EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2013
EMA/18748/2014
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Bravecto (EMEA/V/C/002526/0000)

International non-proprietary name: Fluralaner

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Introduction

The applicant Intervet International BV submitted on 20 November 2012 an application for a marketing authorisation to the European Medicines Agency for Bravecto, through the centralised procedure falling within the Article 3(2)a of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 7 April 2011 as Bravecto contains a new active substance which was not authorised as a veterinary medicinal product in the Community on the date of entry into force of the Regulation. The rapporteur appointed was P. Hekman (replacing G. J. Schefferlie) and co-rapporteur R. Breathnach.

On 12 December 2013, the CVMP adopted a positive opinion, recommending the granting of a marketing authorisation for the veterinary medicinal product Bravecto chewable tablets for dogs (112.5 mg, 250 mg, 500 mg, 1,000 mg and 1,400 mg).

The active substance of Bravecto is fluralaner, a new ectoparasiticide belonging to the isoxazoline group, which is systemically active against ticks and fleas. The benefits of Bravecto are its efficacy in the treatment of flea and tick infestations on dogs. The most common side effects are mild and transient gastrointestinal effects.

The recommended indication is:

"For the treatment of tick and flea infestations on dogs. This veterinary medicinal product is a systemic insecticide and acaricide that provides:
- immediate and persistent flea (*Ctenocephalides felis*) killing activity for 12 weeks, and
- immediate and persistent tick killing activity for 12 weeks (*Ixodes ricinus, Dermacentor reticulatus* and *Dermacentor variabilis);*
- immediate and persistent tick killing activity for 8 weeks (*Rhipicephalus sanguineus*).

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The onset of effect is within 8 hours of attachment for fleas (*C. felis*) and 12 hours of attachment for ticks (*I. ricinus*).

The product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD)."

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

On 11 February 2014, the European Commission adopted a Commission Decision for this application.

Scientific advice

The applicant did not seek scientific advice at the CVMP.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the system of pharmacovigilance, which fulfils the requirements of Directive 2001/82/EC. 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 Community or in a third country.

On 2–3 April 2012, an inspection on the pharmacovigilance system was conducted at Intervet International BV at Boxmeer. The outcome of the inspection on the system was satisfactory.

Manufacturing authorisations and inspection status

The active substance (fluralaner) is manufactured outside the EEA.

The manufacturer of the finished product and batch release are located at Intervet GesmbH in Vienna, Austria.

All relevant sites have valid manufacturing authorisations or valid GMP certificates as appropriate. Hence, no GMP inspections were deemed necessary within the scope of this application procedure.

A satisfactory declaration from the qualified person at the finished product manufacturing site has been provided confirming that the active substance is manufactured in accordance with GMP. The declaration is made on the basis of regular audits by MSD Animal Health.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are considered to be in line with legal requirements.

Part 2 - Quality

Composition

Bravecto chewable tablets for dogs are macrogol-based chewable tablets containing fluralaner, a new ectoparasiticide active substance, in five strengths containing 112.5 mg, 250 mg, 500 mg, 1,000 mg or 1,400 mg fluralaner, suitable for administration to dogs with body weight ranges between 2 kg and 56 kg. The chewable tablets are light brown to dark brown, with a smooth or slightly rough surface, and a practically round shape. Some marbling or specks (or both) may be visible.

In addition to the active substance, the tablets contain the excipients sucrose, maize starch, sodium lauryl sulphate, magnesium stearate, aspartame, glycerol, soya bean oil (refined), macrogol 3350, a known pig liver commercial flavouring and a novel excipient, disodium pamoate monohydrate (INN name: disodium embonate monohydrate).

Container

The tablets are packed in cold-formed, multi polyvinylchloride (PVC)/oriented polyamide (OPA)/aluminium blisters sealed with a paper-backed (aluminium) foil peel open lidding. This is considered suitable packaging for these chewable tablets.

The secondary packaging is a cardboard outer carton. Pack sizes of 1, 2 or 4 tablets are available and justified by the posology.

Development pharmaceutics

The development of the product has been described, the choice of excipients is justified and their functions are explained.

The active substance is micronized and the specification for particle size is based on the active substance particle size specification of the clinical batches. The flavour is already used in an EU authorised veterinary medicinal product. Disodium pamoate monohydrate (INN name: disodium embonate monohydrate) is a novel excipient, although pamoate, the anion of pamoic acid, is a well-known component of veterinary active substance esters, also used for dogs, e.g. pyrantel pamoate (embonate). The lack of pharmacological activity of this excipient has been substantiated. The remaining components of the formulation are commonly used in oral dosage forms.

The pivotal clinical studies have been performed with the proposed commercial formulation.

Method of manufacture

The manufacturing process is well described. In view of the applicant's experience of manufacturing macrogol based chewable tablets via this process, the process can be considered to be a standard process for this manufacturer. Extensive process validation on pilot-scale batches indicates that the manufacturing process yields a robust and reproducible product. Commercial manufacture will be performed using a slightly different tablet forming machine. The process on this machine has been validated by the production of five sub-batches (one for each tablet size), from one large-scale bulk batch. As the manufacture of the bulk batch has not changed, this is considered sufficient and post-approval process validation of commercial scale batches is acceptable. Comparative dissolution profiles of the tablets manufactured on the old and new forming machines have been provided.

Control of starting materials

Active substance

The active substance fluralaner is a new chemical entity. It is a white to pale yellow solid. The substance exhibits polymorphism but only one polymorphic form is obtained with the described manufacturing process.

An ASMF has been provided including details of manufacture and control of the active substance. Adequate characterisation data have been provided for the starting materials. The synthetic pathway and its control are adequately described and the proposed specification for the active substance is acceptable. The active substance provided by the supplier is micronised before it is used in the manufacture of the finished product.

Batch analytical data demonstrating compliance with the proposed active substance specification have been provided for three production scale batches of fluralaner (non-micronised), tested both by the supplier and by the finished product manufacturer, and for three batches of micronised fluralaner tested by the drug product manufacturer.

Stability results have been provided for micronised fluralaner at long-term conditions (25 °C /60% RH) for 12 months, intermediate conditions (30 °C/65% RH) for 12 months and accelerated conditions (40 °C/75% RH) for 6 months. The proposed re-test period of 24 months when stored at not more than 30 °C is acceptable. This re-test period will be calculated from the manufacturing date of the non-micronised fluralaner.

Excipients

A description of the synthesis and control of the disodium pamoate (embonate) monohydrate has been provided.

