EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Bravecto for spot-on solution for dogs and cats (EMEA/V/C/002526/X/0005)

International non-proprietary name: fluralaner

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

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Product profile

Invented name:	Bravecto
Active Substances:	fluralaner
Target Species:	Cats and dogs
Pharmaceutical Form:	Spot-on solution
Strength:	112.5 mg, 250 mg, 500 mg, 1000 mg and 1400 mg
Therapeutic Indication:	For the treatment of tick and flea infestations in dogs and cats
ATCvet code	QP53B E02
Pharmacotherapeutic group	Ectoparasiticides for systemic use
Applicant	Intervet International B.V.

Introduction

On 15 October 2014, Intervet International B.V. submitted an application for an extension to the Community marketing authorisation for Bravecto to the European Medicines Agency (the Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2(d) thereof.

Bravecto (active substance fluralaner) was first authorised in the Community on 11 February 2014, and is available as chewable tablets for dogs for the treatment of tick and flea infestations.

This extension application is submitted to add a new pharmaceutical form (spot-on solution) for dogs and to add a new target species (cats) for this spot-on formulation, including 5 strengths for dogs and 3 for cats in pack sizes containing 1 or 2 pipettes.

The spot-on solution is intended for the treatment of tick and flea infestations in dogs and cats.

The rapporteur appointed was J. Schefferlie and co-rapporteur R. Breathnach.

In the light of the overall data submitted and the scientific discussion within the CVMP, a negative opinion for Bravecto spot-on solution for dogs and cats was adopted, by majority, by the CVMP on 9 December 2015.

Re-examination

On 17 December 2015, the applicant submitted written notice to the Agency to request a re-examination of the CVMP opinion of 9 December 2015. The applicant requested the involvement of a specific expert group in the re-examination.

During its meeting of 19–21 January 2016, the CVMP appointed C. Ibrahim as rapporteur and S. Louet as co-rapporteur for the re-examination procedure. The CVMP also agreed to the establishment of a specific Ad Hoc Expert Group (AHEG), its mandate and a re-examination timetable.

On 5 February 2016, the applicant submitted the detailed grounds for the re-examination.

On 6 February 2016, the re-examination procedure started.

On 10 February 2016, the rapporteur's assessment report and co-rapporteur's critique were circulated to all CVMP members.

At their February 2016 meeting the CVMP appointed an AHEG and adopted a list of questions on user safety for the AHEG to address.

The AHEG consisted of experts in user safety and exposure assessment, toxicology, and good laboratory practice (GLP).

On 14 March 2016, the AHEG meeting was convened at EMA to consider the questions and to provide responses to the CVMP. During this meeting the applicant presented an oral explanation. The report from this meeting was forwarded to all CVMP members and the applicant on 14 March 2016.

On 15 March 2016, the applicant appeared before the Committee for an oral explanation.

During their meeting of 15-17 March 2016, in the light of the scientific data available and the scientific discussion within the Committee, the CVMP re-examined its initial assessment concerning the points raised in the grounds for re-examination.

On 17 March 2016, the CVMP adopted a positive opinion and CVMP assessment report.

On 18 May 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for Bravecto.

Initial assessment

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (version 1.0, effective date 1 April 2014) 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.

Manufacturing authorisations and inspection status

Bravecto spot-on solution is manufactured outside the European Economic Area (EEA). Batch release for the European Union (EU) will be carried out by Intervet UK Limited, Buckinghamshire, UK.

All relevant sites have valid manufacturing authorisations or valid Good Manufacturing Practice (GMP) certificates as appropriate, with the exception of the manufacturer of the finished product for which a GMP certificate is not currently available. However, compliance with GMP was confirmed through an inspection performed by the Dutch Competent Authority during the assessment of the extension application. This was considered acceptable by CVMP.

A satisfactory declaration from the qualified person (QP) at the batch release site is provided covering all active substance sites of manufacture. The declaration is issued by the QP at the batch release site on the basis of on-site audits between August and November 2013.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP compliance of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a non-aqueous spot-on solution. The spot-on solution contains 28 g of the known active substance fluralaner per 100 ml of solution (28% w/v) and is indicated for the treatment of tick and flea infestations in dogs and cats. The excipients in the formulation are dimethylacetamide (DMA), glycofurol, diethyltoluamide (DEET) and acetone. Five strengths (112.5 mg, 250 mg, 500 mg, 1000 mg, and 1400 mg) are available for dog bodyweight ranges between 2 kg and 56 kg. Three strengths (112.5 mg, 250 mg and 500 mg) are available for cat bodyweight ranges between 1.2 kg and 12.5 kg. All strengths are made from the identical bulk solution containing 28% w/v of fluralaner. The different strengths are obtained by filling the pipettes as single dose presentations with different volumes of the bulk solution.

Container

The pipettes are made of an aluminium/polypropylene (PP) laminated foil. The cap is made of high-density polyethylene (HDPE). The materials in direct contact with the solution are PP and HDPE. Statements of compliance with EU Regulations on plastic materials intended to come into contact with food and relevant European Pharmacopoeia (Ph. Eur.) monographs have been provided.

The following pipettes diameters were chosen to fill the five strengths:

- 10 mm diameter pipette for the 112.5 mg and the 250 mg strengths; and
- 13.5 mm diameter pipette for the 500 mg, 1000 mg and 1400 mg strengths.

The length of the pipettes is specific for each strength. The secondary packaging is a sachet made of laminated aluminium foil, packaged into a carton box. A tabulated specification including a specific identification test and incorporating the relevant sections of the supplier's documentation has been provided for each pipette size.

Development pharmaceutics

The development of the product has been described, the choice of excipients is justified and their functions are explained. Physico-chemical parameters were defined to select in vitro formulations suitable for administration in vivo. Several studies were performed to address these parameters.

The clinical studies have been performed with batches of the proposed commercial formulation and manufacturing process which were manufactured at the development site in Angers, France. Bridging from the product manufactured and packed at the development site at pilot scale to the commercial site at production scale is acceptable, in view of the dosage form (solution) and the supportive results obtained with the pilot-scale batches, confirmed by batch analytical data from the commercial site.

Method of manufacture

The manufacturing process of the finished product is straightforward and comprises:

- dissolution of fluralaner in the solvents,
- mixing of the solution to ensure homogeneous distribution of all ingredients in the formulation,
- filling of the pipettes, and
- production of a sachet around the filled pipette.

Bravecto spot-on solution for dogs and cats is a simple solution with a straightforward manufacture and filling process and no complex processing or packaging conditions. The manufacturing process is considered standard. In view of this and in view of the data obtained with the manufacture of the three pilot-scale batches, it is acceptable that data of full scale validation at the commercial scale and site will be obtained prior to commercialisation. A satisfactory process validation protocol for commercial scale batches has been submitted.

Control of starting materials

Active substance

The active substance fluralaner is a white to pale yellow powder and contains one chiral centre resulting in the formation of a racemate. Fluralaner is not described in the Ph. Eur. The active substance for the manufacture of Bravecto spot-on solution is from the same supplier as for Bravecto chewable tablets already authorised. The information regarding chemistry, development, manufacture and control of fluralaner was assessed by the competent authorities during the evaluation and authorisation procedure of Bravecto chewable tablets for dogs. The active substance master file (ASMF) procedure according to the CVMP Guideline EMEA/CVMP/134/02-Rev 3/Corr was followed. The currently submitted information is the same as that approved for Bravecto chewable tablets and is considered acceptable for this application. As the active substance is dissolved during the manufacturing process of the spot-on solution, particle size and polymorphic form are not critical for this extension application. The approved re-test period is 24 months, stored not above 30 °C.

Excipients

For dimethylacetamide and acetone reference is made to the Ph. Eur. Diethyltoluamide is not described in the Ph. Eur. Reference is made to the monograph in the US Pharmacopoeia (USP). Additional tests are not required for this application. Glycofurol is a non-compendial material, which is described neither in the Ph. Eur. nor in the USP. The excipient is known and has been approved in some parenteral formulations in the EU. An in-house specification has been provided which takes into consideration its synthesis and the specification from the manufacturer used during the development of the finished product. Scientific information to support this specification has been provided.

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

None of the starting materials used for the active pharmaceutical ingredient fluralaner 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).

TSE declarations from the manufacturers of the active substance and finished product are submitted accordingly and are acceptable.

Control tests on the finished product

The finished product release specification includes tests for appearance (visual), identity (HPLC retention time and UV spectrum), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), density (Ph. Eur.) and microbial quality (Ph. Eur.). The finished product control tests applied are appropriate. The analytical methods are well described, and data of their validation confirm their suitability. Results of batch analysis have been submitted for the three pilot-scale batches of bulk product manufactured at the development site which are used in the clinical studies and stability studies. Results of batch analysis have also been submitted for one production scale batch of bulk product manufactured at the proposed commercial site. All strengths were tested for each of the bulk batches (pilot and production scale). All results comply with the specification and are consistent.

Stability

The shelf-life specification is the same as for release except one identity test being performed at the end of shelf-life (HPLC retention time) compared to two tests for release (HPLC retention time and UV spectrum).

The shelf-life limits for density in the finished product will be re-evaluated once sufficient stability data on full scale production batches are available. This is considered acceptable by CVMP.

