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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Credelio to add two new tablet strengths of 12 mg and 48 mg, in a new target species - cats (EMEA/V/C/004247/X/0001)

International non-proprietary name: lotilaner

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

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Introduction

The applicant Elanco Europe Ltd submitted on 12 May 2017 an application for an extension to the marketing authorisation for Credelio to the European Medicines Agency (The Agency) in accordance with Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2c thereof (change or addition of a new strength/potency).

Credelio was first authorised in the EU on 25 April 2017 for the treatment of flea and tick infestations in dogs, and is available as chewable tablets in strengths of 56 mg, 112 mg, 225 mg, 450 mg, and 900 mg. This extension application is to add further, lower tablet strengths of 12 mg and 48 mg, for the treatment of flea and tick infestations in a new target species, cats. The application was validated on 7 June 2017.

The applicant applied for the following indication: For the treatment of flea and tick infestations in cats.

The active substance of Credelio is lotilaner, a systemically acting ectoparasitic. The new target species is cats. The proposed new presentations of Credelio chewable tablets contain 12 mg and 48 mg lotilaner, and are presented in packs containing 1 tablet, 3 tablets or 6 tablets.

The rapporteur appointed is Rory Breathnach and the co-rapporteur is Gábor Kulcsár.

On 19 April 2018, the CVMP adopted an opinion and CVMP assessment report.

On 9 July 2018, the European Commission adopted a Commission Decision granting the marketing authorisation for Credelio.

Scientific advice

The applicant received scientific advice from the CVMP on 4 June 2015 (EMA/CVMP/SAWP/230321/2015). The scientific advice pertained to quality issues relating to the designation of the starting materials for lotilaner. The applicant followed this scientific advice, i.e. the proposed starting materials are in line with the conclusions drawn in the scientific advice.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (version: October 2016). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that 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 has been provided.

Manufacturing authorisations and inspection status

Batch release of the dosage form takes place in France at Elanco France S.A.S., Huningue. The site has

a manufacturing authorisation issued by ANSES (Agence nationale du medicament vétérinaire), Fougères, France. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

Secondary packaging takes place at a site in Switzerland which holds a manufacturing authorisation issued by Swissmedic, Switzerland. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and Switzerland, the sites are considered appropriately certified as complying with GMP requirements.

A GMP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration is issued following an audit of each of the sites between August 2014 and September 2015. The audits of the sites of synthesis and micronisation were performed by the dosage form manufacturer. The audit of the site of manufacture of the intermediate was performed by the final active substance site.

Overall conclusions on administrative particulars

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

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a chewable tablet containing the active substance lotilaner in 2 tablet strengths, 12 mg and 48 mg.

Both tablet strengths are compressed from the same (common) granulate to form tablets of different sizes.

The other components of the formulation are powdered cellulose, lactose monohydrate, silicified microcrystalline cellulose (a co-processed excipient comprising microcrystalline cellulose and colloidal silicon dioxide), yeast powder, vanillin, crospovidone, povidone K30, sodium laurilsulfate, silica colloidal anhydrous and magnesium stearate.

Containers

The tablets are packaged in aluminium/aluminium unit dose blisters supplied within a carton box (secondary packaging). The primary packaging material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The pack sizes of 1, 3 and 6 tablets, for all strengths, have been justified.

Development pharmaceutics

The qualitative and quantitative composition of the drug product was based on the existing formulation of the product for use in dogs. The product is manufactured by producing a granulate with the active substance and some of the excipients (intra-granular phase) which is then mixed with the remaining excipients (extra-granular excipients) and compressed into tablets. Initially, it was intended to develop

these granules to become the commercial formulation; and some clinical studies were performed using granules, and not the final formulation. The intra-granular phase of the formulation is qualitatively and quantitatively identical to the existing formulation for dog, the only difference between the cat and dog formulations is in relation to the flavouring agents used in the extra-granular phase and the tablet size which results in different concentrations of the active substance. Due to the similarity of the formulations much of the information provided in the development pharmaceutical section relates to the original development of the product for dogs.

In order to increase palatability in cats, yeast powder and vanillin are used as flavouring agents whereas a dry meat flavour was used in the dog product. No information regarding optimisation of their concentration is provided however, the flavouring agents are used in other veterinary medicinal products and the robustness of the final formulation is seen in the stability studies which demonstrate the product to be a stable one with no adverse trends on storage.

Method of manufacture

The manufacturing process is a standard wet granulation process with all the intra-granulation excipients (powdered cellulose, lactose monohydrate, povidone K30, sodium laurilsulfate and crospovidone) and the active substance mixed in a high shear granulator equipped with spraying nozzles. Purified water is added and granulation stopped at the appropriate endpoint. The granules are then dried under vacuum until the desired loss on drying is obtained. The granules are then milled through a screening mill before preparation of the final blend. The extra granular excipients (silicified microcrystalline cellulose, yeast powder, vanillin and silica colloidal anhydrous) are then mixed with the granules in a diffusion tumble blender. The lubricant (magnesium stearate) is added and mixing performed to produce the final common blend for compression. The tablets are compressed into the desired weight using a rotary tablet press and bulk packaged in double low density polyethylene liners (LDPE) in a drum. The final primary packaging is a cold form aluminium blister with an aluminium/PVC lidding foil. In-process controls are as established during manufacturing process development and are adequate for this type of pharmaceutical form.

The manufacturing process is a standard one and in accordance with the CVMP guideline on Process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), provision of process validation data in the application dossier is not required. A validation plan for commercial scale batches is provided.

Control of starting materials

Active substance

The active substance, lotilaner, is a member of the isoxazoline class of parasiticides. Lotilaner exhibits stereoisomerism due to the presence of one chiral centre. Enantiomeric purity is controlled routinely by chiral HPLC.

Polymorphism has been observed for lotilaner, and it is routinely controlled by X-ray powder diffraction. Data relating to the manufacture and control of the active substance are identical to that already approved for the dog tablets.

Lotilaner is not monographed in a pharmacopoeia. The proposed in-house specification is acceptable, and includes tests for appearance, identification including polymorphic form, assay and related substances, chiral purity, sulphated ash, water content, loss on drying, residual solvents, particle size and microbial quality. Test methods are well described and are validated in accordance with VICH guideline GL2:

Validation of analytical procedures: Methodology, and Ph. Eur. requirements.

Batch analysis data is provided for 6 production scale batches of the active substance and all results comply with the proposed specification and are consistent from batch to batch. Satisfactory information regarding the reference standards has been presented.

Satisfactory stability data are provided to support the proposed re-test period of 3 years with no specific storage precautions.

Excipients

The excipients of the formulation are all controlled in accordance with their respective Ph. Eur. monographs with the exception of the co-processed excipient, the silicified microcrystalline cellulose, and the excipient yeast powder.

Silicified microcrystalline cellulose is composed of intimately associated microcrystalline cellulose and colloidal silicon dioxide particles, derived from aqueous co-processing prior to drying the material during manufacture. It is not monographed in the Ph. Eur. and is therefore controlled in line with its USP/NF monograph.

A satisfactory in-house specification is provided for the yeast powder.

The list of excipients is included in section 6.1 of the SPC.

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

Magnesium stearate used in the formulation is derived from materials of vegetable origin.

Lactose monohydrate is sourced from milk from healthy animals in the same condition as those used to collect milk for human consumption and it is confirmed that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

The yeast powder is food-grade and it is produced by bio-fermentation. It does not contain products of animal origin.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form. Parameters on the specification are: appearance, identification, water content, active substance content, degradation products, uniformity of dosage units, dissolution, enantiomeric purity, tablet weight, hardness, friability and microbiological contamination. The analytical methods are satisfactorily described and their validation conducted in accordance with the VICH guideline GL2. Satisfactory information regarding the reference standards used for assay of active substance has been presented.

Batch data is provided for four pilot scale batches of each tablet strength. The data demonstrates compliance with the proposed specifications.