The flavour is a hydrolysed pork liver extract already used in veterinary medicinal products authorised in EU so it is not considered as a novel excipient. It is gamma-irradiated before use to ensure an acceptable microbiological quality.

The control of the other excipients is according to the European Pharmacopoeia (Ph. Eur.), and is appropriate.

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

None of the starting materials used for production of the active substance fluralaner, or for 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

Not applicable.

Control tests on the finished product

The proposed finished product specification includes tests for appearance, identity, assay, related substances, uniformity of dosage units, water content, microbial quality, dissolution and texture analysis (hardness peak force). The tests and limits on the specification are acceptable and in line with current guidelines. The analytical methods have been described in sufficient detail and have been appropriately validated.

Certificates of analysis have been provided for pilot-scale batches of each tablet strength used in the clinical studies and stability studies. Certificates of analysis have also been provided for pilot-scale batches and a single large-scale batch manufactured at the proposed commercial site. All results comply with the specifications.

Stability

Stability data are provided for pilot-scale batches at long-term conditions (25 °C /60% RH) for 18 months, intermediate conditions (30 °C/65% RH) for 18 months and accelerated conditions (40 °C/75% RH) for 12 months. The use of slightly different packaging in these stability studies is considered acceptable as the commercial packaging is more robust and provides a better barrier to the atmosphere. A bracketing approach has been used in the stability studies and has been justified. The parameters tested are the stability indicating parameters from the specification and are therefore appropriate. A darkening of the tablets from light brown to dark brown was observed at accelerated conditions, even after only three months. This darkening has been explained (due to the flavour) and is addressed by the description of the appearance in the product specifications and in the summary of product characteristics (SPC) and package leaflet. There is limited dissolution data available for the pilot-scale batches and limited data available for the batches manufactured with the alternate forming

equipment but a trend of decreasing dissolution is seen over the course of the stability studies. Therefore a shelf life specification of Q = 45% is considered justified. The applicant has committed to put the full scale validation batches on stability and monitor them for dissolution, using the proposed, initial specifications of Q = 65% (release) and Q = 45% (shelf life). The data will be reviewed and if appropriate an application for revision of the dissolution specification will be submitted when sufficient data is available. The proposed shelf life limits for related substances are wider than those at release. The limits have been accepted based on the limited batch and stability data available to date. However, a commitment has been made to re-evaluate the limits for related substances when additional data becomes available. If no degradation is observed over the course of the shelf life, the shelf life limits should be amended by way of variation. Other trends have not been observed. The proposed shelf life of 2 years with no specific storage conditions is acceptable.

Overall conclusions on quality

The dossier provides a suitable description of the active substance and the chosen formulation, and demonstrates that production of the active substance and the product leads to a stable product with consistent quality. In view of the fact that satisfactory process validation data from pilot scale batches has been provided and that the manufacturer has extensive experience with the production of this type of pharmaceutical form on site, full scale process validation may be performed post-approval.

In general, the active substance and finished product specifications are appropriate and analytical methods are well described and satisfactorily validated.

Stability studies on the finished product have been performed according to VICH guidelines and support the shelf life of 2 years with no specific storage conditions.

Recommendations for future quality development

In the context of the obligation of a marketing authorisation holder to take account of technical and scientific progress the CVMP recommends the following points for investigations:

- The applicant should check the appropriate mixing time or range during technology transfer and process validation and specify the validated time/range in the validation report.
- The applicant should check and confirm the intermediate packaging conditions for the extra small, small and medium chewable tablet sizes.
- The applicant should re-evaluate the specifications of related substances when additional data are available. If no degradation is observed over the course of the shelf life, the shelf life limits should be amended by way of variation.
- The applicant should re-evaluate the dissolution shelf life specification and submit an application for its revision, should the data warrant it, when sufficient finished product stability data is available.

Part 3 – Safety

Pharmacodynamics

The active substance of Bravecto, fluralaner, is an acaricide and insecticide belonging to the isoxazoline group. Isoxazolines act at the central nervous system or the neuromuscular junction of the insect, rather than directly on muscles fibres. Isoxazolines are potent inhibitors of the neurotransmitter gamma-aminobutyric acid (GABA) receptor and glutamate receptor function and work by blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarines.

The binding affinity of fluralaner to receptors of ligand-gated chloride channels was reported significantly lower in mammals than in arthropods. This was confirmed by a study investigating the *in vitro* on-target activities of fluralaner on GABA-receptors of different species (ticks, fleas, flies and rats) compared to standard GABA-receptor antagonists (fipronil, picrotoxin and dieldrin). The studies demonstrated high activities on all tested arthropod GABA-receptors, including the dieldrin resistant variants of the GABA-receptors of *C. felis* and *D. melanogaster*. However, no measurable activity was found against the sole subunit combination of the mammalian (rat) GABA-receptor tested.

Studies investigating interaction with other mammalian receptors have not been presented. The applicant argued that there is no evidence from a range of toxicity studies that fluralaner exerts immediate or delayed secondary pharmacodynamic activity in mammals or organs of general concern (neurological, cardiovascular, respiratory, renal or gastrointestinal system) despite high systemic exposure. While the longest repeat dose toxicity study is 90 days (daily administration of fluralaner), the target animal safety (TAS) studies were conducted over several months (in the pivotal TAS study the product was administered on three occasions with an 8-week between treatment interval) with animals continually exposed to fluralaner for approximately 24 weeks. The CVMP accepted this justification.

The ability of fluralaner to kill fleas and ticks is confirmed in a series of efficacy studies (see Part 4). Based on the findings of these studies, it is accepted that:

- Fluralaner is a potent acaricide and insecticide,
- Fluralaner has a prominent feeding activity against ticks and fleas compared to a less potent contact activity (that is, the primary route of exposure is via feeding),
- Juvenile tick stages (larvae, nymphs) are more sensitive to the effect of fluralaner compared to adult ticks (demonstrated *in vitro* for *R. sanguineus*). Note: as adults are considered the least sensitive tick stage (in comparison to juvenile ticks), tick infestations in laboratory efficacy studies were conducted using adult ticks,
- No conventional ovicidal effect (inhibition of larval hatch) was observed for fluralaner: however, very low doses of fluralaner fully inhibited egg laying (i.e. oviposition) and even lower fluralaner concentrations provided a larvicidal effect,
- Fluralaner demonstrated similar potency for both flea species tested, *C. felis* and *C. canis*.

Pharmacokinetics

Pharmacokinetic studies were provided.