Results of 24 months testing at long-term and intermediate conditions and 6 months at accelerated stability conditions with three pilot-scale batches have been provided. All strengths were tested. A bracketing design has been applied to the stability studies under long-term, intermediate and accelerated conditions according to the CVMP Guideline on bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products (EMA/CVMP/VICH/581467/2007). The bracketing design proposed is considered acceptable. All results comply with the shelf-life specification and the only trends observed are very slight increases in single impurities (<0.3%), total impurities (<0.5%) and density. These trends are more pronounced at accelerated conditions than at the long term conditions. A slight decrease in assay at accelerated conditions is also observed. Photostability, freeze-thaw stability, and stability at 60 °C during 2 hours of the product in pipettes without sachet were verified.

The proposed shelf-life of 24 months can be accepted. The formulation is not photosensitive. However, to protect from solvent loss or moisture uptake, the pipettes should be kept in the original container closure system.

Overall conclusions on quality

The dossier provides a suitable description of the chosen formulation, and demonstrates that production leads to a stable product with consistent quality.

The information submitted regarding chemistry, development, manufacture and control of fluralaner is the same as that previously assessed as part of the documentation for the initial marketing authorisation for Bravecto chewable tablets for dogs and is acceptable.

All the excipients used in the formulation are compendial except glycofurol for which an acceptable in-house specification has been provided.

In view of the standard manufacturing process of the finished product and the validation data on pilot scale batches provided, it is acceptable that full scale process validation at the commercial production site would be performed post-approval.

The product is presented in pipettes packed into individual sachets which are then packaged into a carton box. The pipettes are adequately described and materials of construction comply with relevant EU Regulations and Ph. Eur. monographs.

The finished product control tests applied are appropriate. The analytical methods are well described and data of their validation confirm their suitability. Sufficient batch analysis data have been provided of development and clinical batches and batches manufactured at the commercial production site.

Stability studies on the finished product have been performed according to VICH guidelines. The primary stability studies are on-going. The current results support a shelf-life of 2 years, stored in the sachet to protect from solvent loss or moisture uptake.

Based on the review of the data on quality, the manufacture and control of Bravecto spot-on solution are considered acceptable.

Part 3 – Safety

Safety documentation

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

Single and repeat dose toxicity

No new toxicology data were provided. Reference was made to safety data provided and assessed for the initial marketing authorisation. In the initial assessment the CVMP had concluded that fluralaner is of low acute oral or dermal toxicity (LD_{50} >2000 mg/kg bw). A range of oral and dermal repeat dose studies in rats revealed an overall oral NOAEL of 60 mg/kg bw/day and an overall dermal NOAEL of 50 mg/kg bw/day. Long-term studies were not provided.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Reproductive toxicity

A pivotal one-generation study in rats was submitted. The rats were dosed 0, 50, 100, 500 mg/kg bw/day (by gavage). Adverse effects in the parents were consistent with the effects observed in the repeat dose studies (liver, lungs, thymus and adrenals were affected). No parental NOAEL was established due to the findings in liver, adrenals, and lung at the lowest dose tested. The reproduction NOEL was set at 100 mg/kg bw/day based on reduced litter size due to reduced implantation rate and increased post-implantation loss at the higher dose of 500 mg/kg bw/day. Data from pups demonstrated significant adverse effects on thymus (reduced weight accompanied by lymphoid atrophy) at all doses, therefore no NOAEL in pups can be determined.

Developmental toxicity

Rat (oral):

A developmental toxicity study in rats was submitted. This study was already assessed during the initial application of Bravecto chewable tablets for dogs. The CVMP concluded on a NOAEL of 100 mg/kg bw/day for maternal and foetal toxicity.

Rabbit (oral):

From one of the two pivotal oral studies submitted, a LOAEL of 50 mg/kg bw/day was derived for embryo/foetal toxicity, based on skeletal findings including an abnormality and variations. A NOAEL could not be established, therefore a complementary developmental toxicity study using lower doses of 10, 25

and 250 mg/kg bw/day was submitted. From this study, a maternal NOAEL of 10 mg/kg bw/day was established, based on fatty acid changes of the liver and the related reduction in blood chemistry parameters which were observed at the dose of 10 mg/kg bw/day but considered mild. The NOAEL for embryo/foetal toxicity was also set to 10 mg/kg bw/day, based on findings in foetal body weight and urinary tract at 250 mg/kg bw/day as well as skeleton findings at 250 and 25 mg/kg bw/day. This NOAEL of 10 mg/kg bw/day is the lowest NOAEL for developmental toxicity.

Rabbit (dermal):

In the submitted dermal developmental study in rabbits using fluralaner suspended in 0.5% w/v carboxymethylcellulose aqueous solution containing 0.1% (v/v) polysorbate 80, no maternal toxicity was observed up to a dose of 1000 mg/kg bw/day, the highest dose tested in this study. However, it is noted that while liver appeared the most sensitive target organ, with effects on the liver forming the basis for the maternal NOAEL in the rabbit oral study, relevant parameters were not investigated in the dermal study. For embryo/foetal toxicity the NOAEL can be set to 100 mg/kg bw/day, based on adverse effects observed at 1000 mg/kg bw/day including external and visceral abnormalities and skeletal abnormalities.

Mutagenicity/genotoxicity

During the assessment of the initial application for Bravecto chewable tablets the CVMP concluded that the active substance fluralaner does not have genotoxic potential.

Carcinogenicity

During the assessment of the initial application for Bravecto chewable tablets the CVMP concluded that the active substance fluralaner is unlikely to have carcinogenic potential.

Studies of other effects

Skin irritation:

The active substance fluralaner was considered to be non-irritating to the skin by the CVMP during the assessment of the initial application for Bravecto chewable tablets.

A dermal irritation study using the final spot-on formulation in rabbits was submitted. The test item did elicit mild skin reactions (score 1) at the application site in all three animals within the first hour, which were reversible after 24 hours.

In the clinical studies in cats and dogs, mild and transient skin reactions were observed. Adverse skin reactions were observed in 3 humans representing 2.5% of the number of households in the field study in cats following direct contact with the treated animals. These skin reactions were possibly caused by the product. Local effects were observed in the acute dermal toxicity studies submitted with the substance and the formulation. The excipient DEET (present in a concentration of 14%) is classified as skin irritating. The CVMP therefore concluded that the formulation can cause skin irritation.

Eye irritation:

The active substance fluralaner was considered to be non-irritating to the eye by the CVMP during the assessment of the initial application for Bravecto chewable tablets.

An eye irritation study using the final spot-on formulation was performed in rabbits. Slight to moderate eye irritating effects were observed, which were fully reversible within 7 days.

Based on the eye irritation study, on the fact that the excipient DEET present in a concentration of 14% is classified as serious eye irritating and considering that the product may cause skin irritation, the CVMP concluded that the formulation can be irritating to the eyes.

Sensitisation:

The CVMP previously concluded that the active substance fluralaner has no sensitising potential when tested in the guinea pig maximisation test of Magnusson and Kligman.

A skin sensitisation test (guinea pig maximisation test of Magnusson and Kligman) using the final spot-on formulation was performed in guinea pigs. It appears from this study that the final formulation is non-sensitising.

Observations in humans:

Based on the described adverse skin effects in humans after contact with a treated animal (see field study in cats, Rohdich 2014), it appears that exposure to the product (direct exposure or indirect exposure via the treated animal) can cause adverse skin effects.

Studies on excipients:

Annex VI of Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, classifies DMA in category 4 acute toxicity (H332; harmful if inhaled and H312; harmful in contact with skin) and category 1B reproductive toxicity (H360D at concentration >5%, may damage the unborn child).

The dermal NOAEL for the general population was set to 94 mg/kg bw, however, it is noted this was based on a repeat dose study and the observed effects are not considered acute effects. The oral NOAEL was established to 100 mg/kg bw based on repeat dose toxicity. These two NOAELs are similar and suggest that dermal and oral bioavailability will not differ substantially. For developmental toxicity several oral studies (no dermal studies) were presented resulting in NOAELs varying from 65–400 mg/kg bw. It is therefore concluded that DMA may cause damage to the unborn child when exposed to a significant amount and cause systemic effects after prolonged dermal exposure. A risk characterisation for DMA has therefore been provided in the user safety evaluation.

DEET is in general used as a short-term insect repellent and is classified according to Annex VI of the Regulation above in category 1 specific target organ toxicity – single exposure (STOT SE) (H370; causes damage to organs), category 4 acute toxicity (H302; harmful if swallowed), category 2 eye irritation (H319; causes serious eye irritation) and category 2 skin irritation (H315; causes skin irritation).

As indicated above, the CVMP concluded that the formulation with 14% DEET may cause skin and eye irritation. Systemic effects after dermal exposure may occur only after large doses (in the EU assessment report a dermal LD_{50} >5000 mg/kg bw was reported), therefore systemic effects are not expected to occur for the current product taking notice of the packaging volume and its exposure scenarios. However, DEET may cause adverse systemic effects after significant oral exposure. A NOAEL of 75 mg/kg bw/day was reported. This NOAEL was derived from an oral capsule study in dogs terminated on day 5 due to severe (neuro)toxicity. A risk characterisation for DEET (acute oral exposure) has therefore been included in the user safety evaluation.

No adverse effects are expected for excipients glycofurol and acetone.