Stability

The proposed specification for shelf life is the same as that for release with the following exceptions:

- Uniformity of dosage units and enantiomeric purity are omitted from the shelf life specification. These omissions are acceptable as these parameters are not stability indicating.

A stability study on tablets stored in the proposed bulk intermediate container (double LDPE bags with silica gel desiccant packets in metal drums) was conducted. Testing was conducted on the smallest and largest tablets from two pilot scale batches and samples were stored at monitored warehouse conditions and tested to the release specification. All results are in compliance with the currently proposed specification with no adverse trends observed. Based on the reported results, the proposed bulk tablets shelf life of 13 months stored in the original bulk container is acceptable.

A stability study on tablets stored in the proposed commercial alu/alu blisters was conducted. The tablets were manufactured from pilot scale batches. Samples were stored at 25 ºC/60% RH, 30 ºC/65% RH and accelerated conditions and tested to the release specification up 36 months. Samples were also tested following storage at 50 °C/ambient humidity for 1 month and at 5 °C/ambient humidity. The study is scheduled to continue up to 60 months. A post approval stability protocol is included in the dossier.

All results are in compliance with the currently proposed specification. Dissolution results after 30 minutes are above 85% at all time-points for all batches tested. No degradation products are observed above the reporting threshold and total degradation products remain below the limits

Photostability studies were not conducted as the alu/alu blisters provide protection from light.

As the product has been demonstrated to be extremely stable, the proposed shelf life of 36 months with no special storage conditions when stored in the primary packaging proposed for marketing (alu/alu blisters) is considered acceptable.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product is generally satisfactory. The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and appropriate specifications set.

The active substance lotilaner is manufactured in an eight step synthetic process using four starting materials, followed by micronisation. The applicant received scientific advice from the CVMP on 4 June 2015 (EMA/CVMP/SAWP/230321/2015) pertaining to the designation of the starting materials for lotilaner. The proposed starting materials are in line with the conclusions drawn in the scientific advice and are acceptable. The level of detail included in the description of the active substance manufacturing process is acceptable.

As the manufacturing method is a standard process, it is accepted that full scale validation should be performed post-authorisation in accordance with EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1 Guideline on process validation for finished products.

The finished product specifications are considered appropriate to consistently control the quality of the product. Analytical methods are well described and have been validated in accordance with VICH guideline GL2. Stability data are provided to support the proposed shelf life of the medicinal product of 36 months with no special storage conditions when stored in the primary packaging proposed for marketing (alu/alu blisters).

The product quality is approvable.

Part 3 – Safety

This application is submitted as an extension to the community marketing authorisation of Credelio chewable tablets for dogs. The applicant is proposing the addition of a new target species (cats), for which two new lower strengths tablets have been developed (12 mg and 48 mg). The qualitative and quantitative composition of the cat tablet formulation is based on the existing formulation of the product for use in dogs. The cat tablet formulation is similar to the formulation for dog tablets with the exception of flavouring agents used.

No new safety studies have been conducted with regards to repeat dose toxicity, reproductive toxicity, genotoxicity, or carcinogenicity, and cross-reference is made to data that have already been submitted and assessed for previous application(s). This is considered acceptable.

Pharmacodynamics

Cross-reference has been made to pharmacodynamic studies, which have been submitted and assessed in support of the initial application for Credelio tablets for dogs; this is considered acceptable.

Pharmacokinetics

See Part 4.

Toxicological studies

The CVMP previously assessed two GLP studies investigating the acute oral and dermal toxicity of lotilaner in the rat. The studies were conducted in accordance with relevant OECD guidelines. In the acute oral toxicity study there were no deaths and no clinical signs of toxicity were noted. In the acute dermal toxicity study there were no effects on mortality and no clinical signs were noted. Dermal reactions were confined to incidents of very slight erythema. From the results of both studies it was concluded that the oral LD_{50} and the dermal LD_{50} of lotilaner is greater than the limit dose of 2000 mg/kg.

Two new GLP studies investigating the acute oral toxic and the acute dermal toxic effects of lotilaner administered in the formulation used for the cat tablets were carried out in the rat. The acute oral toxicity study was conducted in accordance with OECD guideline 423 and the acute dermal toxicity study was conducted in accordance with OECD guideline 402. In both studies, it was concluded that the oral LD_{50} is greater than the limit dose of 2000 mg/kg bw and that the active substance lotilaner formulated as tablets for cats it is not toxic to rats by these routes of administration.

The test material is considered to have no significant acute toxicity risk.

Cross-reference has been made to reprotoxicity, genotoxicity and carcinogenicity data, which were previously assessed in support of the initial application for Credelio tablets for dogs; this is considered acceptable.

Tolerance in the target species of animal

See Part 4.

Studies of other effects

In support of the current application, a series of new studies were conducted to investigate the local effects of lotilaner administered in the formulation used for the cat tablets. All studies were conducted to GLP, in accordance with the relevant OECD guidelines and can be accepted as valid.

These studies show that lotilaner, when formulated as Credelio chewable tablets for cats, was not irritant to the skin, was slightly irritant to eyes but did not fulfil the criteria to be classified as an eye irritant and has no potential to induce skin sensitisation.

Excipients

The cat tablet formulation is qualitatively identical (active substance and excipients) to the existing formulation for dog tablets with the exception of flavouring agents used (the dog tablet contains meat flavour, whereas the cat tablets contain yeast and vanilla as flavouring agents). All excipients are either natural food ingredients, approved food additives, or approved for the use in food producing animals (with 'no MRL required' status) or in human pharmaceuticals. During the assessment of the application for Credelio chewable tablets for dogs, the CVMP accepted that '*the excipients are not likely to pose any risk to the user. Therefore, the user safety assessment focuses on the active substance, lotilaner.'* The same conclusion can be drawn for Credelio chewable tablets for cats.

User safety

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

The qualitative and quantitative composition of the cat tablet formulation is based on the existing formulation of the product for use in dogs, the only difference between the two formulations is in relation to the flavouring agents used in the extra-granular phase.

Credelio tablets for cats will be supplied as 12 mg and 48 mg chewable tablets dispensed individually in an aluminium foil/foil blister package with a peelable lid and each tablet strength is available in pack sizes of 1, 3 or 6 tablets. In comparison, Credelio tablets for dogs are authorised to be supplied as 56 mg, 112 mg, 225 mg, 450 mg and 900 mg chewable tablets dispensed individually in an aluminium foil/foil blister package with 1,3 or 6 tablets per blister with blister cavity diameters of 16.6 mm and 34.4 mm.

Given the similarity to the Credelio dog formulation, and noting that there are only minor differences in excipients (flavouring agents), and the fact that the cat tablets are lower in strength of active substance, Credelio tablets for cats are not expected to pose any greater risk to the user than that posed by the authorised Credelio tablets for dogs and the same user risk mitigation measures can be applied.

On this basis the same user safety warnings can be accepted for the cat presentations:

- the inclusion of the statement "Wash hands after handling the product. In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician" in section 4.5 of the SPC, and
- the inclusion of "Keep out of the sight and reach of children" in the product literature.

In addition, adequate information has been presented in the current application to support the claim that the packaging is child proof.

It can be concluded that Credelio for cats, when used as directed in the SPC, will not pose an unacceptable

risk to the user.

Environmental risk assessment

An environmental risk assessment (ERA) was provided according to the guideline on environmental impact assessment for veterinary medicinal products – phase I (CVMP/VICH/592/98-FINAL). Based on the data provided, the ERA can stop at Phase I. The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Cross-reference has been made to toxicological studies, which have been submitted and assessed as part of the initial product application for dogs; this is considered acceptable.

A user risk assessment report in line with current guidance was provided, and the extension does not pose an unacceptable risk to the user, when used in accordance with the SPC.

An ERA was provided according to the CVMP/VICH guidelines. The product is not expected to pose a risk for the environment, when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

Cross-reference has been made to pharmacodynamic studies, which have been submitted and assessed in support of the initial application for Credelio tablets for dogs; this is considered acceptable.