After oral administration to dogs, fluralaner appears to be readily absorbed: at doses of 12.5, 25, and 50 mg/kg bodyweight (bw), mean fluralaner C_{max} were reached within 1 day (T_{max}). Increases in exposure by C_{max} and AUC were statistically dose-proportional. Fluralaner plasma concentrations declined over time. Some secondary concentration peaks were detected, that could be explained by enterohepatic re-circulation. After oral and intravenous administration, fluralaner demonstrated a long mean apparent half-life ($t_{½}$=12–15 days) and long mean residence time (MRT=15–20 days). Fluralaner plasma concentrations were quantifiable for up to 3 months after treatment at all three oral doses.

Prandial state has an effect on absorption: systemic exposure increases when fluralaner is administered to fed animals.

Once absorbed, fluralaner is well distributed to tissues. Highest concentrations were found in fat, followed by liver, kidney and muscle. Also, fluralaner was quantifiable in hair and skin. Volume of distribution was found to be moderate (V_z=3 l/kg), and clearance very low (Cl of approx. 0.1 l/kg/h).

No specific pharmacokinetic studies were performed in lean dogs to determine the depletion rate of fluralaner in such animals; however, various dog breeds and mongrels were included in the effectiveness studies. These studies revealed no obvious difference in effectiveness across breeds.

An *in vitro* study of fluralaner plasma protein binding demonstrated that approximately 100% of fluralaner is bound to plasma proteins in cats and dogs. This high level of protein binding of fluralaner was consistent across different plasma concentrations. The risk of displacement of drugs with high protein binding capacities (e.g. non-steroidal anti-inflammatory drugs) after administration of fluralaner was investigated in *in vitro* studies. Incubation of fluralaner in the presence of carprofen or warfarin in dog plasma at maximum expected plasma concentrations did not reduce the protein binding of fluralaner, carprofen or warfarin.

Unchanged parent fluralaner was found primarily in faeces (approx. 90% of the dose), suggesting that this is the main route of elimination. Renal excretion appears to be a minor route of excretion, with less than approximately 0.001% of the dose found in urine as unchanged fluralaner.

Based on the data presented, it is accepted that the pharmacokinetic properties of fluralaner are well-characterized in dogs.

Toxicological studies

Single dose toxicity

An acute oral good laboratory practice (GLP) toxicity study using the active substance was performed in rats in accordance with The Organisation for Economic Co-operation and Development (OECD) guideline 423. All animals survived until the end of the study period. No adverse effects were observed in this study, except for slightly ruffled fur in all animals. An LD_{50} of > 2,000 mg/kg bw could be derived from this study.

An acute dermal toxicity study using the active substance (limit test: 2,000 mg/kg bw) was performed in rats in accordance with OECD guideline 402. No adverse effects were observed in this study, except for some local effects in some of the animals (erythema, scaling and scabs). An LD_{50} of > 2,000 mg/kg bw could be derived from this study.

In conclusion, fluralaner is of low acute oral and dermal toxicity (LD_{50} > 2,000 mg/kg bw; limit dose).

Repeat-dose toxicity

Oral

The potential subchronic systemic effects of fluralaner have been investigated in one 2-week and one 4-week toxicity study, each with daily oral treatments in rats. The doses used in both studies were 0, 30, 60 and 600 mg/kg bw/day.

The main target organ in the repeated dose toxicity studies was the liver. Effects (increased organ weight, hepatocellular fatty change, effects in related blood parameters) were observed mainly in the highest dose group, thus at large overdoses (in regard to both dose and treatment duration) relative to recommended/proposed use in the target species. A no-observed adverse effect level (NOAEL) of 60 mg/kg bw/day was derived based on these studies.

Additionally, two 90-day oral toxicity studies in rat were provided. No effects were seen at doses of 0, 2, 4 and 8 mg/kg bw/day, resulting in a no-observed effect level (NOEL) of 8 mg/kg bw/day. However, in a study administering 0, 20, 40 and 400 mg/kg bw/day the effects on liver were confirmed. In addition, at the dose of 400 mg/kg bw/day effects on thymus and adrenal weight and microscopic changes in lung and thymus were observed. As the effects were mild at lower doses, a NOAEL of 40 mg/kg bw/day could be derived.

In conclusion, taking all oral studies into account, an overall NOAEL of 60 mg/kg bw/day for oral repeated dose toxicity is considered to be acceptable for use in the risk characterization of user safety.

Dermal

The potential subchronic effects of fluralaner have also been investigated in one 2-week and two 4-week dermal (6 hour semi occlusive) toxicity studies in the rat.

In the first of those 4-week studies, fluralaner was administered to 13-week old rats at dermal doses of 0, 100, 200 or 1,000 mg/kg bw/day (5 rats per sex per dose). Treatment related effects were observed at all doses and included: fatty change in the liver, effects on serum liver enzyme, triglyceride, albumin and globulin and moderately increased liver weights. In addition, at all dose levels, spleen weights were increased in males but there were no histopathological findings correlated with this increase.

Due to the changes in liver and spleen weights, a NOEL could not be established. Therefore, a further 4-week study was conducted using the doses 0, 25, 50 or 100 mg fluralaner/kg bw/day (5 rats per sex per dose). At 100 mg/kg bw, microvesicular fatty change, periportal or diffuse, was observed in the liver of three males and three females. However, there was no other indicator of liver injury. No effects were observed at the other doses defining 50 mg/kg bw as the dermal NOEL.

Taking into account the observations in all three dermal toxicity studies (the effects on liver are considered to be mild and comparable to the effects observed in the oral studies) and taking notice of the oral NOAEL (i.e. 60 mg/kg bw/day; and it is not conceivable that the dermal NOAEL will be lower than the oral NOAEL), a NOAEL of 100 mg/kg bw/day seems appropriate to be used in the risk characterization of dermal exposure.

Conclusion on repeat-dose toxicity

The potential systemic effects following subchronic exposure (oral and dermal) have been comprehensively investigated in the rat. The studies conducted meet with requirements (GLP and relevant OECD guidelines). The liver appears to be the most sensitive organ for effects (increased organ weight, hepatocellular fatty change, effects in related blood parameters).

Based on the repeat dose studies presented, a NOAEL of 60 mg/kg bw/day and 100 mg/kg bw/day seem appropriate to be used in the risk characterization of user safety after respectively oral and dermal exposure.

Tolerance in the target animal species

In total, five target animal safety studies were conducted, of which two were reproductive safety studies. All studies were conducted in accordance with GLP, with pivotal studies conducted in accordance with International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL 43.

