were above the 90% threshold in all trials.

Efficacy against *A. tubaeforme* L4 and *T. cati* L3 and L4 is adequately supported by the results of two studies each and in an additional exploratory laboratory study showing efficacy of a laboratory formulation against *T. cati* L3 and L4 stages. However, in the case of *T. cati* larval stages poor results (0-83.2%) where obtained in a fourth study, which is considered as an isolated, unexplained experimental failure.

Two dose confirmation studies were conducted, using groups of 6–10 animals to investigate efficacy against *A. braziliense*. Natural infestation is used in one study, conducted in South Africa, and experimental infestation is applied in the other. Both studies demonstrate efficacy above 90% against *A. braziliense*.

Two further trials demonstrated > 90% efficacy towards *Toxascaris leonina.* Those are GCP-compliant and involve groups of 11–12 experimentally infested cats.

Cestodes

The product was demonstrated to be effective against *Dypilidium caninum* in one specific dose confirmation study and in one of the non-interference studies (97.7 and 99.2% efficacy, respectively).

Efficacy towards *Taenia taeniaeformis* was addressed in two specific studies. Those studies involve groups of 10–12 cats and carried out in naturally infested animals (in Albania and several countries outside Europe); efficacy was of 98.5 and 100%.

Also, supplementary supportive results can be derived from several studies where those species were recovered incidentally besides the target species.

Study designs and results can be summarized as follows; figures into brackets relate to incidental findings:

GCP compliance	Type of study	Main target	Results for *D. caninum*	Results for *T. taeniaeformis*
Yes	Non-interference	*D. caninum*	**99.2%**	**/**
Yes	Dose confirmation	*D. caninum*	**97.7%**	(100%)
Yes	Dose confirmation	*T. taeniaeformis*	(100%)	**100%**
Yes	Dose confirmation	*T. taeniaeformis*	**100%** (genus *Diplopylidium)*	**98.5%**
Yes	Dose confirmation	*T. cati*	**98.9%**	(100%)
Yes	Dose confirmation	*A. tubaeforme*	**97.9%**	**/**
Yes	Dose confirmation	*A. braziliense*	(100%)	(100%)

The results of those studies clearly demonstrate efficacy against *D. caninum* and *T. taeniaeformis*.

As regards *Echinococcus multilocularis*, two specific laboratory GCP-studies were conducted. Those trials used groups of 10 cats, experimentally inoculated with protoscolices. An efficacy of 100% is shown in both studies, as is desirable in view of the relating public health concerns.

Heartworms

Preventive efficacy against the clinical disease caused by *Dirofilaria immitis* infestations is demonstrated through three laboratory studies, using an experimental model of infestation with *D. immitis* L3. Those trials are GCP-compliant and involved groups of 13–14 cats. In the three studies, 100% killing efficacy is demonstrated against the L4 stage of *D. immitis*, which occurs between 20 and 40 days after inoculation.

Respiratory and vesical worms

The claims as to the lungworms *Aelurostrongylus abstrusus* and *Capillaria* spp., which are considered in a context of minor use, were deemed not acceptable. The claim for efficacy against *A. abstrusus* is supported by only one non-GLP laboratory study with insufficient results when based on worm counts after necropsy. The second claim for *Capillaria* spp. is supported only by data from the endoparasite field study showing efficacy based on *Capillaria* spp. faecal egg counts. Both these claims were therefore rejected and have been removed from the SPC.

The product was shown to be 100% effective against the vesical worm *Capillaria plica*, in one GCP-compliant dose confirmation study using groups of 8 naturally infested animals. Clinical cases have been reported in domestic cats in EU. It can be expected that efficacy results obtained from this study performed in Albania can be extrapolated to *C. plica* isolates elsewhere in Europe.

Target animal tolerance

Beside the specific tolerance studies (assessed in Part 3), Broadline was applied to 500 cats in 39 laboratory efficacy studies and to 423 cats in the 4 field trials.
The results of the laboratory and field clinical efficacy studies report a favourable tolerance profile of the proposed product in cats. In laboratory conditions, only isolated cases of prostration, scratching, and hair spiking following treatment could be identified. In the field studies, both local and general safety were assessed through the attribution of a score (0 – no event; 1 – mild, acceptable reaction; 2 – poor safety, serious reaction) based on the observations of the investigator and the owner. In 3 of the 4 presented field studies, no adverse event was recorded. In the fourth (EU trial for ectoparasites), 3 local reactions and 9 systemic reactions were recorded. Among the local effects two received a score of 2 but required no veterinary care. Among the systemic reactions (prostration, hypersalivation, tongue movement in reaction to grooming, pruritus, vomiting), only one received a score of 2 (fever); the relatedness to treatment was unclear since the cat suffered from an ophthalmic inflammatory condition.