Development of resistance

Lotilaner is a new chemical entity (member of the isoxazoline class of ectoparasiticides). Credelio chewable tablets for dogs was the first veterinary medicinal product containing the active substance lotilaner to be issued a marketing authorisation valid throughout the European Union, in 2017. The applicant stated that there are no reports of resistance to this new class of ectoparasiticides (isoxazolines) in ectoparasites of cats. It can be accepted that that there has not been potential for development of resistance among the target parasites.

Pharmacokinetics

The pharmacokinetic properties of lotilaner in the dog and rat have previously been evaluated by CVMP. In addition, new pharmacokinetic data in cats have been presented. The pivotal pharmacokinetic studies were conducted to GLP standard. Validated methods were used for sample analysis.

Following oral administration to cats, lotilaner is readily absorbed, but slowly eliminated. Following administration of the test product at a single oral dose of 6 mg lotilaner/kg bw in the fed state, the mean maximum blood concentration (C_{max}) was 3079 ng/ml at 4 hours (T_{max}) and the half-life was estimated to be 41.84 days (arithmetic mean) or 28.5 days (harmonic mean). It is suggested that the long terminal half-life provides effective blood concentrations for the entire duration of the inter-dosing interval (one month).

Following oral administration, it was demonstrated that food enhances the absorption of lotilaner and lotilaner displays high systemic absorption in fed cats. In one study, absolute bioavailability following single oral administration was calculated to be 106% in fed cats and 8.4% in fasted cats, and the variability of pharmacokinetic parameters was moderate in the fed group and higher in the fasted group. Therefore, lotilaner should be administered at or around the time of feeding. A statement has been included in section 4.9 of the SPC recommending that the product should be administered with food or within 30 minutes after feeding. In light of the significant difference between oral bioavailability in the fed state compared to the fasting state, and the possible implications for efficacy of the product, a statement has also been included in section 4.4 of the SPC indicating that acceptable levels of efficacy may not be achieved if the product is not administered with food or within 30 minutes after feeding. Furthermore, a statement has been included in section 5.2 of the SPC indicating that lotilaner is approximately 10 times more bioavailable when administered with food.

Based on the ADME study in the target species, it is evident that lotilaner is systemically distributed and reaches the highest tissue concentrations in fat, followed by kidney and liver. The major route of elimination is biliary excretion. Renal clearance is the minor route of elimination (less than 10% of the dose). The unmetabolised lotilaner is the largely predominant form in blood, tissues, bile and faeces. A number of slightly more polar metabolites were identified in faeces. Urinary metabolites were considered more polar but were present at low concentrations and urinary excretion was negligible.

Based on data generated in the context of the target animal safety study, the lotilaner pharmacokinetic profile changed during the course of the study as animals grew from kittens to young cats. The change in pharmacokinetics was attributed to expected growth rather than to any specific changes induced by the repeated administration of lotilaner.

In the pivotal target animal safety (TAS) study conducted in 8 week old kittens at the time of first treatment administration, it was demonstrated that elimination half-life was shorter in very young animals (7.2 days following first administration at 8 weeks), as compared to cats aged approximately 9 months (23.8 days following administration at 40 weeks - end of the study). While toxicokinetic data in a number of safety studies indicate that the potential for accumulation in very young cats is limited (due to the relatively short T1/2), accumulation potential increases as $T_{1/2}$ increases. In the pivotal target animal safety study, systemic exposure to lotilaner, as indicated by $AUC_{0\text{-}672hr}$, increased following repeated administration. Accumulation was assessed by calculating the ratio between $AUC_{0\text{-}672hr/Dose}$ for months 5 or 8 and $AUC_{0\text{-}672hr}$ for month 1. At 26 mg/kg (maximum recommended treatment dose) the mean accumulation ratios were 2.15 and 2.92 for month 5 and month 8, respectively. This suggests that steady state had not been reached with the potential for further accumulation with additional repeated treatments. The applicant was requested to comment on the possibility for continued accumulation of lotilaner following repeated administration in adult cats and its significance in terms of target animal tolerance (that is, can the findings of the pivotal TAS study be extrapolated to adult cats). Based on the applicant's response, it is accepted that the design of the pivotal TAS study with an extended treatment duration of 8 months covered the period of kittens growing to young adults and the period of expected drug accumulation in adult cats. Furthermore, the results of the pivotal target animal safety study indicate a margin of safety of ≥5-fold of the maximum therapeutic dose level (130 mg/kg) for a treatment period of 8 months. Therefore, the target animal safety data can be considered adequate to support safety in adult cats.

In addition, given that elimination half-life is shorter in young animals compared to adult cats, the applicant was requested to comment on potential implications of this phenomenon for efficacy evaluation in kittens (that is, while the effect against target parasites has been shown to persist for 28 days (one month) in adult cats, can a similar duration of persistent effect be assumed for kittens/young cats given the age related effect on clearance).

In response, the applicant provided a statistical analysis of the efficacy data from field studies in kittens aged less than or equal to 5 months at the time of first treatment. Pooled efficacy data from two field studies assessing efficacy against fleas in the EU and USA were analysed for this age group (n=27 at Day 14, n=51 at Day 28/30, n=19 at Day 60 and n=12 at day 90). Following monthly administrations, satisfactory efficacy levels were achieved at Day 28/30, 60 and 90; however, the % efficacy at Day 14 (93.9%) was below the required threshold of 95%.

Efficacy data from the pivotal EU field study assessing efficacy against ticks (*I. ricinus*), was analysed (n=4). Kittens were treated at Days 0, 28±2, 56±2. The % efficacy against ticks was 100% at all timepoints (7±1, 14±2, 21±2, 28±2, 42±2, 56±2, 70±2, 84±2).

In fleas, the sample sizes were considered to be sufficient for the purpose of assessing efficacy in kittens. When all subjects (kittens) are considered, the required efficacy threshold is not achieved at Day 14 (93.9%). While the applicant suggests that one kitten in one study may not have been administered the treatment correctly, no further information to support this theory was provided and the reason for the lack of efficacy observed in this animal at Day 14 remains unclear. That said, it was noted that efficacy was uniformly high and above the required threshold for fleas (≥95%) at all counting times when this animal was excluded from the analysis. Notwithstanding this deviation from the guideline (i.e. an efficacy threshold of 95% was not achieved when all kittens are considered), and taking into account the findings of the pivotal dose determination study , where for *C. felis*, adequate efficacy was achieved (≥95% reduction in flea count, for up to 36 days after product administration at a test product dose of 3 mg/kg and 43 days after test product administration at a dose of 6 mg/kg) together with the PD/PK analysis, there is sufficient evidence to support the applicant's conclusion that the product will be efficacious against fleas (*C. felis* and *C. canis*) in kittens 5 months of age or younger.

In ticks, data were considered insufficient to support efficacy in young cats, and the applicant concluded that the claim for efficacy against *I. ricinus* should be limited to cats over 5 months of age. An appropriate statement has been included in section 4.4 of the SPC.

Target animal tolerance

Four target animal safety (TAS) tolerance studies were conducted. The pivotal study was conducted to GLP standard in accordance with the requirements of VICH GL 43, whereas three other studies were classed as exploratory, non-GLP studies.

The pivotal TAS study was conducted to evaluate tolerance in 8 week-old kittens (4 males/4 females per group) when the test product was repeatedly administered in monthly intervals for 8 months. The final formulation was administered at doses of 0, 26 mg lotilaner/kg bw i.e. the maximum recommended treatment dose (1 x RTD), 78 (3 x RTD) and 130 (5 x RTD). Animals were fed within 30 minutes prior to dosing, which represents a worst-case with respect to maximum plasma concentrations following dosing.

There were no treatment-related (toxicologically relevant) changes in the daily clinical observations; wet cat food consumption; ophthalmoscopic, physical and neurological examinations; coagulation, clinical chemistry or urinalysis parameters. There were no test-article related macroscopic or microscopic findings at terminal necropsy.