In the pivotal TAS study, 32 Beagle puppies aged 8–9 weeks were randomly allocated to treatment groups and administered the product at either 0X, 1X, 3X and 5X the proposed oral dose of fluralaner for 3 occasions at 56 days intervals, mimicking the minimum proposed retreatment interval. Based on the findings of this study, fluralaner was well tolerated when administered to Beagle puppies at up to 5X the maximum exposure dose on three occasions. There was no evidence of test article-related alterations in food consumption, body weight, clinical parameters or physical examination variables, or clinical pathology findings.

In the pivotal reproductive study, forty adult Beagle dogs were treated with 0X (10 females, 10 males) and 3X (10 males and 10 females) the proposed dose of fluralaner 3 times at 8 weeks intervals starting 12 weeks (males) and 4 weeks (females) before expected mating. Treatment continued until the females had whelped (males) or the puppies were weaned (females).

No adverse reactions were observed in adult dogs. In addition, there was no evidence of treatment related effects on reproductive function, no effect on the survival of the puppies, and the number of puppies raised to weaning was comparable to controls. Therefore, based on the findings of the reproductive safety studies, the CVMP concludes that the product is safe for use in breeding, pregnant and lactating dogs.

Additional tolerance data are available from a number of dose determination/confirmatory studies, from a tolerance study in Collies with a deficient multidrug-resistance-protein 1 (administered dose was three times the maximum recommended treatment dose), from a United States (US) field study and from a pivotal European field study. In these studies, the product was in general well tolerated, apart from some mild gastrointestinal adverse events. In the European field study diarrhoea, vomiting, inappetance and drooling were recorded in 1.6% of dogs in the days immediately after treatment with fluralaner. Typically, these effects were mild and transient. An appropriate warning has been included in the SPC (section 4.6).

Conclusions

In total, five TAS studies were conducted, of which two were reproductive safety studies. Fluralaner appears to be well tolerated when administered to Beagle puppies at up to 5X the maximum exposure dose on three occasions.

At the recommended dose, Bravecto was in general well tolerated with common mild transient gastrointestinal events (diarrhoea, vomiting, inappetence and drooling). An appropriate warning has been included in the SPC (section 4.6). The product is safe for use in breeding, pregnant and lactating dogs.

Reproductive toxicity

Potential toxic effects of fluralaner on pregnant females and on embryo-foetal development have been investigated in one range finding and one main study in rats. The studies were performed in compliance with relevant safety guidelines and GLP regulations. No effects on embryo-foetal development were observed below maternal toxic levels and effects were consistent between the two studies.

It was concluded from the prenatal development studies that the lowest oral NOEL of fluralaner in pregnant rats was 100 mg/kg bw/day.

Reproduction toxicity studies in laboratory species are not specifically required for veterinary medicinal products intended for use in companion animals only. Reproductive toxicity for the target animal has been further addressed in the target animal safety studies (see above).

Mutagenicity/genotoxicity

The potential mutagenic effects of fluralaner have been investigated in three *in vitro* tests and one *in vivo* test on genotoxicity. The studies were chosen in compliance with the current guideline VICH GL 23 recommending a standard battery of three tests, i.e. a test for gene mutation in bacteria, an *in vitro* test for chromosomal effects in mammalian cells, and an *in vivo* test for chromosomal effects using rodent hematopoietic cells. All studies were performed in compliance with the respective OECD guidelines and GLP regulations.

The results of all four mutagenicity tests were negative (fluralaner was non-mutagenic in the Ames test, non-clastogenic and non-aneugenic in the chromosome aberration test, and did not induce mutations in the mouse lymphoma thymidine kinase locus assay and the *in vivo* micronucleus test). It was concluded that fluralaner does not have mutagenic potential.

Carcinogenicity

Studies on fluralaner for carcinogenic potential were not submitted. This is justified by the negative results in all mutagenicity assays and the absence of pre-neoplastic lesions in repeated dose toxicity studies (tested up to 90 days, i.e. there is no evidence for a carcinogenic potential of fluralaner, at the relevant exposure levels).

Studies of other effects

Dermal irritation

A dermal irritation study using the active substance was performed in rabbits. This study was performed in accordance with OECD guideline 404 and GLP requirements. The test item did not elicit any skin reactions at the application site of any animal at any of the observation time points (all scores 0). Based upon this study, fluralaner is considered to be non-irritating to the skin.

Eye irritation

An eye irritation study using the active substance was performed in rabbits in accordance with OECD guideline 405 and GLP requirements. Slight reddening of both the conjunctiva and the sclera and slight ocular discharge were observed in all three animals at the 1-hour observation. These effects were reversible and were no longer evident 24 hours after treatment and may be due to the mechanical

effect when administering a fine dust. No other effects were observed. Based upon this study, fluralaner is considered to be non-irritating to the eye.

Skin sensitisation

A skin sensitisation test using the active substance was performed in guinea pigs in accordance with OECD guideline 406 and GLP requirements.

During challenge, the skin on the flank of test animals was exposed to 25% fluralaner (highest non-irritant concentration) in aqueous polysorbate 80 (0.1% (v/v)) or vehicle alone during 24 hours under an occlusive dressing.

After challenge, no effects were noted in all control animals. Slight erythema (score 1) was observed in 4 out of 10 fluralaner-exposed test animals at 24 hours after removal of the dressing (i.e. 48 hours after start of challenge), however these effects were no longer evident at 48 hours after removal of dressing (i.e. 72 hours after start of challenge). Moreover, the effects were not observed at 24 or 48 hours after re-challenge (25% fluralaner, same test group, opposite flank), which would have been expected if the effects observed at 24 hours would be the result of sensitising properties of fluralaner. Therefore, the effects observed after the first challenge at 24 hours are considered to be non-specific.

Based upon this study, fluralaner is considered to be non-sensitising.

Conclusions

Fluralaner is not irritating to skin and eyes.

Fluralaner did not display hypersensitivity reactions in the skin sensitisation study, and local skin effects are not expected.

User safety

The applicant has presented a User Safety Assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1.

Hazard characterisation

Systemic toxicity of this product will be determined by its active substance fluralaner as the excipients are of low toxicity and/or present at low concentrations.

Exposure

Anticipated users are pet-owners or professionals (including veterinarians and breeders) administering the product, and children which may accidentally get access to the product.