Based on the physico-chemical properties of the formulation (particularly due to acetone), the product is considered highly flammable. Acetone is described in the Ph. Eur. monograph as a volatile, clear and colourless liquid, and its vapour is flammable. In Annex VI of Regulation (EC) No 1272/2008 acetone is classified in category 2 flammable liquid (H225 – highly flammable liquid and vapour). The formulation has a flash point (lowest temperature at which it can vaporise to form an ignitable mixture in air) of 2 °C

which is considered low and therefore, appropriate warnings related to the flammability of the product have been included in the draft SPC.

User safety

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

Hazard characterisation

Fluralaner and the product have a low acute oral and dermal toxicity (LD_{50} >2000 mg/kg bw; limit dose). No adverse systemic effects were observed in the oral and dermal acute toxicity studies using the active substance or formulation to be authorised. However, these studies are limited in examined parameters.

As indicated above, the excipients DMA and DEET are also of potential concern and so are included in the user safety evaluation. DMA may cause damage to the unborn child following significant oral or dermal exposure and DEET may cause adverse systemic effects after significant oral exposure.

Hazard characterisation for use in relation to acute oral exposure and acute dermal exposure due to spillage

The main target organ of fluralaner after repeated exposure is liver (increased organ weight, hepatocellular fatty acid change, effects in related blood parameters). The critical NOAEL was 10 mg/kg bw/day, based on liver changes observed in the oral developmental toxicity study in rabbits. This NOAEL was used to assess the risk of acute oral exposure following accidental ingestion or incidental hand-to-mouth contact by children. For acute dermal exposure due to spillage also the oral NOAEL of 10 mg/kg bw/day was used. The CVMP noted that higher dermal NOAELs were derived from dermal repeat-dose toxicity studies. However, these dermal NOAELs could not be used because the test formulation was not representative of the final formulation which contains a penetration enhancer expected to affect dermal absorption.

The CVMP noted that the NOAEL of 10 mg/kg bw/day was derived from a developmental toxicity study with repeat dose exposure; the NOAEL was based on liver effects which are not considered to occur after acute exposure. This was taken into account when performing the risk characterisation for acute exposure scenarios.

The excipient DMA is considered in relation to its reproductive toxicity only. The lowest oral NOAEL for developmental toxicity was 65 mg/kg bw/day. As oral and dermal bioavailability are similar this value is also considered appropriate for use as an estimated dermal NOAEL.

For the excipient DEET an oral NOAEL of 75 mg/kg bw/day was reported.

Hazard characterisation for use in relation to repeated oral exposure

For repeated oral exposure to fluralaner (due to hand-to-mouth contact after stroking) also the NOAEL of 10 mg/kg bw/day was used. However, exposure to fluralaner due to stroking the treated animal and subsequent hand-to-mouth contact may occur (sub)chronically because the product can be used year-round. The exposure duration in the developmental study was only 22 days. Therefore, an assessment factor of 3 for duration extrapolation was applied to the NOAEL.

Hazard characterisation for use in relation to repeated dermal exposure

To assess the risk of repeated dermal exposure to fluralaner (after stroking), a NOAEL of 50 mg/kg bw/day, based on liver effects observed in the 90-day dermal toxicity study in rats, was used. For

repeated exposure (after stroking) it is expected that the penetration enhancers in the formulation are no longer present in significant concentrations on the fur and therefore the use of this NOAEL is considered appropriate for this scenario.

Hazard characterisation for use in relation to acute dermal exposure after stroking

Also for acute dermal exposure (after stroking a treated animal) the dermal NOAEL of 50 mg/kg bw/day can be used, as the excipients used in the final formulation are volatile and evaporate within 24 hours (i.e. the time point at which the highest dislodgeable fraction was derived).

Exposure

User exposure due to contact with the treated animal is considered the most relevant exposure for adults and children. Contact with a treated animal, resulting in dermal exposure and oral exposure (due to hand-to-mouth contact) may occur throughout the year, as the product is recommended to be administered every 12 weeks year-round. In addition, adults may become dermally exposed every time they administer the spot-on, i.e. at 12-week intervals. Eye contact (splashed or due to hand-to-eye contact) and oral contact (due to hand-to-mouth contact) may occur if personal hygiene measures (i.e. washing hands after administration) are not maintained. Accidental ingestion by a child may also occur if the packaging of the product is opened and left unattended.

Acute oral exposure - accidental ingestion of entire contents of pipette

The worst case scenario for oral exposure is ingestion of the total content of one large pipette, which is 5 ml (1400 mg fluralaner) and would result in an oral exposure of 93.3 mg/kg bw for a 15 kg child.

For the excipient DEET the oral exposure due to the ingestion of the total contents of one large pipette, i.e. 5 ml, results in an oral exposure of 46.7 mg DEET/kg bw for a 15 kg child; or 0.255 mg DEET/kg when ingesting the residual volume of a used pipette which corresponds to 27 µl of product.

Acute dermal exposure to fluralaner following spillage

Acute dermal exposure due to spillage of the product is considered a realistic scenario, especially as the product has to be administered onto the skin, which may require some parting of the hair and therefore a risk of spilling some of the product onto the fingers. It is assumed that two animals are treated on the same occasion, and that one drop is spilled during each administration. This would result in a dermal exposure of 0.46 mg fluralaner/kg bw for the average 60 kg person.

Acute dermal exposure to DMA following spillage and acute oral exposure to DMA following hand-to-mouth contact

For the excipient DMA, significant exposure may cause damage to the unborn child. Potentially relevant exposure scenarios were considered to be dermal exposure during product application and oral exposure resulting from hand-to-mouth transfer following contact with a treated animal. The dermal exposure during application would be 0.6 mg/kg bw for the 60 kg person. Oral exposure due to hand-to-mouth contact was estimated to be significantly less, at approximately 24 µg/kg bw (for calculation of exposure to DMA the dislodgeable fraction derived for fluralaner was used).

The applicant uses the US EPA 2012 equations to calculate dermal exposure after contact with a treated animal (for stroking dogs as well as cats). Currently no EU guidance is available, therefore this is considered acceptable.

Dislodgeable fractions (FAR) for acute and chronic exposure were derived from a wipe test in dogs. The FARs are 7.83% for acute exposure and 0.44% for chronic exposure. Although no specific FARs for cats were provided, the CVMP considered it acceptable to use these fractions also for cats, as cats are expected to do more self-grooming, resulting in lower residue levels on the skin and hair.

Acute and chronic dermal exposure to fluralaner following hand-to-mouth contact

Acute dermal exposure from stroking a recently treated dog or cat was estimated to be 1.018 mg/kg bw and 1.160 mg/kg bw for a 11 kg child respectively. Chronic dermal exposure was estimated to be 0.057 mg/kg bw/day and 0.065 mg/kg bw/day respectively.

Acute and chronic oral exposure to fluralaner following hand-to-mouth contact

Acute oral exposure due to hand-to-mouth contact after contact with a recently treated dog or cat was estimated to be respectively 0.0535 mg/kg bw and 0.0609 mg/kg bw for a 11 kg child. Chronic oral exposure was estimated to be respectively 0.0030 mg/kg bw/day and 0.0034 mg/kg bw/day.

Risk characterisation

Qualitative:

Studies with the final formulation in laboratory animals and information on the excipient DEET suggest that the product can cause skin irritation.

Regarding the adverse skin reactions in humans observed in the field study in cats, even though there can be many factors involved in skin disorders all 3 cases occurred after intensive contact with the application site within 5 days after treatment. Therefore, the CVMP concluded that these adverse events in humans should be considered possibly treatment-related.

Although exposure to high doses is not expected, a warning that the product and the wet skin of recently treated animals may be irritating to skin is included in the draft product information.

Studies with the final formulation in laboratory animals suggest that the product can cause eye irritation. Although exposure to high doses is not expected, a warning that the product may be irritating to the eye is included in the draft product information.

The final formulation was also tested in a skin sensitisation test in guinea pigs, from which it was concluded that the product did not cause hypersensitivity reactions.

A standard warning with respect to flammability is necessary and is included in the draft product information.

Quantitative:

An in vitro percutaneous absorption study performed to compare the penetration of fluralaner in human skin versus rat skin (Craig 2014) using polyethylene glycol 200 as the vehicle resulted in rat/human skin penetration ratio of 3.7. An additional study using the final formulation including its penetration enhancers resulted in a skin penetration ratio of 5.7 for rat/human and of 7.8 for rabbit/human. The factor of 3.7 is used to correct the dermal NOAEL derived in rat to estimate the equivalent human NOAEL, which is the lower value and therefore acceptable for the risk characterisation when exposed to a treated animal. The factor of 7.8 can be used to correct the NOAEL derived in rabbit to estimate the equivalent human NOAEL for the risk characterisation when exposed to the product due to spillage.

Accidental oral ingestion of fluralaner and DEET:

For accidental ingestion by a child, a margin of exposure (MOE) of 0.1 (10/93.3) was calculated for the active substance fluralaner as part of the assessment, which is far below the acceptable level of 100.

However, the CVMP noted that the ingestion of the total content of large volume pipette (5 ml) is the worst case and the NOAELs are derived from repeated exposure studies. The NOAEL was based on liver effects which are not considered to occur after acute exposure. Moreover, in the oral acute toxicity studies with fluralaner or the product no adverse effects were observed.

For DEET, a MOE of 1.6 (75/46.65) was calculated for the accidental ingestion by a child. Although the ingestion of 5 ml of product is the worst case, the ingestion of smaller amounts is still a concern considering the acute neurotoxic effects that may appear due to ingestion of DEET.

Accidental access by children is limited by the addition of appropriate warnings in the draft product information. Furthermore, each pipette is sealed in an individual sachet, which has been demonstrated to be child-resistant.