One female cat treated at 78 mg/kg bw (3 x RTD) was found dead on Day 143 following administration of anaesthesia for ECG measurements. Mild unilateral tubular regeneration in the kidneys were observed at necropsy; however, these were not considered treatment related and the cause of death was undetermined based on post-mortem evaluations. The death was considered most likely an aberrant response to anaesthesia.

A decrease in dry food consumption was observed in males compared to controls at all dose levels. Body

weights of the males at 78 mg/kg bw (3 x RTD) were significantly less than those of the control males, averaged over all timepoints. The changes were considered small and non-adverse, and since no effects were observed in males at the higher dose of 130 mg/kg bw (5 x RTD), there is no clear relationship to treatment.

One animal treated at 130 mg/kg bw (5 x RTD) had electrical alternans on the terminal ECG. A test article related effect was considered possible; however, given that intraventricular conduction disturbances are not associated with clinical signs, the conduction disturbance was not considered adverse. Although no electrical alterans was observed in the pilot TAS studies, it is noted that in one of these studies 'the heart rate was slower and the RR interval longer in males following the 160 and 200 mg/kg bw doses on Days 6 and 87. Similar results were observed in heart rate of females following the 80, 160, and 200 mg/kg bw dose and the RR interval was longer in females following the 80 and 160 mg/kg bw doses.' The applicant was requested to clarify if there is any association between the observed cardiac effects in both studies and to comment further on the need for information on the potential for effects on the cardiovascular system to be included on the SPC.

Based on the response provided by the applicant, it is accepted that electrical alternans occurred as a single event (one animal in one study) in the four TAS studies. It is considered that the conduction disturbance is not test item related and is considered of no clinical relevance. The statistically significant differences in heart rate between the high dose treated groups (160 and 200 mg/kg bw, approximately 6-8 x RTD) and the control group in the pilot TAS study were due at least in part to a heart rate increase from pre-dose values in the control group rather than changes resulting from the test article administration.

The applicant therefore concluded that there does not appear to be an association between the cardiac effects observed in the two studies. Taking account of the findings above, the CVMP agreed with the applicant's conclusion and concluded that it is not necessary to include a warning statement regarding cardiac effects associated with treatment in the SPC.

In relation to haematology, a statistically significant decrease in neutrophils was consistently observed in males and females at multiple timepoints (Day 8 through 223) at all dose levels in comparison with control. However, the effects were considered small, not dose-dependent and did not result in adverse clinical signs. On this basis, it is not considered necessary to include a warning statement regarding the reduction in neutrophils associated with treatment on the SPC.

Statistically significant organ weight changes in the brain, thyroids/parathyroids, kidney, adrenal, spleen, and thymus were observed. However, as neither changes in microscopic examinations nor relevant clinical pathology changes were seen, these findings were considered incidental. This can be accepted.

The conclusion of the applicant can be accepted that the changes observed in this study are unlikely to be toxicologically relevant given they were either not associated with clinical signs, were transient or inconsistent in terms of gender or time and/or without a dose response relationship. For further information on the toxicokinetics, see the pharmacokinetic section above.

Although not a feature of the pivotal target animal safety study, it is noted in various laboratory and clinical efficacy studies that mild gastrointestinal effects (vomiting/loose stool/diarrhoea/blood in faeces) were observed in a number of cats within a short period of time following treatment. While the effects are accepted as being mild and transient, given their proximity to treatment administration, the applicant was requested to comment on a possible association with treatment and the need for such effects to be stated in the SPC. However, based on the applicant's response, a causal association between the test product and such effects was considered to be unlikely. Consequently, it can be accepted that it is not necessary to include a warning statement regarding such adverse events associated with treatment in the SPC.

No data have been provided to support safety for use in pregnant or lactating queens. However, given

that the laboratory studies in rats have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity of males and females, it is accepted that the product should be used according to the benefit/risk assessment by the prescribing veterinarian. An appropriate recommendation is included in section 4.7.

Dose justification

The minimum recommended dose was determined first by pharmacokinetic/pharmacodynamic modelling using early development studies. A similar approach to dose finding was used in support of the application for the authorisation of Credelio chewable tablets for dogs and the CVMP concluded that '*the used approach to dose determination is generally acceptable. It is accepted that the approach of informing the dose determination by dose-concentration-response modelling is well established across therapeutic areas and can equally be applied in the field of ectoparasiticides.'* On this basis, the approach used to support the proposed dose and treatment interval in the current application is considered acceptable.

The objective of this modelling and simulation activity was to characterise the dose-concentration-response relationship of lotilaner in cats, integrating data from different studies and experimental conditions (e.g. discovery, dose ranging, and pilot efficacy studies), and to support the choice of doses to be carried into the next stage of development. Data from eight studies were used to characterise the dose rate-blood concentration-effectiveness relationship of lotilaner in cats.

Based on a concentration-response analysis, it appears that *Amblyomma americanum* and *Dermacentor variabilis* were the least susceptible tick species of the spectrum tested followed by *Dermacentor reticulatus* and *Ixodes scapularis* followed at some distance by *I. ricinus*. *Ctenocephalides felis* was more sensitive to lotilaner than *Ixodes ricinus*. Therefore it can be accepted that fleas are more susceptible to lotilaner than ticks.

The outcome of the dose-concentration-response analysis was that in cats, a monthly lotilaner dose (formulated as tablet or granule/gravy) of 17.50 mg/kg bw and 21.25 mg/kg bw is expected to provide 90% efficacy in at least 75% of the population throughout the entire dosing period against *Amblyomma americanum* and *Dermacentor variabilis*, respectively. For *Ixodes ricinus*, the effective dose was estimated to be 5.50 mg/kg bw. Given the susceptibility of fleas to lotilaner, a dose of 3.00 mg/kg bw was expected to provide 95% efficacy in at least 75% of the cat population for a period of 28 days.

Although simulations were performed for all parasites included in the model (*A. americanum, D. variabilis, D. reticulatus, I. ricinus, I. scapularis* and *Ctenocephalides felis*), the claimed target parasites in the current application are fleas (*Ctenocephalides felis* and *Ctenocephalides canis*) and *Ixodes ricinus* only.

Based on the presented data, it appears that a minimum dose of 6 mg lotilaner/kg bw should ensure satisfactory efficacy against the claimed target parasites for the duration of the proposed treatment interval of one month. The adequacy of this dose has been further investigated and confirmed by dose determination and dose confirmation studies. However, the CVMP also noted that the data presented indicate that a dose of 6 mg lotilaner/kg bw is unlikely to be effective against a number of other tick species that are found in Europe and which may also infest cats. (See further comment below on the adequacy of the recommended minimum treatment dose.)

Dose determination / finding studies

One pivotal dose determination study under GLP conditions was conducted in Ireland to determine the minimum effective dose of lotilaner administered orally against *Ctenocephalides felis* and *Ixodes ricinus* in experimentally infested adult cats. The study was conducted in accordance with the CVMP Guideline for

Testing and Evaluation of the Efficacy of Antiparasitic substances (EMEA/CVMP/EWP/005/2000-Rev.3).

Lotilaner was administered as a preliminary 20% w/w granule formulation at dose rates of 0, 1.5 mg/kg bw, 3 mg/kg bw, 6 mg/kg bw, and 12 mg/kg bw with "gravy" (a liquid made out of meat extracts) and at a dose of 6 mg/kg bw without gravy. The fleas and ticks used in this study were obtained from colonies which were sourced from countries in Europe.

Based on the results of this study, adequate efficacy (≥90% reduction in live tick count) against *I. ricinus* was achieved for up to 36 days after product administration at a dose of 6 mg lotilaner/kg with or without gravy.

For *C. felis*, adequate efficacy (≥95% reduction in flea count) was achieved for up to 36 days after product administration at a dose of 3 mg lotilaner/kg bw with gravy; up to 43 days at a dose of 6 mg lotilaner/kg bw with gravy and for up to 50 days at a dose of 6 mg lotilaner/kg bw without gravy. For both test parasites, the duration of activity (persistent effect) increased with increasing dose. Taking the findings of this study together with the PD/PK analysis detailed above, it would appear that 6 mg/kg bw at monthly intervals is an appropriate dose rate to be used in the confirmatory efficacy studies.