The most relevant exposure routes are dermal for adults and oral ingestion for children. Adults can become dermally exposed every time they administer the tablets, which is at 12-week intervals according to the treatment schedule. Also eye contact due to hand-to-eye contact and oral contact due to hand-to-mouth contact may occur if personal hygiene measures (i.e. wash hands after administration) are not maintained. Veterinarians and other health care professionals may have more frequent contact with the product than animal owners; however, they are not expected to administer the product daily and non-frequent exposure is also considered relevant for this type of users. Oral exposure by children is likely to be infrequent/one-off. As the chewable tablets should not be broken/split, the possibility for inhalation of dust is considered negligible.

An external (dermal) exposure of 0.30 mg/kg bw is calculated for adults. As dermal toxicity studies are available, the anticipated external dermal exposure level can be used in the risk characterization (there is no need to estimate the internal exposure level).

Potential oral exposure due to hand-to-mouth contact by adults is estimated to be 10% of dermal exposure (that is 0.030 mg/kg bw).

The calculated exposure caused by accidental intake of a large size tablet by a 15 kg child is 93.3 mg/kg bw.

Risk characterisation

Qualitative

Local reactions are not expected, taking into consideration the concentrations of the substances present in the product, the pharmaceutical form (i.e. a tablet), and the anticipated level of exposure. Including advice to maintain personal hygiene during and after use of the product in the product information in order to prevent accidental hand-to-eye or hand-to-mouth contact is however appropriate and will further lower potential exposure.

Quantitative

A NOAEL of 60 mg/kg bw is considered the most relevant NOAEL for oral exposure; a NOAEL of 100 mg/kg bw is considered the most relevant NOAEL for dermal exposure (see repeat dose toxicity studies).

For dermal user exposure (adults) the margin of exposure (MOE) is > 100 (i.e. 333=100/0.3), therefore acceptable.

For oral user exposure (adults) the MOE is > 100 (i.e. 2,000=60/0.030), therefore also acceptable.

For accidental ingestion of a tablet by children a MOE of 0.64 is calculated (i.e. 60/93.3), which is far below the acceptable MOE of 100. However, it is acknowledged that the NOAEL is derived from studies where the substance is administered daily for up to 90 days, while accidental ingestion is considered incidental (i.e. once). Moreover, for this substance it is acknowledged that the adverse effects even at higher dose levels are not considered to be severe or life-threatening. The acute oral toxicity study revealed a NOAEL > 2,000 mg/kg bw. Finally, the tablets are individually packaged in an aluminium foil blister with a paper/foil laminated peelable lid, which will limit the accessibility. Appropriate advice (to keep the tablet in the original packaging until immediately before use) is included in the product information to prevent children from getting direct access to the tablet.

Conclusions

Based on the data presented, the product does not pose an unacceptable risk to the user, which are pet-owners (administering the product) and children (when getting accidentally access to the product), when used in accordance with the SPC.

Environmental risk assessment

A Phase I environmental impact assessment is provided in line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL). According to the Phase I decision tree, no Phase II assessment is required since the product is intended for the treatment of non-food producing animals only, and furthermore, the treatment is given on an individual basis; therefore exposure of the environment to the product is considered insignificant.

The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Pharmacodynamics: Fluralaner is a potent inhibitor of the GABA receptor function with a high binding to arthropod receptors, blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarines. Binding of fluralaner to mammalian GABA receptors is expected to be low.

Pharmacokinetics: Following oral administration, fluralaner is rapidly absorbed, reaching maximum plasma levels within 1 day. Volume of distribution is moderate and plasma clearance very low, with fluralaner plasma concentrations quantifiable for up to 3 months after treatment. The main route of elimination is via faeces.

Single dose toxicity: An oral LD_{50} of > 2,000 mg fluralaner/kg bw in rats could be derived, concluding that fluralaner has a low acute toxic potential.

Repeat dose toxicity: A NOAEL of 60 mg/kg bw/day and 100 mg/kg bw/day can be established after respectively oral and dermal exposure.

Target animal safety: Bravecto was in general well tolerated, with common mild transient gastrointestinal events (diarrhoea, vomiting, inappetence and drooling). The product is safe for use in breeding, pregnant and lactating dogs.

Reproductive toxicity: No effects on embryo-foetal development were observed below maternal toxic levels. It was concluded from the prenatal development studies that the lowest oral NOEL of fluralaner in pregnant rats was 100 mg/kg bw/day.

Genotoxicity/Mutagenicity: From the battery of *in vitro* and *in vivo* tests on genotoxicity provided it was concluded that fluralaner does not have mutagenic potential.

Carcinogenicity: Studies on carcinogenicity were not conducted. This is justified by the negative results in all mutagenicity assays and the absence of pre-neoplastic lesions in repeated dose toxicity studies.

Studies of other effects: Fluralaner is considered to be non-irritating to the skin and eyes. Fluralaner did not display hypersensitivity reactions in the skin sensitisation study, and local skin effects are not expected.

User safety: Based on the assessment presented, it would appear that the product does not pose an unacceptable risk to the user when used in accordance with the SPC. As result of the user safety assessment the appropriate warnings for the user have been included in the product literature.

Environmental risk assessment: The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

See part 3.

Development of resistance

Fluralaner is a new active substance. Given that the substance has yet to be used in the general animal population, there has been no potential for resistance development among the target tick and flea species listed.

Fluralaner was tested *in vitro* against isolates of *Rhipicephalus microplus*, isolates of the red fowl mite (*Dermanyssus gallinae*), isolates of *Ctenocephalides felis* (*in vivo*), or in isolates of sea-lice (*Lepeophtheirus salmonis*). These isolates were known to have reduced efficacy against either fipronil (phenyl pyrazole), or dieldrin (cyclodiene), or chlorpyrophos (organophosphate), or flumethrin and cypermethrin (pyrethroids), or amitraz (amidine), or fluazuron (benzophenyl urea), or emamectin benzoate (macrocyclic lactones), or propoxur (carbamates). All isolates tested were sensitive towards fluralaner.

Pharmacokinetics

See part 3.

Target animal tolerance

See part 3.

Pre-clinical studies

General study design

All preclinical efficacy studies in dogs were conducted using the same basic study design as detailed in the 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). All parasite isolates used in laboratory studies originated from the field and were multiplied *in vivo* (i.e. on host animals) in the laboratory.

Tick infestations (i.e. *I. ricinus*, *D. reticulatus*, *D. variabilis* and *R. sanguineus*) in laboratory studies were conducted using adult ticks, which were proven to be the least sensitive tick stage, for demonstration of efficacy. For flea infestations, adults were used.

The infestation levels for ticks and fleas were appropriate and in compliance with guideline recommendations. Adequacy of infestations was verified by assessment of the infestation level of control animals and the levels required by the guideline were reached in most studies; minor deviations at single time-points for single dogs were reported and justified.