Overall it is considered that the use of child-resistant packaging and appropriate warnings included in the draft product information would adequately mitigate against the risk of direct oral exposure.

Acute dermal exposure during application:

For acute dermal fluralaner exposure during application, a MOE of 22 (10/0.46) was calculated as part of the assessment which is below the acceptable level of 100. However, given that the NOAEL was derived from a repeat dose toxicity study and was based on liver effects which are not considered to occur after acute exposure, serious effects after incidental spillage of this product are not anticipated. Warnings included in the draft product information are intended to also limit exposure.

For developmental toxicity of fluralaner a NOAEL of 10 mg/kg bw/day was derived. This oral NOAEL was used as a surrogate for a dermal NOAEL and corrected by a factor 7.8 as it was demonstrated that the skin penetration of rabbit skin for this product is higher than human. The resulting MOE of 170 (78/0.46) is acceptable. No specific warnings need to be in place for pregnant women.

The excipient DMA was classified as possibly harmful to the unborn child. However exposure to DMA due to spillage does not pose a risk; a MOE of 108 (65/0.6) was calculated.

Acute dermal exposure after contact with (stroking) the treated animal:

The estimated acute exposures to fluralaner were compared to a dermal NOAEL of 185 mg/kg bw, i.e. 50 mg/kg bw/day as derived from the 90-day dermal toxicity study in rats corrected by a factor of 3.7 to account for difference in skin penetration. This resulted in a MOE of 182 (185/1.018; dogs) or 159 (185/1.160; cats) for acute dermal exposure when stroking a recently treated dog or cat, respectively, which is acceptable.

Acute oral exposure due to hand-to-mouth contact after contact with (stroking) a treated animal:

The estimated exposures to fluralaner were compared to the critical oral NOAEL of 10 mg/kg bw. This resulted in a MOE of 187 (10/0.0535; dogs) or 164 (10/0.0609; cats) for acute oral exposure due to hand-to-mouth contact when stroking a recently treated dog or cat, respectively, which is acceptable.

For combined dermal and oral exposure after stroking a dog or cat it is difficult to estimate the MOE. Based on the pharmacokinetic data in dogs it appears that oral and dermal bioavailability for the product is similar. Based on this, the risk for combined exposure was considered to be covered by the MOE for acute dermal exposure.

For acute oral exposure to excipient DEET due to hand-to-mouth contact when contacting a treated animal, a MOE of 3125 (75/0.024) was calculated. Although exposure was calculated using the FAR derived for active substance fluralaner, the MOE was considered to be sufficiently large to accommodate any differences in the FAR. Moreover, warnings are included in the draft product information with respect to avoiding exposure until the application site is dry. Therefore, it is concluded that the risk when exposed post application to DEET is negligible.

(Sub)chronic dermal exposure after contact with a treated animal:

The estimated chronic exposures to fluralaner were compared to a dermal NOAEL of 185 mg/kg bw/day, i.e. 50 mg/kg bw/day (derived from the 90-day dermal toxicity study in rats) corrected by a factor 3.7 to

account for the difference in skin penetration between rats and humans. This resulted in a MOE of 3246 (185/0.057; dogs) or 2846 (185/0.065; cats) for chronic dermal exposure when stroking a treated dog or cat, respectively, which is acceptable.

(Sub)chronic exposure due to hand-to-mouth contact after contact with (stroking) a treated animal:

The estimated exposures to fluralaner were compared to an oral NOAEL of 3.3 mg/kg bw/day, i.e. 10 mg/kg bw/day (the maternal NOAEL as derived from the developmental toxicity study in rabbits) corrected by a factor 3 to extrapolate from subacute exposure to subchronic exposure. This resulted in a MOE of 1100 (3.3/0.030; dogs) or 971 (3.3/0.0034; cats) for chronic oral exposure due to hand-to-mouth contact when stroking a treated dog or cat, respectively, which is acceptable.

Exposure via environment:

Contamination of control animals in the GLP target animal safety (TAS) studies occurred (see Part 4 – Target animal tolerance), even though these animals were housed individually under GLP conditions without possibility of physical contact to other animals or their direct environment. Sometimes high levels were observed and it was not single study site specific or target animal specific. In the pivotal TAS study in dogs, all control dogs were contaminated. Fluralaner plasma levels were up to 740 ng/ml. The CVMP noted that a plasma level <25 ng/ml is still proven to be efficacious for the indications of the product. These findings indicate that this product may contaminate the environment in a home setting, including humans indirectly. The exact cause of contamination of control animals in the TAS studies is not clear. Therefore, the observed levels in control animals should be considered as this may also apply to humans.

Although according to the guideline for user safety all possible exposure scenarios should be identified, characterised, and assessed, the applicant did not perform specific studies to investigate the extent of environmental (household) contamination using fluralaner under field conditions. To calculate the indirect human exposure from potential environmental contamination after application of Bravecto spot-on solution a study was submitted using a household simulation model, however, with fipronil spot-on as surrogate. The applicant concluded that indirect exposure to the active substance is under worst case not more than 14% of direct exposure and therefore of no concern for the user.

However, the CVMP is of the opinion that the conclusion derived from studies with other active substances cannot be extrapolated to Bravecto spot-on solution. Consequently the environmental contamination study performed with fipronil was not considered to be relevant for the current evaluation of Bravecto.

In the absence of fluralaner-specific information on exposure via the direct environment under normal conditions of use, the CVMP estimated a dermal exposure level using the pharmacokinetic study in dogs, based on the mean plasma levels of the control animals in the TAS study in dogs and assuming that these levels may also occur in humans. A comparison of the estimated dermal exposure level to the dermal NOAEL indicated that exposure via the environment (e.g. contact with contaminated area) can significantly contribute to total dermal exposure of the user. A MOE of ca 40 was calculated, which is lower than 100 and therefore considered insufficient to protect the user. In addition, subsequent oral exposure due to hand-to-mouth contact or ingestion of house dust (which is well known scavenger for hydrophobic substances) may be significant for children. Fluralaner is a lipophilic substance (logP 5.4; water solubility 0.1 mg/L) and hence not easily cleaned from the environment. It has an elimination half-life of 21 days in the body (as determined in dogs). In addition, the product may be administered every 12 weeks year-round.

Another possibility of environmental exposure would be via aerogenic transmission. The vapour pressure of fluralaner is very low, therefore, inhalation of vaporised fluralaner is unlikely. The possibility of inhalation of contaminated indoor dust has not been explored.

Warnings and safety measures

As a result of the user safety assessment of direct exposure to the product or to treated animals the following warnings for the user are appropriate:

- This product is harmful after ingestion. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. A used pipette should immediately be disposed of. In case of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician.
- This product and the wet skin of a recently treated animal may be slightly irritating to skin and/or eyes. Avoid contact with skin and/or eye, including hand-to-eye contact. Do not eat, drink or smoke while handling the product. Do not contact, or allow children to contact the application site until it is dry; it is therefore recommended to treat the animal in the evening. On the day of treatment, treated animals should not be permitted to sleep with their owner, especially children. Wash hands and contacted skin thoroughly with soap and water immediately after use of the product. In case of contact with the eyes, immediately rinse thoroughly with water.
- The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

However, treated animals can contaminate the household environment, as is evident from the GLP TAS studies. The applicant did not produce any data on user exposure in a home following the use of the fluralaner spot-on product in cats or dogs. In contrast to the GLP studies, where treated and non-treated animals were housed separately and measures were taken to avoid cross-contamination, the situation is different in the home setting where people and their pets live, eat and sleep in the same house. The potential for contamination is considered to be greater in a home setting than in a GLP setting. No measures can be taken to prevent such contamination, of which the extent is unknown.

Conclusion on user safety

Short term exposure to fluralaner may cause adverse skin reactions and be irritating to the eyes. In a developmental toxicity study in rabbits with repeat exposure, fluralaner caused adverse effects in the liver in maternal animals, and on the foetal skeleton. In addition the excipients DMA and DEET have also been associated with toxicity.

According to the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03 - Rev.1), all routes of exposure must be addressed, and the exposure must be quantified for each exposure scenario.

Potential exposure to the product resulting from accidental ingestion, direct dermal contact during application, dermal contact resulting from stroking the treated animal following application, as well as subsequent oral ingestion as a result of hand-to-mouth transfer could all be adequately mitigated through use of child-resistant packaging and inclusion of appropriate warnings in the product information.

However, no experimental data with Bravecto spot-on solution have been submitted to quantify the level of user exposure to fluralaner via the household environment. This is a concern as plasma concentrations of fluralaner were measured in all control animals - which were housed separately - in the pivotal TAS study in dogs at up to 740 ng/ml which is considered high. These results indicate that the exposure via the direct environment can be significant. The environmental levels necessary to achieve these plasma concentrations in dogs are likely to represent a risk to users living in the same environment as the treated animals. Furthermore, fluralaner concentrations were also measured in all cats of the control group in the pivotal GLP target animal safety study in cats. However, the contamination (≤ 68.07 ng/ml) was not as high as in the dog study.

In the absence of a satisfactory explanation for the contamination of control animals in both TAS studies and in the absence of data to demonstrate that significant environmental contamination can be avoided, a risk to the user cannot be ruled out.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to the VICH GL6 on Environmental impact assessment (EIAS) for veterinary medicinal products (CVMP/VICH/592/98 - FINAL) and the CVMP Guideline on the Environmental impact assessment for veterinary medicinal products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005 - Rev.1).