However, this study was conducted in adult cats (15-85 months old) and the applicant was requested to comment to what extent the findings of this study (and the various dose confirmation studies) can be extrapolated to kittens/young cats, given that systemic exposure is expected to be less in young compared to adult cats. This is considered an important consideration because it is clear that a 50% reduction in systemic exposure will have a significant impact on efficacy (e.g. for *I. ricinus*, the required efficacy threshold was not achieved at Day 22 and thereafter at a test product dose of 3 mg/kg bw). Based on the results of a statistical analysis of the efficacy data from field studies in kittens aged less than or equal to 5 months at the time of first treatment together with the PD/PK analysis, it is accepted that the product will be efficacious against fleas (*C. felis* and *C. canis*) in kittens 5 months of age or younger. However, the claim for efficacy against ticks (*I. ricinus*) should be limited to cats over 5 months of age (see further comment above on pharmacokinetics).

Dose confirmation studies

Clinical studies evaluating efficacy against *I. ricinus* and *C. felis* consisted of one pivotal dose determination study (summarised above), thirteen laboratory dose confirmation studies and three field studies.

C. felis was the only flea species evaluated in the laboratory studies; however, since available *in vitro* data suggest that *C. felis* is the least sensitive (susceptible) of the two flea species the CVMP accepted that the efficacy findings for *C. felis* can be extrapolated to *C. canis.*

Laboratory dose confirmation studies were conducted in Europe, the USA and South Africa. All studies were parallel group design, blinded, randomized, negatively controlled and performed according to VICH GL 9: Good Clinical Practices (GCP). The pivotal studies conducted in Europe were largely performed according to the CVMP Guideline for Testing and Evaluation of the Efficacy of Antiparasitic substances (EMEA/CVMP/EWP/005/2000 - Rev.3). The animals that were included in the studies were mainly European domestic shorthair cats, male and female, ≥ 6 months old, were in good health and were not lactating or pregnant. The number of cats used in the pivotal laboratory studies was in line with the guideline (a minimum of 6 cats per group).

In the pivotal laboratory studies, group allocation was by ranking the cats by descending parasite infestation rates and random allocation to the study groups, including at least 8 cats in each treatment group. Cats received either a single oral dose of 6 mg lotilaner/kg bw or no treatment (negative control). Given the increased bioavailability after feeding (see pharmacokinetic section), the test item was administered within 30 minutes after feeding, in line with the recommendations in the SPC.

Fleas

Nine laboratory dose confirmation studies were conducted to demonstrate efficacy against fleas.

Killing effect (fleas)

The pivotal dose confirmation study was conducted in Switzerland with European flea isolates. Flea infestations (*C. felis*) were conducted 24 hours before treatment administration, and weekly after treatment administration (up to five weeks), by placing approximately 100 adult unfed fleas directly on each cat. Flea comb counts that covered the entire body surface of the animals were conducted 24 hours after treatment administration (on Day 0) and after each subsequent weekly infestation.

The available data showed that a reduction of more than 95% in flea count was achieved within 24 hours after treatment administration, and this level of efficacy persisted up to day 35 post treatment. The data support a claim against *C. felis* when the test product is administered at a dose of 6 mg/kg bw to adult cats.

Results from another study conducted in the USA supported these findings. The test product administered to adult cats as a single minimum dose of 6 mg/kg bw treated existing fleas and showed an acceptable level of efficacy for 28 days (>95% reduction in flea count achieved within 24 hours after treatment administration, and this level of efficacy persisted up to day 35 post treatment).

In a third study efficacy results could not be reliably interpreted, due to an inadequate flea retention rate in a number of control animals at various study timepoints in this pilot study. Therefore, the study was not considered further.

Speed of kill (fleas)

In addition to the standard dose confirmation laboratory studies, four GCP studies were conducted to investigate the speed of kill against fleas at timepoints up to 12 hours after treatment or infestation.

The pivotal study was a blinded, randomized, negative controlled laboratory efficacy study conducted in Switzerland using an EU flea isolate (n=32). Lotilaner tablets were given at a dose of 6 mg/kg bw. Flea counts were performed weekly (D0, D7, 14, 21, 28 and 35), 8h and 12h after product administration and subsequent weekly flea infestations. The test product was efficacious against existing and new flea (*C. felis*) infestations at 8 and 12 hours after administration or flea infestation until Day 35.

In addition, the applicant provided three further studies:

A pilot study conducted in Switzerland used an EU flea isolate with flea counts at 4, 6 and 8 hours after product administration and subsequent weekly flea infestations. Satisfactory efficacy (>95%) was achieved at 6 hours post infestation on Day 14 only. On Days 21 and 28, efficacy was below the standard threshold at 6 hours and 8 hours post-infestation, respectively. The available data do not support a speed of kill claim against fleas of less than 8 hours.

Another pilot study was conducted in South Africa using a US flea isolate. Satisfactory efficacy (>95%) was achieved at 12 hours post infestation on Days 21 and 28; however, efficacy was below the standard threshold at 8 hours post-infestation on those days. The available data do not support a speed of kill claim against fleas at 8 hours.

A third supportive study was conducted in South Africa using a US flea isolate. Satisfactory efficacy (>95%) was achieved at 12 hours post treatment on Day 0; however, efficacy was below the standard threshold at 6 hours post-infestation on Days 0, 7 and 14. In addition, efficacy was below the standard threshold at 12 hours post-infestation on Days 7 and 14. Due to lower than expected efficacy, the study was terminated early (that is, flea infestation and counting was not conducted on Days 21 and 28). The available data do not support a speed of kill claim against fleas at 8 hours.

While it is acknowledged that the findings of the pivotal European speed of kill study demonstrated a speed of kill of 8 hours against both existing and new flea infestations in accordance with the current guideline, it is noted that efficacy was assessed after the claimed 8 hours on Day 0 for pre-existing flea infestations in three other studies. Adequate efficacy against fleas at 12 hours post treatment/infestation was confirmed at all timepoints in three of four studies conducted. Accordingly, the claimed speed of kill of 8 hours against fleas is restricted to existing flea infestations, and a speed of kill claim of 12 hours against new flea infestations can be accepted. Section 5.1 of the SPC has been updated accordingly.

Simulated home environmental studies (fleas)

Two studies, one conducted in the EU and one from the USA, investigated the efficacy of the product when administered at the recommended dose on two occasions at monthly intervals in the prevention of *Ctenocephalides felis* infestations on cats in a simulated home environment. The simulated home environment contained a wooden resting box containing a raised floor with sisal carpet and a raised shelf with carpet. In both studies, the test product was administered orally on two occasions at a dose rate of 6 mg/kg bw, once on Day 0 and once on Day 30. Each cat was experimentally infested with 100 ± 5 viable unfed adult *C. felis* on a number of occasions prior to Day 0 and animals were re-infested with fleas removed at the time of counting. Each cat was infested with fleas in its pen. Flea counts were performed on Study Days 9, 14, 21, 29, 39, 44 and 51. Fleas were counted and removed on Day 60.

The EU GCP study was conducted in Ireland using a European flea isolate. Fleas at the time of counting were categorized as live, moribund or dead. Efficacy was based on live flea counts only (that is, for the purpose of calculating efficacy, moribund fleas were classified as dead). In accordance with the current guideline (EMEA/CVMP/EWP/005/2000-Rev.3), this approach is not accepted – moribund should be classified as live. Furthermore, efficacy could not be demonstrated at all post-treatment timepoints (flea count reduction of 94.5% on Day 21). The applicant was requested to recalculate the results of the study on the basis that moribund fleas are classified as live fleas and, noting that the standard efficacy threshold of >95% is expected to be achieved at each sampling timepoint, to justify how the results of the study can be considered supportive of the claim that the product "kills existing and newly emerged fleas on cats before they can lay eggs. Therefore, the product breaks the flea life cycle and prevents environmental flea contamination in areas to which the cat has access." Based on the recalculated results in which moribund fleas are reclassified as live fleas, adequate efficacy still falls below the guideline requirements at one time point (93.8% on Day 21) following administration of the product; however, adequate efficacy (≥95%) was achieved at all other timepoints (on Days 9, 14, 29, 39, 44, 51 and 60) following a repeat administration of the test item. While it is acknowledged that in accordance with the current guideline, the standard efficacy threshold of >95% is expected to be achieved at each sampling time point, based on the pharmacokinetic data, the flea speed of kill data, noting the biology of the parasite and the supporting data of the simulated home environment studies, it can be accepted that the product will kill existing and newly emerged fleas on cats before they can lay eggs.