In a supplementary field trial conducted in Japan and provided to support efficacy against ticks, no local or systemic reactions were observed in 33 cats treated with the proposed product.

In conclusion, the product is well tolerated in the target species, as shown by well-conducted specific tolerance studies in the target species, laboratory efficacy studies and field trials.

All recorded effects are adequately reflected in the SPC.

Field trials

A total of four field trials were conducted, three targeting ectoparasites (among which two were conducted in Japan) and one targeting endoparasites.

Ectoparasites

For ectoparasites (fleas and ticks), one pivotal EU trial is presented. One field trial from Japan involving fleas and a second field trial in Japan involving ticks were also provided.

The pivotal, GCP EU trial was conducted in 18 veterinary clinics located in France, Hungary, Italy and Sweden. A total of 178 cats were treated with Broadline and 98 with the selected comparator, i.e., Frontline Combo (fipronil and (S)-methoprene). The recruited cats were 2 months to 16 years old. Both genders and spaying/castration status were adequately represented, and 48 long-haired cats were included. In the Broadline-treated group, 13.5% of the enrolled cats were diagnosed with mixed tick and flea infestations, 55.0% with fleas only and 31.5% with ticks only. The corresponding figures in the comparator group were 3.1, 67.3 and 29.6%, respectively. Efficacy and safety were assessed at visits on Day 14, Day 21 and Day 30; efficacy was assessed through parasite counting and identification, and the per cent efficacy was calculated at all time-points in comparison to baseline values (day 0).

Safety results of the above study are presented under *Target species tolerance.* Efficacy of 86.0–87.2% was shown against adult fleas for Broadline throughout the 30 days follow-up period, which is better than the results obtained for the comparator (75.5–81.9%). Statistical non-inferiority was shown, with a non-inferiority margin of 1.5 for the ratio flea count for test product/flea count for comparator product. When it comes to ticks, the results for Broadline (85.3–92.9%) are lower than those for the comparator (91.8–97.6%), and are under the 90% threshold at the last time point (Day 30, 85.3%) whereas this is not the case for the comparator; no non inferiority analysis was carried out.

The flea trial in Japan was conducted in accordance with GCP and was multicentre. It involved a total of 125 cats, treated either with the proposed product (82 cats) or with the comparator (selamectin containing product authorised in the EU). The results show efficacy of 98.8% at Day 2 and Day 30, which is equivalent to the comparator product.

The tick trial in Japan was also conducted in accordance with GCP and was also multicentre. It involved a total of 74 cats; the comparator is an equivalent of Frontline Combo. Efficacy at Day 30 of the candidate product was 94.1%, versus 90.8% for the comparator.

In view of the above results, and of the results of the laboratory studies, it can be considered that a one month efficacy duration is supported for fleas, and a 3 weeks duration for ticks.

Endoparasites

One GCP EU field trial was carried out for endoparasites, in 8 sites located in 7 European countries. A total of 130 cats were treated with Broadline and 66 with the selected comparator, i.e., emodepside and praziquantel containing product. The recruited cats were 2 months to 13 years old. Both genders and spaying/castration status were adequately represented. Infestations by *T. cati*, hookworms, taeniids, *Dypilidium* spp. and *Capillaria* spp were diagnosed. In the Broadline treated group, five cats were diagnosed with mixed cestode/hookworm infections and 18 cats were diagnosed with mixed cestode/ascarid infections. In the comparator group, five cats were diagnosed with mixed cestode/hookworm infections and 11 cats were diagnosed with mixed cestode/ascarid infections.

Efficacy and safety were assessed at Day 14; efficacy was assessed trough the faecal egg count and parasite identification, and the per cent efficacy was calculated in comparison with baseline (Day 0) results. The results show near to 100% efficacy for both the candidate product and the comparator against *T. cati*, hookworms, taeniids and *D. caninum*, although the non-inferiority analysis was not powerful enough to be conclusive in the case of *D. caninum.* A claim against *C. aerophila* was also proposed on the basis from this study, but was not accepted taking also into account the lack of data from laboratory studies.

It was noted that field data as to *D. immitis* and *E. multilocularis* are not required as per the current guidance (VICH GL 20).

Other studies

No other studies are provided.