According to the phase I decision tree the risk assessment would normally stop at question 3 because the product will be used only in non-food animals.

However, specifically for ectoparasiticides applied topically to dogs, the phase I assessment does not stop here and risk mitigation measures according to the summary of product characteristics (SPC) guideline would need to be presented. Alternatively, additional assessment is required to address the potential exposure of watercourses by swimming dogs, and this way was performed.

It was concluded that the topical formulation will dry within the first 24 hours after administration and that after this period, the probability of fluralaner to end up in a watercourse after swimming will be extremely low. The exposure to the aquatic environment is very unlikely when the application site is dry. However, because the probability of exposure of watercourses was not assessed for dogs shortly after treatment when the application site is not dry and since the first time point of the bathing/water-immersion study is only 3 days after application, a warning not to allow the dog to swim in watercourses within 3 days after treatment is required.

Conclusions on the environmental risk assessment

The veterinary medicinal product is intended for use in non-food producing animals. Bravecto spot-on solution is not expected to pose a risk for the environment when used according to the draft product information. A warning not to allow the dog to swim in watercourses within 3 days after treatment is in section 4.5 (Special precautions for use in animals) of the draft SPC for dogs.

Overall conclusions on the safety documentation

The CVMP concluded during the assessment for the initial marketing authorisation for Bravecto (chewable tablets) that fluralaner is of low acute oral or dermal toxicity and has NOAELs of 60 and 50 mg/kg bw/day following oral or dermal repeated administration. It was also concluded that fluralaner does not have genotoxic potential and is unlikely to have carcinogenic potential.

With regard to reproductive toxicity, a NOAEL of 10 mg/kg bw/day was established for maternal and embryo/foetal toxicity in rabbits.

Bravecto spot-on solution may be harmful after ingestion including neurotoxic effects, however each pipette is sealed in an individual sachet which is child-resistant. Incidental spillage of the product during application is not expected to result in adverse effects, especially when hands are washed after administration of the product.

Bravecto spot-on solution is non-sensitising, however it can cause skin and eye irritation. Skin reactions were also observed in 3 humans representing 2.5% of the number of households in the field study in cats following direct contact with the treated animals.

In relation to user safety, potential exposure to the product resulting from accidental ingestion, direct dermal contact during application, dermal contact resulting from stroking the treated animal following application, as well as subsequent oral ingestion as a result of hand-to-mouth transfer could all be adequately mitigated through use of child-resistant packaging and inclusion of appropriate warnings in the product information.

However, an appropriate justification explaining the observed active substance contamination of untreated control animals in the pivotal target animal safety studies was not provided. This raises concerns about potential contamination of the direct (household) environment following use of the product. No experimental data with Bravecto spot-on solution have been submitted to quantify the level of user exposure to fluralaner via the household environment. The CVMP therefore concluded that there is a probability for user exposure to the active substance through cross-contamination via the household environment. The extent of this exposure is unknown.

There is therefore uncertainty over the potential user exposure following application of the product and consequently a risk to the user cannot be ruled out.

In conclusion concerning user safety, the documentation provided is not deemed satisfactory and the risk to the user is considered unacceptable.

Concerning environmental risk assessment, Bravecto spot-on solution is not expected to pose a risk for the environment as such, when used according to the draft product information.

Part 4 – Efficacy

Pharmacodynamics

The ectoparasitic properties of the active substance in Bravecto spot-on solution, fluralaner, have already been assessed in the initial application for Bravecto chewable tablets. Fluralaner is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA-receptor and glutamate-receptor). Parasites need to start feeding on the host to become exposed to fluralaner; therefore the risk of the transmission of parasite borne diseases cannot be excluded. The CVMP concluded that fluralaner is a potent acaricide and insecticide, with activities against fleas and ticks on both dogs and cats.

Development of resistance

Since fluralaner and other members of the isoxazoline group have not been widely used yet in the general animal population, there has not been potential for development of resistance among the target parasites.

Pharmacokinetics

The pharmacokinetic studies were conducted with the proposed new formulation, i.e. a spot-on solution, which is applied directly on the skin either between the shoulder blades and on the medio-dorsal line (dog) or at the base of the skull (cats). In order to obtain its ectoparasiticidal effect fluralaner needs to be absorbed through the skin into the blood in target animals and the ectoparasites need to attach and commence feeding.

All *in vivo* pharmacokinetic studies were conducted in beagle dogs and in European short hair cats

including two pivotal GLP-compliant pharmacokinetic studies, one in dogs and one in cats.

There are no marked gender related differences in bioavailability, distribution or excretion.

Absorption

In dogs T_{max} was not markedly influenced by dose after topical administration (T_{max} ranged from 7-63 days). Mean bioavailability of racemate fluralaner was 25% (19.49–31.45%) after topical application of 25 mg fluralaner/kg bw. Oral bioavailability is comparable to topical bioavailability with mean values of 27% at doses of 25 mg/kg bw. AUC and C_{max} increased proportionally with dose. Half-life was constant at increasing topical dose levels.

In cats T_{max} occurred earlier than in dogs and peak plasma levels were reached between days 3–21. Bioavailability (F%) is low, a topical dose of 40 mg/kg bw resulted in a mean bioavailability of 27%. There is a dose proportional increase in AUC_{0-t} and C_{max} parameters in the dose range of 20–80 mg/kg bw after topical administration.

Distribution

Fluralaner is found to be highly bound to plasma proteins of cat and dog (approximately 100%). Plasma concentrations were quantifiable after topical treatment in both cats and dogs (at all doses) for more than 3 months. After absorption, fluralaner is well distributed and accumulates to a large extent in the skin and hair (predominantly at the application site but also in other parts of the skin and hair e.g. inner hind limb), it accumulates in visceral fat of the target animals, followed by liver, muscle and kidney (in cats kidney had higher concentration than muscle) and is still quantifiable 84 days after treatment.

Metabolism

No metabolites could be detected in the faeces of the target animals however in the 90 day oral repeat dose toxicity study in rats as well as in the developmental study in rabbits a metabolite could be detected in substantial amounts in plasma.

Excretion

After intravenous administration the same patterns in cats and dogs were observed. Fluralaner undergoes a slow elimination process (63–77 days). Total clearance was low in comparison to hepatic blood flow. Excretion of unchanged fluralaner in the faeces is the major route of elimination of fluralaner in both cats and dogs (urine: less than 0.01%).

Effect of shampooing or water immersion

Efficacy against artificially induced infestations of beagle dogs with ticks, *Ixodes ricinus* and fleas, *Ctenocephalides felis*, was unaffected when dogs were shampooed (using a commercial shampoo) or water immersed (e.g. swimming and bathing) 3, 21, 49, 77, 105 days after topical application with doses according to the SPC (25.3–46.3 mg fluralaner/kg bw). No major difference in pharmacokinetic parameters between treated and water immersed and treated and shampooed dogs were observed.

In the absence of any studies investigating an earlier time, the following warning is therefore included in section 4.5 (Special precautions for use in animals) of the SPC for dogs: 'Do not wash or allow the dog to become immersed in water or swim in watercourses within 3 days after treatment'.

Dose determination/justification

All efficacy studies were well conducted using the same basic study design in line with the relevant 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). Concerning

study design and assessment method(s), reference is made to the initial submission for Bravecto chewable tablets for dogs. Below, assessment aspects specific for the new formulation and target species are outlined.

Dogs:

Dose determination studies for *I. ricinus* (2010, GLP), and *R. sanguineus* (2012) were not carried out using the final formulation but one with the same excipients in slightly different quantities. From the results of these dose determination studies, 25 mg fluralaner/kg bw was chosen as the final clinical dose. 10 mg fluralaner/kg bw was not able to provide immediate and persistent efficacy for 12 weeks against *I. ricinus* (2010). 40 mg fluralaner/kg bw did not show any additional benefit concerning the intended 12-week dosing interval.

In the dose confirmation studies topical treatment using the minimum dose (i.e. 25 mg fluralaner/kg bw) provided sufficient immediate (therapeutic) efficacy and persistent (prophylactic) efficacy for 12 weeks (i.e. the intended dosing interval) against ticks (*I. ricinus, D. reticulatus* and *R. sanguineus)* and fleas (*C. felis*) in dogs. It should be noted that in dose determination studies as well as dose confirmation studies a substantial number of *I. ricinus* are engorged before they die; this finding suggests that the risk for transmission of tick borne diseases cannot be excluded.

It can be concluded that efficacy of fluralaner at a dose of 25 mg/kg bw in dogs is sufficient against ticks (>90%) for at least 84 days. It has a strong flea killing effect which lasts at least 114 days (>95%).

Cats:

In cats, dose finding studies for *I. ricinus* have been carried out using the final formulation; however, for *C. felis* dose determination studies were performed with an alternative topical formulation using different excipients (DMSO based). The tick dose finding studies concluded an optimal dose of 40 mg/kg bw, demonstrating sufficient efficacy up until day 86.

Several dose confirmation studies demonstrate very good efficacy in cats against *C. felis* (>95%) and sufficient efficacy against *I. ricinus* (>90%) for at least 84 days at the minimum dose of 40 mg/kg bw using the final formulation.

Overall in both cats and dogs, breed does not influence flea or tick efficacy.