USA study: This study was conducted in the USA using a US flea isolate. Efficacy was assessed on the basis of total live flea counts (live+moribund) using an efficacy threshold of ≥ 95% (in accordance with current guidance). Efficacy was below the standard efficacy threshold for fleas at two timepoints (88.21% on Day 21 and 85.33% on Day 30); however, adequate efficacy was achieved at all timepoints (98.77% on Day 39, 98.44% on Day 44, 99.53% on Day 51 and 99.53% on Day 60) following a repeat administration of the test item. Notwithstanding the failure to achieve adequate efficacy at two timepoints following first administration of the product, it can be accepted that monthly oral administration of the test item at approximately 6 mg/kg bw was effective at reducing *C. felis* infestations on cats held in a flea infested environment.

Ticks

Four studies were conducted to demonstrate the efficacy against ticks (*I. ricinus).*

Killing effect (ticks):

Two GCP confirmatory studies conducted in Europe using tick isolates that originated in Europe were provided in support of the killing effect of the product against *I. ricinus*. Both studies were generally conducted in line with guideline requirements. The negative control animals maintained adequate tick infestations. It can be accepted from the findings of these studies that the immediate (on Day 2) acaricidal efficacy of lotilaner against *I. ricinus* in adult cats was ≥90% and the residual efficacy (on Day 9 through 37) was ≥90% for 37 days after treatment. However, in line with the previous comment regarding the adequacy of the dose (see dose determination), the applicant was requested to comment "to what extent the findings of this study (and the various dose confirmation studies) can be extrapolated to kittens/young cats given that systemic exposure is expected to be less in young compared to adult cats. This is considered an important consideration because it is clear that a 50% reduction in systemic exposure will have a significant impact on efficacy (for *Ixodes* [in the pivotal dose determination study], the required efficacy threshold was not achieved at Day 22 and thereafter at a test product dose of 3 mg/kg bw)." Due to insufficient data to support efficacy against fleas in young cats, the applicant concludes that the claim for efficacy against *I. ricinus* should be limited to cats over 5 months of age. See further comment above on pharmacokinetics.

Speed of kill (ticks)

Two studies were conducted to characterize the speed of immediate acaricidal efficacy of lotilaner following treatment administration on pre-existing infestations and the speed of acaricidal efficacy following weekly re-infestations after treatment against *I. ricinus.*

A pilot study conducted in South Africa using an EU tick isolate was terminated prematurely on Day 16 due to unexpectedly poor efficacy. Therefore, the study was not considered further.

The pivotal dose confirmation study was conducted in Ireland using an EU tick isolate. Ticks were counted at three timepoints (12, 18 and 24 hours) post treatment (Study Day 0) or infestation (Study Days 7, 14, 21, 28 and 35). Given that information on speed of kill for ticks should be based on the time point when ≥90% efficacy (standard efficacy threshold for ticks) is achieved and should be relevant to the whole treatment period (in this case, Day 0 to at least Day 28), the data generated support a speed of kill for ticks of 18 hours against ticks (*I. ricinus*) already attached to the animal prior to administration, and 24 hours against new tick infestations.

The CVMP agreed that the findings of the pivotal European speed of kill study provide sufficient scientific evidence of the claimed speed of kill against ticks (*I. ricinus*) in accordance with the current guideline.

Palatability

A non-GLP study was conducted to evaluate the palatability of two tablet strengths (final formulation) containing either 12 mg or 48 mg of lotilaner in fasted laboratory cats (n=18) when freely offered without food. Based on the results of this study, it would appear that the 12 mg and 48 mg chewable tablets for cats can be considered equally palatable: under the conditions of the study both tablet strengths showed acceptance scores higher than 80%. However, in this study, the assessment of palatability was not conducted in accordance with the CVMP guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011).

Acceptance/palatability was also assessed in two of the three field trials submitted in support of this application (see below). In both of these studies (representing field use), voluntary consumption (accepting unaided) of the test item by cats was less than 50%, and did therefore not fulfil the

requirements outlined in the CVMP Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011).

Based on the totality of data, it is not accepted that the product will be voluntarily accepted by the majority of the target population (under normal conditions of use). The wording in section 4.9 of the SPC has been amended accordingly.

Clinical field trials

Three field studies were submitted. Two of the studies were conducted in the European Union and one study was conducted in the USA. All studies used lotilaner tablets for cats at a minimum dose rate of 6 mg/kg administered orally to cats at monthly intervals for either one or three months, in the treatment and control of natural infestations of fleas and/or ticks. The test product was administered under fed conditions. The test product used in the field studies is the product intended to be marketed.

Field studies were conducted in accordance with the VICH GL9 guideline on Good Clinical Practices (CVMP/VICH/595/1998) and the European field studies were largely performed according to the Guideline for Testing and Evaluation of the Efficacy of Antiparasitic substances (EMEA/CVMP/EWP/005/2000 - Rev.3). Field studies were designed as randomised, single blinded, multi-centre studies where efficacy was evaluated against an appropriate positive control. The cats that were included in the studies were of various breeds; long and shorthair, males and females; in good health; at least eight weeks of age and were not lactating or pregnant. In all three studies, the test populations are considered representative of the target population.

Fleas

EU study

This one-month GCP multicentre field study conducted in 17 veterinary practices in France and Spain aimed at demonstrating the efficacy and safety of lotilaner chewable tablets at the minimum dose of 6 mg/kg in the treatment of fleas on naturally infested cats. Efficacy against flea allergy dermatitis was also evaluated. The primary efficacy criterion was the average efficacy of the test product compared to the control product over the entire treatment period compared to baseline based on counts of fleas (percentage reduction in flea counts from baseline at the post-treatment timepoints, average of all visits). The secondary efficacy criteria were the efficacy of test product compared to the control product for each visit compared to baseline based on flea counts (percentage reduction of flea counts for each visit, separately) and assessment of signs of Flea Allergy Dermatitis (FAD) (alopecia, crusts, erythema, hyperpigmentation, military dermatitis, papules, pruritis, scales, eosinophilic granuloma, eosinophilic plaque and eosinophilic ulcer and total FAD score) for primary cats with FAD on Day 0 (FAD Scores were assessed on Days 0, 14±2, 28±2).

Study animals were administered Credelio chewable tablets orally by the animal owner under fed conditions (last meal taken less than 30 minutes before treatment) or a topically applied flea treatment product containing fipronil and (s)-methoprene on Day 0. Lotilaner was administered at the recommended minimum dose 6 mg/kg bw (exposure range 6-22.9 mg/kg bw) and the positive control was administered in accordance with the label recommendations. Households with a maximum of 3 cats and 2 dogs were eligible to be included into the study. Each household had one primary cat which was evaluated for efficacy and safety. Secondary cats in the household were treated with the same product as the primary cat but were only assessed for safety during the study. All cats in the same household received the same treatment (the test product or the control product).

Efficacy was evaluated in 182 primary cats (53 pure bred and 129 crossbreeds, 105 males and 77 females, 0.17 to 14.00 years, 1.0 to 8.7 kg bodyweight). 121 primary cats were administered the test product and

61 primary cats were administered the control product. Safety was determined in 320 cats. A total of 318 of 320 cats completed the study on D 28±2. Flea counts and clinical signs were monitored at Day 0, 14±2 and 28±2.