It is noted that the possible impact of rainfall (and possible bathing) was not addressed in this application. This is however considered not necessary taking into account that this was done for the Frontline (fipronil) and Frontline Combo products (fipronil and (S)-methoprene) and that efficacy of eprinomectin and praziquantel is not expected to be persistent and not directly related to levels in the hair coat.

A warning reflecting the lack of data concerning impact of bathing is included in the SPC.

Overall conclusion on efficacy

Each of the four substances in this fixed combination product broadens the activity spectrum of the product to specific groups of parasites, which are considered to be of medical importance and possibly present in cats as concurrent infestations or high risk of infestation. While fipronil and (S)-methoprene target ectoparasites, primarily fleas and their immature forms, eprinomectin is effective against gastro-intestinal nematodes and heartworm larvae, and praziquantel against tapeworms. The proposed combination, under the conditions of use as recommended in the SPC, was adequately justified as per the provisions of the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

In a European epidemiological multicentre, multinational survey 0.69% of the study population was diagnosed as carrying all three target types of parasites (ectoparasites, nematodes and cestodes). This was considered as the lower limit for the actual target population, which comprises in addition the animals deemed as likely infested or at risk of infestation. Regional differences are likely however at present unknown in the veterinary field. The product is exclusively indicated where all those three groups are targeted specifically at the same time. On the basis of data, it is expected that the target population for the product will be limited.

The minimum recommended doses of the active substances were sufficiently justified by appropriately designed and well conducted studies: fipronil 10 mg/kg, (S)-methoprene 12 mg/kg, praziquantel 10 mg/kg and eprinomectin 0.5 mg/kg.

After topical application the active substances are distributed from the site of application (between the head and shoulder blades) across the body of the animal.

The pharmacokinetic characteristics of the substances when given as the fixed combination have been well investigated. Studies showed that the peak plasma concentrations of the absorbed fraction of fipronil and (S)-methoprene, were reached in 8 to 9 h. Fipronil is mainly excreted in the faeces as unchanged drug. (S)-Methoprene, once absorbed, is very quickly metabolized and excreted. Eprinomectin and praziquantel are absorbed and act systemically, with plasma concentrations reaching a maximum within 48 h and 6 h after treatment, respectively, reaching mean maximal concentrations (C_{max}) of 20.1 ng/ml for eprinomectin and 157 ng/ml for praziquantel.

The average bioavailability after minimum recommended doses is 38% for fipronil, 16% for (S)-methoprene, 45% for praziquantel and 31% for eprinomectin.

Once absorbed, eprinomectin is highly bound to plasma proteins (> 99%), has low clearance from blood, and distributes well into tissues. Its metabolism is limited, and it is mainly excreted unchanged in the faeces. The average half-life for this compound is 4.75 days. Praziquantel has moderate tissue distribution, and about 64–84% of praziquantel is bound to plasma proteins. Praziquantel undergoes hepatic metabolism followed by renal excretion. The average half-life for praziquantel is 3.08 days.

In vitro metabolism assays and *in vivo* studies have demonstrated that there are no pharmacodynamic or pharmacokinetic interactions between fipronil, (S)-methoprene, eprinomectin and praziquantel.

The product is well tolerated in the target species, as shown by well-conducted specific tolerance studies in the target species, laboratory efficacy studies and field trials. Temporary clumping or spiking of the hair may be seen at the application site after treatment. Reported adverse reactions include mild and transient skin reactions at the application site (itching, hair loss), excessive salivation, vomiting and/or in transient neurological signs such as ataxia, disorientation, apathy and pupil dilation. In the studies, all reactions were transient and resolved within 24 h and some are considered related to oral ingestion of the product after topical application, e.g. as a result of grooming.

Development of resistance is of concern in general. Reduction of the frequency of treatment is the most important factor in diminishing selection pressure for resistance. In order to delay development of resistance, the use of antiparasitic drugs should in general be strategical and focused on best possible efficacy with as limited exposure as feasible.

Efficacy of Broadline against fleas and immature flea stages was adequately demonstrated through well-conducted laboratory and field studies, for a period of one month.

Efficacy against ticks was demonstrated in well-conducted laboratory studies and field trials, substantiating three-week duration of efficacy.

Efficacy against lice was deemed unacceptable due to the absence of product-specific data and therefore the proposed indication was rejected.

The product also largely demonstrated its effectiveness against ascarids and hookworms (including larval stages) and cestodes, including a 100% efficacy against *E. multilocularis*.

Adequate prevention of the clinical disease possibly caused by *D. immitis*, through killing of the L4 stage, was demonstrated.