Beagle dogs were used in most laboratory studies. For pivotal dose determination and dose confirmation studies, the number of dogs used was appropriate and in line with guideline recommendations (i.e. at least 6 dogs). Group allocation was done as recommended by ranking the dogs by descending tick or flea infestation rates within each sex and random allocation to the study groups.

Efficacy assessment

Immediate and (long-term) persistent efficacy for both ticks and fleas was evaluated at 48 hours after treatment and 48 hours after re-infestation every 4 weeks, respectively.

Regarding the approach used by the applicant for efficacy assessment for fleas, this is in accordance with the CVMP guideline (EMEA/CVMP/EWP/005/2000-Rev.2) recommendations and is accepted as appropriate.

However, for ticks, the current guideline only addresses the evaluation of acaricides that are topically applied, and there is no specific guidance for the evaluation of acaricides for systemic use. The applicant therefore proposed an alternative approach to that detailed in the current CVMP guideline, in line with proposals outlined in the recently published the World Association for the Advancement of Veterinary Parasitology (WAAVP) "Guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestations on dogs and cats (Marchiondo et al., 2013)". This approach does not follow the categorisation outlined in the current CVMP guideline. The WAAVP guideline simplifies the categorization of ticks into alive and dead (i.e. does not take into account attachment or engorgement status), with assessment of acaricidal activity based on a comparison of the number of live ticks in untreated control animals compared to those on treated dogs at the same time point.

The CVMP considered this approach and agreed that it could in principle be accepted for orally administered acaricides provided that the SPC and product literature clearly state that the use of the product is for treatment only (not preventive use), that ticks and fleas must attach to the host and commence feeding in order to be exposed to the active substance and, given that parasites need to start feeding on the host to become exposed to fluralaner, the risk of the transmission of parasite-borne diseases cannot be excluded.

Dose selection

In order to select an appropriate dose for clinical investigation, the applicant provided a number of preliminary studies in which efficacy (both immediate and persistent) against fleas and ticks was evaluated over a range of doses (0.3 to 50 mg fluralaner/kg bw) and for two administration routes (oral and topical).

The preliminary studies showed that fluralaner is a potent insecticide/acaricide. Adequate immediate efficacy against fleas and ticks (*R. sanguineus*) was achieved following oral administration of doses as low as 0.3 mg/kg bw.

With increasing dose, the persistence of effect increases: persistent effect against fleas was demonstrated for 6, 12 and 14 weeks following administration of oral doses of 0.3, 1.25 and 5.0 mg fluralaner/kg bw, respectively. For ticks, a similar dose dependant effect was seen, but overall the duration of effect against ticks is less than that seen against fleas.

Based on the findings of the preliminary studies, 12 weeks persistent effect against ticks (longer against fleas) was achievable at an oral dose of 20 mg fluralaner/kg bw. However, the applicant noted that the duration of effect may be influenced by factors such as different dog breeds, different parasite species and isolates originating from different areas. In order to overcome potential variability in efficacy from these factors, a slightly higher dose of 25 mg/kg bw was selected as the recommended treatment dose for confirmatory tests.

In addition to the studies to investigate efficacy of fluralaner following oral administration, the applicant also provided two dose determination (DD) studies investigating efficacy of fluralaner when administered topically as a spot-on formulation: one GLP compliant study in *I. ricinus* and *C. felis* and one GCP-compliant study in *R. sanguineus* and *C. felis* using different dose rates of fluralaner (i.e. 10, 25, 40 mg fluralaner/kg bw). From the results of these studies, 25 mg fluralaner/kg bw was selected

as the clinical dose, as this dose provided sufficient immediate (therapeutic) efficacy and persistent efficacy for 12 weeks (i.e. the intended dosing interval) for ticks and fleas.

It was agreed that fluralaner is a potent insecticide/acaricide with a long duration of action; and persistence of effect appears to increase with increasing dose. The CVMP considered that while the approach to dose selection was not particularly robust (dose determination studies performed using a different formulation and a different route of administration), the selection of 25 mg/kg bw as the minimum recommended treatment dose could be accepted to take forward to the dose confirmation studies.

Dose confirmation

Fleas:

Three good quality dose confirmation (DC) studies were provided investigating the efficacy of a single oral dose of 25 mg fluralaner/kg bw on fleas (*C. felis)* in a minimum number of 6 dogs per group. Based on the findings of these studies, it is accepted that the test product when administered orally at the minimum recommended treatment dose of 25 mg fluralaner/kg is effective against fleas (effect exceeds the efficacy threshold of 95%) and that this effect persists in excess of 12 weeks.

Ticks:

Dermacentor spp.

The results from three dose confirmation studies were presented (one relating to *D. reticulatus* and two relating to *D. variabilis*). For all three studies, efficacy exceeds the threshold of 90% at all-time points up to and including 86 days (12 weeks). While only one dose confirmation study is available for *D. reticulatus*, CVMP accepts a claim for this tick species given that: 1) in the dose confirmation study conducted, 100% efficacy was achieved at all-time points; and 2) adequate efficacy against this tick species was demonstrated up to Day 84 post treatment in the European field study.

Rhipicephalus sanguineus

For *R. sanguineus* a total of five dose confirmation studies were presented. All five studies confirmed efficacy against *R. sanguineus* for up to eight weeks; however, in four of the five studies, efficacy at Day 86 was less than 90%. Taking all available data, a consistent effect at 86 days post-treatment was not apparent. Consequently, for this tick species, a claim for persistent efficacy is limited to 56 days (8 weeks).

Ixodes spp.

Efficacy of the product proposed for marketing against three different *Ixodes* species was evaluated at five different study sites (two dose confirmation studies with *I. ricinus*, two with *I. scapularis* and one with *I. holocyclus*). Efficacy greater than 90% for up to 86 days was achieved in four of the five studies. In one study (*I. scapularis*), efficacy based on arithmetic mean counts was 85.5% at Day 86. In conclusion, based on the data available for *Ixodes* spp., CVMP accepts an immediate treatment claim for *I. ricinus* with a persistent effect for 84 days (confirmed in two studies).

To conclude based on the available dose confirmation data conducted with the formulation proposed for marketing, CVMP accepts the following indication:

- immediate and persistent flea (*Ctenocephalides felis*) killing activity for 12 weeks, and

- immediate and persistent tick killing activity for 8 weeks (*Rhipicephalus sanguineus*) or 12 weeks (*Ixodes ricinus*, *Dermacentor reticulatus* and *Dermacentor variabilis)*.