Prior to treatment on Day 0, the arithmetic mean flea count was 15.75 for cats treated with the test product and 16.92 for cats treated with the control product. Based on the primary efficacy parameter the test item was confirmed to be non-inferior to the control product at all timepoints. The percentage efficacy for the entire study period was 97.4% (arithmetic mean) for the test product group and 47.6% (arithmetic mean) for the control product group. The efficacy on Day 14 was 96.9% and 50.6% for animals treated with the test product and the control product, respectively. By Day 28, the efficacy was 97.9% (test product) and 44.5% (control product). Analysis of the confidence intervals for flea counts revealed that non-inferiority could be established for lotilaner and also superiority could be demonstrated in favour of lotilaner on days 14, 28 and for the entire study period.

FAD was diagnosed in 16 cats included in the study on day 0, 10 cats in test product group and 6 cats in the control product group. Comparison of clinical signs of FAD showed that animals treated with the test product had statistically significantly lower levels of pruritus on days 14, 28 and for the entire study period ($p<0.05$) compared with animals treated with the control product. The total FAD score was significantly lower ($p<0.05$) in animals treated with the test product compared with the control product on day 28 and for the entire study duration. Given that the findings of the study support the efficacy claim against fleas, and noting the improvement in clinical signs of FAD over the course of the study, the proposed claim for use as part of a treatment strategy for the control of flea allergy dermatitis can be accepted.

Occasional adverse events were observed in animals treated with the test product. These included vomiting in two animals; one administered the test product on Day 0 and the other on Day 4. Given the low frequency of emesis observed in the various laboratory and clinical efficacy studies, the effects are considered more likely to reflect normal/sporadic occurrence of vomiting in cats than a treatment related effect.

Pruritus and alopecia in three animals and behavioural disorders (two animals were quieter than usual, one animal was self-licking and one animal was anxious) were reported. The skin and behavioural disorders are possibly related to the infestation with parasites and handling during clinical examination, respectively; and not considered an effect of lotilaner.

Based on the results of this study, it is accepted that a single oral dose of the tested product is efficacious for the treatment of flea infestation (*Ctenocephalides canis, C. felis*) under natural conditions and may support the treatment of the FAD. The test item is generally well tolerated.

USA study

This 3-month GCP multicentre field study conducted in 11 small animal veterinary clinics in the USA aimed to demonstrate the efficacy and safety of lotilaner for cats. The study also aimed to assess the effect of lotilaner tablets on clinical signs (pruritus, erythema, scaling, papules, alopecia, and dermatitis/pyodermatitis) associated with flea allergy dermatitis (FAD) and to evaluate the activity of the product against ticks on cats naturally infested. Acceptance of the tablets was also assessed.

A total of 343 cats from 208 households were enrolled. Cats were at least 8weeks old, with a bodyweight of at least 0.9 kg, clinically healthy and from households with at least 3 cats. Primary cats were evaluated for treatment efficacy, safety, and when applicable the effect of lotilaner tablets on clinical signs associated with FAD. Supplementary cats (i.e. other treated cats in the same household), regardless of flea count on Day 0 had no further flea or tick counts performed during the study. Cats were allocated in a ratio of 2:1 to one of two treatment groups: test product or control product in a randomized block design. Overall 188 cats (126 cats administered the test product and 62 cats administered the control product) were included in the assessment of effectiveness against fleas. The safety population included 341 cats (180 females and

161 males; 228 cats were administered the test product and 113 cats were administered the control product). In order to identify the primary cat in a household, all cats had flea and tick comb counts performed on Day 0 (combing the entire body of the cat for a minimum of 10 minutes). In addition to Day 0, flea comb counts were performed within ±2 days of Days 30, 60 and 90 on the primary cats only.

Enrolled cats received either lotilaner or a topically applied flea treatment product containing fipronil and (s)-methoprene once monthly on Day 0, 30+/-2 and 60+/-2 approximately 30 minutes after food. Mean dose rates for the three dosing periods of the test product were approximately 11 mg/kg bw and the control product was administered in accordance with label recommendations.

In terms of efficacy, according to the current guideline, flea infestations and counts should be conducted every 2 weeks in field studies and the efficacy of the proposed product should be ≥95% for adult fleas. However, in the present study, flea infestation and counts were only conducted monthly. The mean efficacy (reduction in flea count) compared to baseline was above 95% at all times (day 30, 60 and 90 after treatment) when using the arithmetic mean and the product was non-inferior to the control product at all timepoints. Seventy seven animals in the test product group and 34 animals in the control product group were used in the FAD population; some of these subjects were excluded from the FAD analysis on a per-visit basis. Cats in the test product group improved in terms of pruritus (96%); erythema (100%); desquamation (100%); papules (100%); alopecia (100%); pyodermatitis (100%) between day 0 and Day 90. In comparison, cats in the control product group improved in terms of pruritus (62%); erythema (38%); desquamation (69%); papules 75%); alopecia (50%); pyodermatitis (64%). Noting the improvement in clinical signs of FAD in the test product group over the course of the study, the findings of this study can be considered supportive of the proposed claim for use as part of a treatment strategy for the control of flea allergy dermatitis in cats.

Lotilaner chewable tablets were voluntarily consumed (unaided acceptance or in food) on 46.9% of all 648 occasions offered to primary and additional test cats.

Regarding safety, 60 cats (26%, 120 clinical signs) treated with the test product experienced adverse events. The most common adverse events were skin-related signs which are considered most likely to be related to the parasite infestations. While the nature and frequency of adverse events in the test product and control product groups were largely comparable, there were some differences noted: diarrhoea, renal insufficiency, sneezing and oedema were recorded for 4, 4, 4 and 3 animals in the test item group, whereas they were observed in 0, 1, 0 and 0 cats in the control product group. The applicant was requested to comment on a likely association with treatment. Based on the applicant's response, a causal association between the test product and such effects is unlikely. Consequently, it is not necessary to include a warning statement regarding these effects in the SPC.

Ticks

EU study

This 3-months multicentre field GCP study conducted in Germany, Hungary and Portugal aimed at demonstrating the efficacy, safety and voluntary acceptance of lotilaner chewable tablets at the minimum dosage of 6 mg/kg bw at monthly intervals for three months, in the treatment of ticks on naturally infested cats.

309 animals were enrolled in the study (53 purebred and 256 crossbreeds, 148 males and 161 females, 0.2-17 years of age at enrolment, 1.5 to 8.1 kilograms body weight at enrolment. The majority of the population (>80%) were kept outdoors). Forty seven percent (n =79) of the cats came from a single cat household, 24% (n =40) of the primary cats were included from multi-cat household with one supplementary and 30% (n =50) of the primary cats with 2 supplementary cats. At enrolment 104 cats were infested with *Ixodes ricinus*, 46 cats were infested with *Rhipicephalus sanguineus*, 41 cats were infested with *Dermacentor reticulatus* and 12 cats were infested with *Ixodes hexagonus.*

The efficacy of the test product (n=112) and the control product (n=57) was evaluated based on live, attached tick counts over the entire treatment period and for each time point separately in primary cats. All cats (primary and supplementary) were included in the safety assessment. Cats were administered the test product or an authorised topically applied positive control product containing fipronil. The efficacy and safety of lotilaner tablets was investigated on D 0, 7, 14, 21, 28, 42, 56, 70, and 84 at the recommended dosage (exposure dose range 6 to 22.86 mg/kg bw) when administered monthly on three occasions (Days 0, 28 and 56) for the treatment of ticks (*Ixodes ricinus*) on naturally infested cats.

The test item was confirmed to be non-inferior to the control product. In this study, the mean percent efficacy of the test product was 99.3% (arithmetic mean) against ticks over the whole study period. Specifically in relation to efficacy against *I. ricinus*, the mean percent efficacy of the test product was 98.8% (arithmetic mean) against ticks over the whole study period and efficacy was ≥ 94.9% at each timepoint up until Day 84. Although the efficacy was demonstrated for other tick species *Rhipicephalus sanguineus, Dermacentor reticulatus* and *Ixodes hexagonus*, only the indication for the treatment of *I. ricinus* is justified because there are no dose confirmation studies to support an indication for the other tick species (this is the only tick species proposed for inclusion in the indication).