Speed of kill

Dogs:

Cross-reference was made to two GLP studies submitted with the initial application of Bravecto chewable tablets for dogs evaluating the speed of kill of fluralaner against ticks (*I. ricinus*) and fleas (*C. felis*) on dogs when administered orally and topically at a dose of 25 mg/kg bw.

Cats:

Two GLP studies (2013 and 2014) were performed in Germany to investigate the speed of kill of fluralaner administered once topically at a dose of 40 mg/kg bw against ticks and fleas in cats.

In the first study the speed of kill for ticks and fleas (assessment at 8 and 12 hours) was studied whereas the second study speed of kill for ticks was assessed at 24 hours. In both studies assessment was performed comparing treated animal groups with untreated control groups and there were 7 animals per group.

Based on the speed of kill data presented, the CVMP concluded:

For dogs: "The onset of efficacy is within 8 hours for fleas (C. *felis*) and 12 hours for ticks (I. *ricinus*)."

For cats: "The onset of efficacy is within 12 hours for fleas (*C. felis*) and within 48 hours for ticks (*I. ricinus*)."

Simulation of a home environment

Two studies were submitted investigating the influence of fluralaner treatment on the possibility of flea infestation from the environment in dogs (2014) and cats (2013), both carried out in the USA.

Study design: all dogs or cats were individually housed in cages with a carpet for use as a bedding to simulate a home environment where flea eggs might develop further. The carpet was placed in each pen on day -56 (dogs) or day -28 (cats) before treatment with fluralaner. All animals were infested weekly with 100 adult unfed *C. felis* fleas per animal, beginning on day -56 (dogs) or on day -28 (cats) through day -21. A flea count was conducted to determine the number of fleas on each dog or cat at day -1, the fleas were removed and the dogs or cats were held overnight in clean pens (the carpets were removed prior to flea counting on day -1). At day 0, Group A (n=10 in both studies) was treated with 25 mg fluralaner/kg bw (dogs) or 40 mg fluralaner/kg bw (cats) topically, Group B (n=10 in both studies) was treated with a placebo. After treatment, the carpets were returned into each pen. Post treatment flea counts were done on day 1, and further every week until day 84.

To simulate introductions of new fleas in cats, each cat was infested with 50 newly unfed adult fleas on days 22, 50 and 78. Adequacy of post-treatment infestation was shown by the presence of live adult fleas on control dogs and cats. Efficacy was calculated using arithmetic means with Abbott's formula.

From day 21 till day 84, the control group carried on average over 25 fleas or 17 fleas (for dogs and cats, respectively) whereas the treatment group was free of fleas in this period. In this model, removal of adult fleas from the host reduced new flea infestations from the environment significantly for at least 14 days. Efficacy of treatment to control environmental infestation is sufficient (>95%) from day 21 on in this model.

The CVMP considered the model used by the applicant as representative to simulate the home environment (e.g. ratio of egg/larvae/pre-adults in the carpet in the pen vs adults on the dog/cat), and concluded that the efficacy of treatment to control environmental infestation appeared to be sufficient (>95%).

Target animal tolerance

Pivotal target animal safety studies in dogs and cats (2013):

Both GLP studies were designed according to VICH GL43 on target animal safety for pharmaceuticals. Treatment groups received a spot-on with 1x, 3x and 5x the maximum clinical amount of Bravecto spot-on solution (respectively 56, 168 and 280 mg fluralaner/kg bw for dogs and 93, 279 and 465 mg fluralaner/kg bw for cats). A negative control group was included. 32 beagle puppies and 32 kittens were randomly allocated to treatment groups. The studies lasted until day 168, and the animals were treated three times every 8 weeks (days 0, 56 and 112). The total dose volume of the control or test items were split and administered on two dosing occasions approximately 4 hours apart. Minimum age of the dogs was 56 days and minimum weight was 1.96 kg at day -1. Minimum age of kittens included in the study was 78 days, minimum weight 1.15 kg on day -1. Treatment with Bravecto spot-on solution is therefore restricted to dogs and cats with a minimum age and bodyweight.

Blood sampling for haematology and clinical chemistry was carried out one week before each treatment i.e. seven weeks after the previous treatment. Data derived from these samples can be considered 'chronic'. For 'acute toxicity' blood samples were taken on day 21 (at this timepoint fluralaner has reached approximately the highest plasma levels). The study was designed to compare data of clinical

chemistry, haematology, urinalysis and pathology derived from the treatment groups with the data obtained from the negative control group.

Dogs: no adverse events were noticed either at the application site or post dosing veterinary examinations except for one animal that developed rash on the ventral abdomen, followed by dermatitis during the study (day 29–42), which resolved after treatment. Fluralaner administered as a spot-on solution did not appear to give significant dose related deviations in haematology, urinalysis and clinical chemistry (in comparison with control groups, with baseline levels or reference ranges derived from literature). Incidental significant differences between treatment and control groups were considered of no clinical relevance. No parameter fell outside the range, derived from literature or baseline values, which could be considered clinically relevant.

Cats: fluralaner administered as a spot-on solution did not produce significant dose-related deviations in haematology, urinalysis and clinical chemistry (in comparison with control groups, with baseline levels or reference ranges derived from literature) and the incidental significant differences between treatment and control groups were considered not clinically relevant. Positive fat staining in kidney and liver, and hepatocyte vacuolization were detected in almost all samples (including control group). Serum concentrations of fluralaner were very low in the control group (≤ 68.07 ng/ml) but PK studies demonstrate that the active substance has a long terminal half-life and can be stored for a long period in the skin, kidney and liver.

Pivotal lick off studies in dogs (2012) and cats (2012):

Study design: The objective was to evaluate the safety of 28% w/v fluralaner spot-on solution as final formulation for dogs and cats at the highest expected dose in clinical use of fluralaner (i.e. 56 mg/kg bw for dogs, 93 mg/kg bw in cats) when administered once orally to a fed target animal. Response to treatment was assessed by performing general health observations, clinical assessments (post dosing observations), veterinary examinations, bodyweight and diet consumption monitoring, urinalysis (day -7 and day 7), haematology and clinical chemistry (day -14, 8), necropsy at day 28, and histopathology of liver tissue and any gross lesions. Blood samples were taken weekly and were analysed for plasma concentrations of fluralaner by a validated method.

Dogs: immediately after administration salivation was observed in 5/6 of the fluralaner treated animals (0/6 in the control group), and vomiting in 1/6 dogs. It is likely that the salivation is caused by the excipients in the spot-on solution but the applicant concluded that the observed vomiting was not thought to be related to the test item. However, during the assessment for the initial marketing authorisation for Bravecto (chewable tablets), vomiting was also observed several times and was considered test item related. No clinically relevant differences between treatment group and control group were observed concerning haematology, clinical chemistry and (histo)pathology, including differences in organ weights.

In a pilot study (2011) with 3 dogs receiving oral administration of 56 mg/kg of 28% w/v fluralaner spot-on solution no adverse events were observed except a transient minimal reddening of the pharyngeal mucosa. The spot-on solution is well tolerated after oral administration.

Cats: In fluralaner treated cats salivation (6/6 cats) and coughing (4/6 cats) was noted, and vomiting in two cats (one treated and one from the control group). Coughing and salivation might be due to the oral administration of excipients of the spot-on solution. One treated animal had slightly red mucous membranes.

Overall the test article was well tolerated after oral administration and there were no clinically relevant differences between treatment group and control group concerning haematology, clinical chemistry and (histo)pathology, including differences in organ weights.

A pilot study (2011) concluded that the oral administration of the topical formulation 28% w/v fluralaner

spot-on solution for dogs/cats was well tolerated in three cats. Severe to moderate hypersalivation after administration is most likely due to excipients in the formulation.

The CVMP concluded that Bravecto spot-on solution is generally well tolerated by both dogs and cats after (accidental) oral administration.

Contamination of controls with fluralaner:

In the pivotal target animal safety study in dogs (GLP, 2013, see above), all dogs in the control group had quantifiable fluralaner plasma levels varying between 11 and 100 ng/ml at several time points during the study. In addition, concentrations of fluralaner in plasma of 3 dogs in the control group were in the range of 100.6–739.87 ng/ml, measured between days 56 and 140. This study met stringent GLP conditions and the animals were housed individually without possibility of physical contact. It is unclear how control animals could have developed plasma levels as high as 739 ng fluralaner/ml (these C_{max} levels approached C_{max} after a single treatment with 25 mg fluralaner/kg bw). It should be noted that this contamination is not an isolated case and does not solely occur at a single study site. It has occurred before in a pivotal GLP safety study for Bravecto chewable tablets (2012) and also in the pivotal GLP target animal safety study in cats (2013) where all cats in the control group had positive plasma fluralaner concentrations (>LLOQ) though the contamination (≤ 68.07 ng/ml) was not as high as in the dog study. Cats were housed individually without physical contact. In target animal safety pilot GLP study in cats (2011) one control animal had a plasma sample containing fluralaner on day 115. In another GLP study (2010) two dogs had quantifiable plasma concentrations of fluralaner, albeit very low, in their pre-treatment samples. Positive pre-treatment samples were also found in 14 out of 18 cats in another study (2009). Since it seems difficult to manage control groups as 'clean' in these GLP laboratory settings, the CVMP concludes that the topical test article can easily contaminate the home environment, including other pet animals and humans (including children), without necessity of physical contact. Because of lack of knowledge relating to the route of contamination, no adequate preventive actions can be taken.