Onset of action (ticks and fleas)

Two laboratory studies were performed in Germany to investigate the onset of action against ticks and fleas (*I. ricinus, C. felis*) at time points less than 48 hours.

In the first study, six dogs per group were assessed for live ticks and fleas at 12 and 24 hours after treatment for immediate efficacy. All collected live parasites were kept under controlled conditions and re-assessed (live/dead) after 24 hours. All assessments were performed in comparison with an untreated control group. Bravecto chewable tablets for dogs killed ticks (*I. ricinus*) and fleas (*C. felis*) within the first 12 hours immediately after treatment and for a duration of 12 weeks following treatment.

The results from the first study suggested that an onset of action less than 12 hours may be achievable. Therefore, a second study was conducted to investigate killing effect at 4 and 8 hours following the oral administration of Bravecto at the recommended dose.

Based on the findings of these studies, efficacy rates above 95% against fleas and above 90% for ticks were consistently achieved for the 12 week study period within 8 hours (fleas) and 12 hours (ticks) after infestation.

Additional studies

In addition to the dose determination studies using a topical formulation, the applicant also provided several dose confirmation studies using a topical formulation at doses of 25 mg fluralaner/kg bw. The studies were conducted at 3 different study sites within the EU (Ireland, Germany) and South Africa, and involved fleas (*C. felis*) and different tick species (*D. reticulatus, R. sanguineus).*

These were good quality GCP studies; however, the CVMP considered that the efficacy profile following administration of the same dose in mg/kg bw by the oral route and the topical route were not comparable, and the studies were therefore not considered in this assessment.

Overall conclusions on dose confirmation

Fluralaner is a potent insecticide and acaricide. Based on the data provided, the CVMP considered that a dose of 25 mg/kg bw was effective.

When administered to dogs at a dose of 25 mg/kg bw, fluralaner demonstrates immediate efficacy against fleas within 8 hours, and this effect persists for at least 12 weeks.

For ticks (*I. ricinus)*, immediate efficacy was shown within 12 hours. Persistent tick killing activity for 12 weeks could be accepted for some tick species (*I. ricinus, D. reticulatus* and *D. variabilis)*. However, for *R. sanguineus* a claim for persistent effect was adequately demonstrated for 8 weeks only.

Field trials

One multinational, multicentre efficacy study for ticks and fleas was conducted in 2012 under European field conditions. In addition, one US field study and one field palatability study were conducted.

Field palatability study

A field study was conducted in 2012 to evaluate the palatability of Bravecto chewable tablets in dogs. The study was conducted in accordance with GCP. The study was designed as a multi-centre, non-

controlled and non-blinded field study in Germany with 144 private-owned dogs of both genders and various breeds and age.

The overall palatability (score 1 (immediate uptake within 5 minutes) and score 2 (delayed uptake within 6 to 20 minutes)) was 91.7% (132 out of 144 animals).

The CVMP concluded that Bravecto chewable tablets are well accepted by most dogs, and that adequate information is provided in the SPC in the event that a tablet is not accepted by a dog.

European field efficacy study

The pivotal field study was conducted to confirm the duration of efficacy of 12 weeks for Bravecto chewable tablets for dogs in dogs naturally infested with ticks and/or fleas under field conditions. The study was a randomized, controlled and blinded multicentre field study performed in accordance with GCP. It was conducted in Germany, France and Spain in 2011/2012.

Dogs were included in the study on the basis of their household. A household was included if at least one dog met a detailed list of inclusion criteria, including a minimum infestation level of 4 ticks and/or 4 fleas at the first visit, and if none of the exclusion criteria were met (e.g. treatment with other ectoparasiticides, bad health status).

Dogs were randomly allocated to either Bravecto chewable tablets for dogs treatment or an authorised spot-on product containing fipronil treatment in a 2:1 ratio. Test product was given once on day 0 (visit 1), resulting in individual doses between 25 and 56 mg fluralaner/kg bw. Dogs were fed within 1 hour before or after administration. Fipronil was given three times 28 days apart, i.e. according to the label instructions.

The study schedule involved 5 visits to veterinary clinics over a period of 84 days. At all visits (day 0 = visit 1, day 14±2 = visit 2, day 28±2 = visit 3, day 56±2 = visit 4 and day 84±2 = visit 5), the veterinary surgeon performed tick and flea counts before treatment and evaluated the presence of clinical signs of flea allergy dermatitis (FAD). A standardized clinical examination of the animal was also conducted on these occasions. Throughout the study, owners were requested to indicate whether any abnormal observation (e.g. marked itching, skin irritation, loss of hair, abnormal general condition) or ticks and/or fleas on the dogs were detected.

Primary efficacy was based upon the percentage reduction of ticks in the initially infested dogs and percentage reduction of fleas in flea infested households.

There were 253 households with 561 dogs included in the study: 383 dogs were treated with Bravecto chewable tablets for dogs, and 178 with the spot-on containing fipronil.

There were 479 dogs (325 test product and 154 fipronil) in 214 households (144 test product and 70 fipronil) eligible for statistical analysis in the per protocol (PP) population, thereof 176 flea households (115 test product and 61 fipronil) and 162 dogs infested with ticks (108 test product and 54 fipronil).

For both live ticks and fleas the parasite counts were significantly higher pre-treatment compared to each follow-up visit ($p<0.0001$). At all follow-up visits, fluralaner was statistically non inferior compared to the fipronil spot-on control product for the percentage of dogs free of ticks, the percentage of households free of ticks and the percentage of households free of fleas.

A total of 1,237 ticks were collected at inclusion; the most frequent tick species found was *R. sanguineus* (n=431, 34.84%). *I. hexagonus* (n=314, 25.38%), *I. ricinus* (n=312, 25.22%) and *D. reticulatus* (n=119, 9.62%) were also found as well as *Ixodes* spp. larvae (n=49, 3.96%) and *Ixodes* spp. nymphs (n=12, 0.97%).

A total of 53 dogs (PP, 53 of 479, 11.1%), thereof 35 fluralaner-treated dogs (35 of 325, 10.8%) and 18 fipronil-treated dogs (18 of 154, 11.7%) had clinical signs of FAD at inclusion. In the fluralaner group, 85.7% (30 of 35) of these dogs were evaluated as clinically cured at the end of the study.