Efficacy against lungworms (*A. abstrusus* and *C. aerophila*) was insufficiently substantiated and therefore the proposed indication was rejected.

Efficacy against vesical worms (*C. plica*) is acceptable.

Part 5 – Benefit-risk assessment

Introduction

Broadline is a new fixed combination product and contains four active substances: fipronil, (S)-methoprene, praziquantel and eprinomectin. The active substances are well-known, however eprinomectin is new in this target species (cat).

The dossier is a stand-alone application as per Article 13b (new fixed combination) of the Directive 2001/82/EC as amended.

Benefit assessment

Direct therapeutic benefit

Broadline is intended for use in the cat from 7 weeks of age and the fixed combination of fipronil, (S)-methoprene, praziquantel and eprinomectin has been duly justified.

The product is to be administered as a spot-on formulation and doses of the individual substances have been justified for the fixed combination.

Well-conducted laboratory efficacy trials and clinical studies showed that the product is efficacious for mixed infestations by ectoparasites, nematodes and cestodes.

Efficacy against fleas (*C. felis*) and immature flea stages for a period of one month has been demonstrated.

Efficacy against ticks (*I. ricinus*) for a period of 3 weeks has been demonstrated.

Efficacy was shown against L3, L4 larvae and adults of *T. cati*, L4 larvae and adults of *A. tubaeforme*, and adult forms of *T. leonina* and *A. braziliense* (including larval stages).

Efficacy against cestodes (*D. caninum, T. taeniaeformis, E. multilocularis*), including a 100% efficacy against *E. multilocularis*.

Adequate prevention of the clinical disease possibly caused by *D. immitis*, through killing of the L4 stage, was demonstrated.

Efficacy against vesical worms (*C. plica*) is acceptable.

The epidemiological and medical relevance of concurrent infestations (or risk of) involving the three target parasite groups, was demonstrated through epidemiological data from the literature and through an own European multicentre survey. The product would benefit to a well-defined target cat population, also protecting indirectly the in-contact animals and humans.

Additional benefits

Broadline is easy to apply by the owner and allows treating or preventing concomitantly a series of infestations that may be encountered together in cats, which increases both the compliance to treatment and the safety of the treatment. The product can be used as part of a treatment strategy for the control of FAD. Prevention of environmental flea contamination can be achieved by inhibiting the development of flea immature stages (eggs, larvae and pupae) for over a month.

Risk assessment

For the target animal

Preclinical and clinical data show that the product was well tolerated in the target species from the age of 7 weeks. All the reported adverse reactions (mild and transient skin reactions at the application site (itching, hair loss), excessive salivation, vomiting and neurological signs such as ataxia, disorientation, apathy and pupil dilation) resolve spontaneously within 24 hours.

Overdoses may also cause the above adverse reactions.

For the user

The user risk assessment is considered acceptable and adequate risk management measures are introduced through SPC warnings and the packaging design.

For the environment

Broadline is not expected to pose a risk for the environment when used according to the SPC. Standard advice for the disposal of any unused product or waste material is included in the product literature.

For the consumer

Not applicable.

Resistance

Development of resistance is of concern in general. Reduction of the possibility of misuse or unnecessary use is the most important factor in diminishing selection pressure for resistance.

Other

The possible risk to co-housed ivermectin-sensitive dogs was addressed in a specific study and a precautionary warning has been included in the SPC.

Risk management or mitigation measures

Appropriate warnings have been included in the SPC to inform on the potential risks to the target animals and the user and the environment and to provide advice for reducing these risks.

As a general principle, limited exposure is expected to prevent or delay development of resistance. A general warning about the risk of resistance emergence is also included in section 4.4 of the SPC.

In addition to standard warnings, the risk to the user is mitigated by the packaging design, by a warning advising to keep out of reach of children, and by warnings limiting the contacts with recently treated animals.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. The product has been shown to be efficacious for the indication for cats with existing, or at risk from, mixed parasitic infections with ectoparasites, gastro-intestinal nematodes or heartworms, and cestodes.

The formulation and manufacture of Broadline is well described and specifications set will ensure that product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings has been included in the SPC.

The product is exclusively indicated for a target population of cats suffering from mixed infestations of ectoparasites, nematodes and cestodes and including cats deemed as likely infested or at risk of such mixed infestation. This population is expected to be limited and the prevalence of the mixed infestations is estimated as low. Regional differences are likely however unknown at present in the veterinary field.

Conclusion

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete SPC and product literature.

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Broadline are considered to be in accordance with the requirements of Directive 2001/82/EC.