Target animal tolerance under field conditions:

From the safety findings in the various clinical studies conducted, the following effects are considered possibly treatment related:

In dogs, commonly observed adverse reactions (1.2% of treated dogs) in clinical trials were mild and transient skin reactions such as erythema or alopecia at the application site.

In cats, commonly observed adverse reactions (2.2% of treated cats) in clinical trials were mild and transient skin reactions at the application site, such as erythema and pruritus or alopecia. The following other signs shortly after administration were observed: apathy/tremors/anorexia (0.9% of treated cats) or vomiting/hypersalivation (0.4% of treated cats).

In the various clinical studies conducted other skin related adverse effects were recorded; however, in many cases, there was no association in time with treatment and/or the lesions were distant from the application site and/or it is more likely that the findings related to ectoparasite infestation.

The adverse reactions are adequately reflected in the draft product information.

The safety of use in pregnant and lactating dogs following oral administration of fluralaner was accepted in the context of the assessment of the application for marketing authorisation for Bravecto chewable tablets. Given that systemic exposure following oral administration is higher than that following topical administration, extrapolation of these safety data to the topical route of administration can be accepted. For the cat, safety of use in pregnant or lactating animals has not been investigated. These warnings are adequately reflected in a draft SPC.

Field trials

Two well conducted multi-site GCP field studies were submitted, one in dogs (2014) and one in cats (2014). The field study in dogs was conducted in France, Germany, and Spain and the one in cats in France, Germany, Spain and the Netherlands. For each target species, all parasites listed in the proposed indication were identified on test animals. The studies can be considered representative of the European situation.

The objective of the studies was to confirm the duration of efficacy of 12 weeks for Bravecto spot-on solution in dogs or cats naturally infested with ticks and/or fleas under field conditions. The studies were randomized, controlled and blinded.

Dogs/cats were included in the study on the basis of their household. In the study on dogs a household was included if at least one dog had a minimum infestation level of 4 ticks and/or 4 fleas at the first visit, whereas the minimum infestation level for cats was of 2 ticks and/or 2 fleas.

All animals in the same household were randomly allocated to treatment with the test product or an authorised spot-on product containing fipronil as active substance. The test product was administered once topically at a dose rate of 25 mg fluralaner/kg bw to dogs and 40 mg fluralaner/kg bw to cats. Treatment with fipronil was administered according to the label instructions.

The studies' schedules involved 5 visits to veterinary clinics over a period of 84 days. At all visits, 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 studies, 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 animals were detected.

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

In terms of efficacy, the overall conclusions of the field studies are accepted: the product when administered to dogs/cats under field conditions of use was effective against the claimed tick and flea species for up to 12 weeks after treatment. For the percentage of dogs/cats and households free of ticks and dogs/cats and households free of fleas, non-inferiority of fluralaner compared to fipronil at each follow-up visit was shown.

Over the course of the study, there was a reduction in the number of animals with clinical signs of FAD in both target species.

The test product appears to have been well tolerated in both species. Adverse events are described in the target animal tolerance section.

In the field study for cats 3 humans that had intensive skin contact with the application site of the cat, developed rash and in one case skin pustules (face or neck) within 5 days after topical Bravecto treatment of the cat. According to the CVMP these adverse events should be considered possibly related to the test article based on the provided information (see user safety section above).

Overall conclusion on efficacy

Dose determination studies were conducted using a slightly different formulation from the final formulation, however the determined minimum dose was justified by 2 dose confirmation studies per tick species and for fleas.

Dose confirmation studies demonstrated sufficient immediate (therapeutic) efficacy and persistent (prophylactic) efficacy for 12 weeks (i.e. the intended dosing interval) for ticks *I. ricinus* (dogs and cats), *D. reticulatus* (dogs only) and *R. sanguineus* (dogs only) as well as fleas *C. felis* (dogs and cats).

Conclusion speed of kill

Based on the speed of kill data presented, the following can be accepted:

Dogs: "The onset of efficacy is within 8 hours for fleas (*C. felis)* and 12 hours for ticks (*I. ricinus).*"

Cats: "The onset of efficacy is within 12 hours for fleas (*C. felis)* and 48 hours for ticks (*I. ricinus).*"

Conclusion on simulation of a home environment

Efficacy of treatment to control environmental infestation is sufficient (>95%).

Conclusion efficacy field studies

Two well conducted multi-site GCP field studies were submitted one in dogs (2014) and one in cats (2014) using fipronil spot-on solution as positive control. In both studies efficacy against fleas was shown. Reduction in flea counts at all visits was more than 95% in the fluralaner group. Percentage of households free of fleas was overall significantly non-inferior compared to fipronil. Also the percentage tick reduction was >90% at all visits compared to the pre-treatment tick count in both studies.

Benefit-risk assessment

Introduction

This extension application to the marketing authorisation for Bravecto is submitted to add a new pharmaceutical form (spot-on solution) for dogs and to add a new target species (cats) for this spot-on formulation. Bravecto is authorised as chewable tablets for the treatment of tick and flea infestations in dogs. The proposed indication for the spot-on formulation is the same as the one for the tablets (i.e. treatment of tick and flea infestations in dogs and cats). The proposed single topical dose for dogs is 25–56 mg/kg bw, and for cats 40–94 mg/kg bw, both with a treatment duration of 12 weeks.

Benefit assessment

Direct therapeutic benefit

The benefit of Bravecto spot-on solution is its efficacy in the treatment of flea and tick infestations in dogs and cats.

Controlled clinical trials conducted in accordance with GCP demonstrated that the product is efficacious in dogs against fleas (*Ctenocephalides felis* and *Ctenocephalides canis*) and ticks (*Ixodes ricinus*, *Rhipicephalus sanguineus* and *Dermacentor reticulatus*), and in cats it is efficacious against fleas (*Ctenocephalides felis*) and ticks (*Ixodes ricinus*).

The effect in both target species persists for 12 weeks.

Additional benefits

None.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

For the target animal:

Administration of the product in accordance with draft SPC recommendations is generally well tolerated by both dogs and cats.

For the user:

The CVMP identified a probability for user exposure through cross-contamination via the direct environment (household). The extent of this exposure is unknown and, there is therefore uncertainty over the potential user exposure following application of the product. Consequently a risk to the user cannot be ruled out.

For the environment:

Bravecto spot-on solution is not expected to pose a risk for the environment when used according to the draft product information.

Risk management or mitigation measures

Appropriate information has been included in the draft product information to inform of the risks of this product relevant to the target animal and the environment and to provide advice on how to prevent or reduce these risks.

However, the risk for the user cannot be managed due to uncertainty relating to exposure to the product and therefore its effect.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the treatment of flea and tick infestations in dogs and cats.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for the environment when used as recommended.

The CVMP identified a probability for user exposure through cross-contamination via the direct environment (household). The extent of this exposure is unknown and there is therefore a risk for user exposure that cannot be managed. Consequently the risk for the user is considered unacceptable.

Conclusion on the benefit-risk balance

The CVMP considered that the overall benefit-risk evaluation for the product is negative.

Conclusion on the initial assessment

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application to add a new pharmaceutical form (spot-on solution) for dogs and to add a new target species (cats) for this spot-on formulation was not approvable since the data on user safety were unacceptable. Since safety was not sufficiently demonstrated, the data did not satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 1234/2008 in conjunction with Directive 2001/82/EC).

The CVMP considered that the overall benefit-risk balance was negative and, therefore, recommended the refusal of the granting of the extension to the marketing authorisation for the above-mentioned medicinal product.

Re-examination assessment

Following the negative CVMP opinion for Bravecto spot-on solution for dogs and cats of 9 December 2015, Intervet International B.V. requested the re-examination of the CVMP opinion under Article 34(2) of Regulation (EC) 726/2004, regarding this extension application for Bravecto to add a new pharmaceutical form (spot-on solution) and a new target species (cats) for this spot-on formulation.

Detailed grounds for re-examination submitted by the applicant

The applicant argued that the CVMP's approach to extrapolate data from the target animal safety (TAS) study to determine the potential for indirect user exposure was not appropriate for the following reasons:

- The conditions of use of the product during the TAS studies do not reflect the situation in the household situation (laboratory environment, use of overdoses, random-treatment versus group-treatment).
- Fluralaner plasma concentrations in control animals suggest that contamination occurred at the time of treatment via direct contact with fluralaner (cross-contamination), but not through indirect contamination via the environment.
- Other laboratory efficacy studies, submitted with the initial dossiers for Bravecto chewable tablets for dogs (8 studies) and Bravecto spot-on solution for dogs and cats (2 studies), did not show contamination of the untreated control animals.
- There is currently no agreed specific guidance on the approach or methodology to be applied when conducting user risk assessment for products for topical use, and the applicant followed the limited guidance available (CVMP Guideline on user safety for pharmaceutical veterinary medicinal products). Generic/surrogate exposure modelling is an appropriate tool, and the chosen fipronil spot-on solution was an appropriate surrogate to estimate the relative magnitude of indirect exposure from potential household contamination. Also, a variety of existing authorised antiparasitic spot-on formulations might have similar potential for indirect user exposure via the household environment, but there were not requests to provide a more in-depth data package.
- Based on the existing data, the applicant also provided a revised risk assessment. Two different models were used to calculate the indirect human exposure in the household environment. Estimations were made for dogs as the worst-case scenario since the treatment dose for cats is markedly lower and the potential for transfer from cats to home environment is lower compared to dogs, due to grooming behaviour resulting in removal of fluralaner from the hair coat.