A total of 57 adverse events were reported, 40 within the fluralaner group and 17 in the fipronil group. In particular, there were a number of instances of diarrhoea/vomiting/inappetance recorded in the days immediately after treatment with fluralaner. Typically, these effects were mild and transient. However, similar observations were not made in the positive control group. These adverse reactions are included in the SPC and product literature.

Based on the findings of this study, it was concluded that Bravecto chewable tablets for dogs were efficacious for 12 weeks against ticks (*I. ricinus, I. hexagonus, D. reticulatus* and *R. sanguineus*) and fleas (*Ctenocephalide*s spp.) on naturally infested dogs. The product was well tolerated with only mild and transient gastrointestinal adverse reactions, and the percentage of parasite free cases was significantly non-inferior compared to the authorised control product, a spot-on for dog containing fipronil.

US field study

The applicant conducted a field trial in the US with repeated administration of Bravecto chewable tablets for dogs. The primary purpose of the US field study when presented in this dossier is to support the safety of repeated administrations of the product under field conditions.

This study included 224 dogs treated with Bravecto chewable tablets for dogs according to the proposed SPC, i.e. dogs received one tablet of the respective weight band, or a combination of tablets in case the dog was greater than the biggest tablet size available, immediately prior to feeding. Dogs were administered Bravecto chewable tablets for dogs three times at intervals of 12 weeks.

The Bravecto treated group included dogs of various breeds, sizes, ages and gender. The most commonly represented breeds in this group were mixed breeds (small, medium and large size), Chihuahua, Jack Russell and Labrador Retriever. Body weights of Bravecto treated dogs ranged from 2 to 69 kg (mean 16.6±13 kg). All available tablet sizes, including combinations of tablet sizes to cover dogs greater than 56 kg, were used in this field trial. The age range of Bravecto treated dogs was 0.2 to 15.0 years (mean 5.1±3.65 years) and the Bravecto group included intact females, spayed females, intact males and neutered males. Physical examinations were performed on all dogs at regular intervals, clinical pathology samples were taken at three time points and adverse events were recorded throughout the study as investigators became aware of them.

Physical examinations showed a similar frequency of normal results for the Bravecto treated and the control item-treated group. The incidence of abnormal results did not increase with the number treatments. There were no clinically significant trends in clinical pathology variables. There were no serious adverse events related to Bravecto treatment. Within the adverse events that were considered to have "probable" or "possible" association with Bravecto treatment the most frequently reported one was vomiting. Other adverse events recorded included anorexia and diarrhoea. The frequency of these observations, as well as the frequency of adverse events in general, did not increase with repeated Bravecto treatment.

Overall conclusion on efficacy

Based on the data presented, it is evident that fluralaner is a potent insecticide and acaricide.

Fluralaner is well tolerated.

A field study was conducted to evaluate the palatability of 'Bravecto chewable tablets' in dogs, confirming that the chewable tablets are well accepted by most dogs.

When administered to dogs at a dose of 25 mg/kg bw, fluralaner demonstrates immediate efficacy against fleas within 8 hours, and this effect persists for at least 12 weeks. Consequently, the product can be recommended to be used as part of the treatment strategy against FAD.

For ticks (*I. ricinus)*, immediate efficacy was shown within 12 hours. Persistent tick killing activity for 12 weeks could be accepted for some tick species (*I. ricinus, D. reticulatus* and *D. variabilis)*. For *R. sanguineus* a claim for persistent effect was adequately demonstrated for 8 weeks.

Based on available field data, Bravecto chewable tablets for dogs were efficacious against ticks (*I. ricinus, I. hexagonus, D. reticulatus* and *R. sanguineus*) and fleas (*Ctenocephalide*s spp.) on naturally infested dogs. The percentage of parasite free cases was significantly non-inferior compared to the authorised control spot-on product containing fipronil. Bravecto was well tolerated, with only mild and transient gastrointestinal adverse reactions (vomiting, diarrhoea, inappetence and drooling) shortly after administration.

Part 5 – Benefit-risk assessment

Introduction

Bravecto chewable tablets contain fluralaner as the active substance and are presented in five strengths (112.5 mg, 250 mg, 500 mg, 1,000 mg and 1,400 mg). The product is indicated for the treatment of tick and flea infestations in dogs. The product is presented in blister packs, within a cardboard carton, containing either 1, 2 or 4 tablets. The route of administration is oral use.

Benefit assessment

Direct therapeutic benefit

Fluralaner is a potent insecticide and acaricide.

When administered to dogs at the recommended dose (25–56 mg/kg bw), there is immediate efficacy against fleas within 8 hours after treatment, and this effect persists for at least 12 weeks.

For ticks (*I. ricinus)*, onset of effect is within 12 hours. Persistent tick killing activity over 12 weeks could also be shown for some tick species (*I. ricinus, D. reticulatus* and *D. variabilis)*. For *R. sanguineus* a claim for persistent effect was demonstrated for 8 weeks.

Additional benefits

Additionally, the effective control of fleas on treated dogs will directly benefit the risk of infestation of other animals in contact with infested dogs.

Bravecto may be administered by the animal owner at home. The presentation is a chewable tablet formulation which has been designed to be palatable for most dogs. The method and route of administration of the product may be considered an additional benefit in that there is limited potential for the user to be exposed to the active substance.

Risk assessment

Although adverse reactions (diarrhoea, vomiting, inappetence and drooling) were commonly seen shortly after treatment (1.6% of dogs), they were mild and transient; and it was concluded that the product is well tolerated when administered to the target species at the recommended treatment dose.

It is not expected that the product will pose an unacceptable risk to the user when used in accordance with SPC recommendations.

It is not expected that the product will pose a risk to the environment when used in accordance with the SPC recommendations.

Risk management or mitigation measures

Warnings and other risk management measures have been included in the SPC to mitigate possible risks to the user, target animal, other animal species and the environment.

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 the treatment of tick and flea infestations on dogs. This veterinary medicinal product is a systemic insecticide and acaricide that provides:

- immediate and persistent flea (*Ctenocephalides felis*) killing activity for 12 weeks, and
- immediate and persistent tick killing activity for 12 weeks (*Ixodes ricinus, Dermacentor reticulatus* and *Dermacentor variabilis);*
- immediate and persistent tick killing activity for 8 weeks (*Rhipicephalus sanguineus*).

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The onset of effect is within 8 hours of attachment for fleas (*C. felis*) and 12 hours of attachment for ticks (*I. ricinus*).
The product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD)."

The formulation and manufacture of Bravecto 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.

Conclusion on benefit-risk balance

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 Bravecto are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit-risk evaluation is deemed positive with sufficiently clear and complete product information.