  Based on the re-calculations, the amount of fluralaner from indirect exposure was calculated using EPA SOPs to represent 2.8% to 13% (pet transfer rate-based primary exposure model) or 4.4% to 21.6% (ADME-based confirmatory model) of the amount from direct contact with the treated animal.

The applicant concluded that the benefit-risk balance for Bravecto spot-on solution for dogs and cats is favourable, given that the efficacy of the product in both target species for the claimed indications have already been confirmed by the CVMP as well as the risk for the target animal and for the environment.

Advice by Ad Hoc Expert Group (AHEG)

Overall, the AHEG was asked to consider if the results of the TAS studies and the topics addressed in this re-examination procedure raise a particular concern in relation to possible household contamination and consequently user safety. Specific questions were raised in relation to the contamination of the controls in

the TAS studies, the conditions used in these studies and their applicability to the household situation, the suitability of the simulated household model using fipronil as surrogate, and the revised risk assessment for indirect human exposure.

The AHEG concluded on the following:

- The contamination of untreated control animals in the dog TAS study was considered a result from single exposure, since the shape and the timing of the fluralaner plasma concentrations versus time curves for control and treated animals are comparable.
- The TAS laboratory study would not reflect the normal household situation due to differences related to the method of application, and the large doses and volumes of the test product applied.
- The fipronil surrogate marker was considered an appropriate model based on the physicochemical properties of the active substance. However, some additional considerations may be needed in relation to the difference between the formulations.
- With regard to the revised risk assessment, the primary indirect exposure model was considered the most appropriate simulation. However, concerns were raised regarding the exposure averaging over 84 days and the derivation of the 'floor to humans' factor of 0.48%. The ADME based indirect exposure model is a useful confirmatory model. The factors used to extrapolate the daily reduction of transferable fraction and the reduction rate via weekly vacuum cleaning were considered appropriate for this highly lipophilic substance which firmly binds to surfaces. The inhalation exposure was not considered to be significant as the active substance is tightly bound to hair or skin flakes from the animal, and the bioavailability is likely to be low.

  Since the product is to be applied up to 4 times/year and has a long half-life (21 days), the AHEG recommended that further considerations should be given to long-term human exposure. As the point of departure is the NOAEL from a 90-day repeat dose toxicity study, a factor 2 could be applied to extrapolate to a chronic NOAEL as per REACH guidance. The extrapolated NOEL would be comparable with the NOAEL that would be calculated by dividing by a safety factor up to 3 the LOAEL of 50 mg/kg bw/day from the one-generation reproduction toxicity study. Additionally, it was proposed to (re)consider the impact of the above deliberations on the direct exposure risk assessment.

The AHEG also discussed the GLP status of the TAS studies and concluded that the results of the two pivotal TAS studies in dogs and cats are not invalidated by the related findings.

Overall assessment and conclusions on grounds for re-examination

The CVMP assessed the detailed grounds for re-examination and additional argumentations presented by the applicant and considered the advice provided by the AHEG.

The Committee concluded on the following:

- The contamination of untreated control animals in the dog TAS study is considered most likely due to a single direct exposure to the active substance (cross-contamination) at or around the time of treatment. However, no clear explanation was provided on how the cross-contamination occurred in the GLP TAS study.
- The laboratory study does not reflect a normal household situation.
- The risk of indirect exposure via cross-contamination is usually not addressed for topically applied antiparasitic spot-on formulations, and currently harmonised specific guidance on the user risk assessment for topically applied products is not available.

However, the documentation provided for Bravecto spot-on solution showed contamination of control animals in the TAS study. Therefore, the potential indirect human exposure via household environment was explored. In the absence of product-specific exposure data the applicant presented a household simulation model using fipronil as surrogate.

From the assessment of data from the initial extension application and based on calculations of the applicant, a reasonable worst-case for indirect (environmental) exposure is 14% of direct exposure. Factoring this into the margin of exposure (MOE) calculation results in a MOE for total dermal exposure (direct plus indirect) that remains above 100. This is considered acceptable. In the household simulation model using fipronil as surrogate indirect exposure to the active substance is ~1-2% of direct exposure and, therefore, of no concern. The CVMP accepted the fipronil surrogate model given that the results from this model were confirmed by the updated user risk assessment provided with fluralaner-specific data. These data were already provided during initial assessment of the extension application.

- The primary indirect exposure model is considered the most realistic worst-case scenario. This primary model assumes that the same fraction of the dose that may be transferred via direct contact with the animal as determined from the pet transfer rate study (acute: 7.8%, subchronic: 0.237%) may also be dislodged and distributed in the household environment. The calculation considers 2 treated dogs (> 40 kg b.w., 1400 mg fluralaner dose each) on 26 m^2 household area, and intimate daily contact with soft floor surfaces for 4–8 hours for a child (11 kg) and an adult. The second model is based on the mass distribution determined in a non-radiolabelled AD(M)E study which the CVMP considered confirmatory. In both models, identical EPA algorithms and exposure factor values were used to calculate the potential dose humans could be exposed via household environment according to Environmental Protection Agency (EPA) SOPs for residential pesticide exposure assessment for indoor environment.

  The CVMP accepted the exposure averaging over 84 days as this rationale is used and accepted by CVMP for direct exposure. The derivation of the subchronic average percent transfer value of 0.48% raised by the AHEG was appropriately addressed. New calculations were provided by the applicant following the experts' recommendations on the application of a factor of 2 to the NOAEL of 50 mg/kg to extrapolate from the NOAEL of the 90-day repeat toxicity study to a long-term NOAEL. The MOEs calculated from the new NOAELs confirm the acceptable risk to the user being well above of 100 (i.e. 1578 and 5007 for child dermal exposure and oral exposure respectively, and 3671 for adult dermal exposure).

Overall, the CVMP considered that the data provided would confirm the safety of Bravecto spot-on solution for dogs and cats when used in accordance with the SPC recommendations.

Benefit-risk assessment further to re-examination

Benefit assessment

Direct therapeutic benefit

The benefit of Bravecto spot-on solution is its efficacy in the treatment of flea and tick infestations in dogs and cats.

Controlled clinical trials conducted in accordance with GCP demonstrated that the product is efficacious in dogs against fleas (*Ctenocephalides felis* and *Ctenocephalides canis*) and ticks (*Ixodes ricinus*,

Rhipicephalus sanguineus and *Dermacentor reticulatus*), and in cats it is efficacious against fleas (*Ctenocephalides felis*) and ticks (*Ixodes ricinus*).

The effect in both target species persists for 12 weeks.

Additional benefits

Bravecto spot-on solution for dogs and cats increases the range of available treatment possibilities for cats.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

For the target animal:

Administration of the product in accordance with the SPC recommendations is generally well tolerated by both dogs and cats.

For the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Appropriate safety advice is included in the SPC.

For the environment:

Bravecto spot-on solution is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, the user and the environment and to provide advice on how to prevent or reduce these risks.

It is recommended to re-start the PSUR cycle for Bravecto to ensure more frequent pharmacovigilance monitoring due to the addition of a new target species (cats). The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 August 2016.

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the treatment of flea and tick infestations in dogs and cats.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for

the user and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion on the benefit-risk balance

The CVMP considered that the overall benefit-risk evaluation for the product is positive.

Final conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded by majority of votes that the application to add a new pharmaceutical form (spot-on solution) for dogs and to add a new target species (cats) for this spot-on formulation is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 1234/2008 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the extension to the marketing authorisation for the above mentioned medicinal product.

Divergent position on a CVMP opinion on the re-examination of the CVMP opinion on the granting of an extension to the marketing authorisation of Bravecto (EMEA/V/C/002526/X/0005)

The undersigned wish to express a divergent position to the CVMP Opinion on this application for a marketing authorisation for a new pharmaceutical form, in particular in relation to the user safety of the product. The concern for user exposure is based on findings in the target animal safety (TAS) studies.

Contamination of control animals in the GLP TAS studies occurred, even though these animals were housed individually under GLP conditions without possibility of physical contact to treated animals or their direct environment. Sometimes high plasma levels were observed in the control animals and it was not single study site specific or target animal specific. In the pivotal TAS study in dogs, all control dogs were contaminated. Fluralaner plasma levels were up to 740 ng/ml. This is not an insignificant level, given the fact that a plasma level of <25 ng/ml in target animals is still proven to be efficacious for the indications of the product. Also in the pivotal TAS study in cats, all control animals were contaminated. How these contaminations in dogs and cats actually took place, could not be elucidated. Because the exact cause of the contamination is unknown, there is uncertainty whether or not the events leading to the contamination are relevant for the household situation.

It is noted that in the GLP TAS studies, great care was taken to avoid cross-contamination. Still, all control dogs and cats got exposed to significant levels of fluralaner. It is therefore uncertain whether or not user safety warnings can actually be sufficient to ensure user safety.

Exposure modelling indicated that indirect user exposure would be of no concern. However, the modelling results are not in line with the findings of indirect exposure as observed in the TAS studies. The undersigned are of the opinion that exposure modelling alone cannot overrule the findings in the TAS studies, and that the findings in the TAS studies must not be ignored.

In conclusion, fluralaner has a high potential for cross-contamination, and there is insufficient information to ascertain that this will not happen in a household situation. People in the household, including children, therefore have insufficient guarantees that the product can be used safely.

London, 17 March 2016

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