Under the conditions of the current study, it is evident that *I. ricinus* is the most common tick infestation encountered in the cat. However, it is clear that a substantial proportion of tick infested cats carry other tick species (*Rhipicephalus sanguineus*, *Dermacentor reticulatus* and *Ixodes hexagonus*). While the findings of this study suggest that the test product when administered in the dose range 6.00 to 22.86 mg/kg bw is effective against these species, the information presented in support of dose justification suggests that the recommended minimum treatment dose of 6 mg/kg bw is unlikely to be effective against these tick species. Given that it is likely that cats treated with the test product will be infested with tick species other than *Ixodes ricinus* (as evidenced by this study), the applicant was requested to comment on the appropriateness of a claim for a single tick species (from a cat health/welfare perspective) and the implications of 'low-dose' exposure on resistance development for the isoxazoline class in other major tick species. In response, the applicant notes that there are currently no indications in published literature of Isoxazoline resistance in ticks. Further, it is acknowledged that other recently centralised approved ectoparasiticides for cats also only claim tick efficacy against a single tick species. Based on the applicant's justification, the proposed claim against a single tick species can be accepted.

Based on the results of this study, it is accepted that a single oral dose of the tested product, administered on a monthly basis, is efficacious for the treatment of tick infestation of *Ixodes ricinus* in cats under field conditions and the test item is generally well tolerated. However, due to insufficient data to support efficacy against ticks in young cats, the claim against ticks (*I. ricinus*) should be limited to cats over 5 months of age.

Palatability

This study also aimed to demonstrate the palatability of Credelio chewable tablets taking into account the recommendations of the CVMP Guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011). According to the guideline acceptance is defined as voluntary full consumption within the maximum offering time (e.g. two minutes) and to be granted a palatability claim, the overall voluntary acceptance rates should at least reach the threshold of 70% in cats. Palatability was assessed for all primary and supplementary cats in the test product treatment group. The test product and control product were administered by the owners of the included cats in their home. The test product was considered palatable if the animal accepted Credelio chewable tablets when offered in an empty bowl or trough or on the ground during 60 seconds, or if it accepted the tablets when subsequently offered by hand for an additional 60 seconds. The test products were voluntarily and fully consumed within two minutes on 48.0% of 629 occasions offered to primary and supplementary cats, which did not meet the

voluntary acceptance rate of 70% required by the guideline. These results are in line with the voluntary acceptance findings reported in the US flea field study.

Based on the totality of data (laboratory studies and field studies), it is not accepted that the product will be voluntarily accepted by the majority of the target population, and reference to the palatability of the tablet acceptance in the SPC and product information has been deleted.

Overall conclusion on efficacy

Pharmacodynamics: Lotilaner is a potent inhibitor of gamma-aminobutyric acid (GABA)-gated chloride channels, resulting in rapid death of ticks and fleas.

Resistance: Credelio chewable tablets for dogs was the first veterinary medicinal product containing the active substance, lotilaner, to be issued a marketing authorisation valid throughout the European Union in 2017. It can be accepted that that there has not been potential for development of resistance among the target parasites.

Pharmacokinetics: Following oral administration to the cat, lotilaner is rapidly absorbed, but is slowly eliminated. In fed conditions, the mean maximum blood concentration (C_{max}) was 3079 ng/ml at 4 hours (T_{max}) after a 6 mg/kg bw oral dose. The terminal half-life is approximately 4 weeks (harmonic mean) or 6 weeks (arithmetic mean). Food enhances the absorption and lotilaner displays high systemic absorption in fed cats. Therefore, lotilaner should be administered at or around the time of feeding. In light of the significant difference between oral bioavailability in the fed state compared to the fasting state, and the possible implications for efficacy of the product, a statement has been included in section 4.4 of the SPC to the effect that the product may not achieve an acceptable level of efficacy if administered to cats in the fasted state. Furthermore, section 4.9 has been updated with regard to timing of treatment relative to feeding, namely, that the product should be administered with food or within 30 minutes after feeding.

The major route of elimination is biliary excretion.

It is noted that elimination half-life was shorter in very young animals, as compared to adults. In the pivotal target animal safety study, systemic exposure to lotilaner increased following repeated administration for eight months. At 26 mg/kg bw (maximum recommended treatment dose) the mean accumulation ratios were 2.15 and 2.92 for month 5 and month 8, respectively. This suggests that steady state had not been reached with the potential for further accumulation with additional repeated treatments. The applicant was requested to comment on the possibility for continued accumulation of lotilaner following repeated administration in adult cats and its significance in terms of target animal tolerance (that is, can the findings of the pivotal TAS study be extrapolated to adult cats). Based on the applicant's response, the target animal safety data can be considered adequate to support safety in adult cats. In addition, the applicant was requested to comment on potential implications of this phenomenon for efficacy evaluation in kittens (that is, while the effect against target parasites has been shown to persist for 28 days (one month) in adult cats, can a similar duration of persistent effect be assumed for kittens/young cats given the age related effect on clearance). Based on a statistical analysis of the efficacy field data in kittens aged less than or equal to 5 months at the time of first treatment together with the PD/PK analysis, efficacy against fleas in kittens of this age group can be accepted. However, due to insufficient data to support efficacy against ticks in young cats, it is considered that the claim for efficacy against *I. ricinus* should be limited to cats over 5 months of age.

Tolerance: The target animal safety data presented in support of this application suggest that lotilaner, when administered orally as chewable tablets at 1X, 3X, and 5X the maximum intended clinical dose once monthly for 8 consecutive doses to 8-week old kittens, is well tolerated. In the pivotal study (conducted in

accordance with VICH GL 43), there were a number of changes observed, however, none of the findings were considered adverse or toxicologically relevant.

Dose justification/ determination studies: The minimum recommended dose rate of lotilaner was determined firstly by pharmacokinetic / pharmacodynamic modelling using early development studies. It is noted that a similar approach to dose finding was used in support of the application for the authorisation of Credelio chewable tablets for dogs. The outcome of the analysis is that in cats, a monthly lotilaner dose (formulated as tablet or granule/gravy) of 5.50 mg/kg bw (*Ixodes ricinus)* is expected to provide 90% efficacy in at least 75% of the population throughout the entire dosing period. Given the susceptibility of fleas to lotilaner, a dose of 3.00 mg/kg bw is expected to provide 95% efficacy in at least 75% of the cat population. A single oral dose of 6 mg/kg bw of lotilaner was chosen as the minimal efficacious dose over a period of one month.

The adequacy of this dose has been further investigated in a pivotal dose determination study and dose confirmation studies. Taking the findings of the pivotal dose determination study (flea and tick), together with the PD/PK analysis, it would appear that 6 mg/kg bw monthly is an appropriate dose rate to be used in the confirmatory efficacy studies. However, this study was conducted in adult cats (15-85 months old) and the applicant was asked to clarify to what extent the findings of this study (and the various dose confirmation studies) can be extrapolated to kittens/young cats given that systemic exposure is expected to be less in young compared to adult cats. This is considered an important consideration because it is clear that a 50% reduction in systemic exposure will have a significant impact on efficacy (for *Ixodes*, the required efficacy threshold was not achieved at Day 22 and thereafter at an oral dose of 3 mg/kg bw). The applicant's response clarified that while the efficacy against fleas in kittens 5 months of age or younger could be accepted, there is insufficient data to support the efficacy claim against ticks in kittens of 5 months of age or younger.

Dose confirmation studies: The data from one GCP study conducted in Europe using a European flea isolate and from one GCP study conducted in the USA using fleas of US origin support a claim that Credelio chewable tablets administered to adult cats as a single minimum dose of 6 mg/kg bw will treat existing fleas and will have an acceptable level of efficacy for 28 days.

The findings of the pivotal European speed of kill study demonstrated a speed of kill against fleas of less than 8 hours in accordance with the current guideline; however, three of the speed of kill studies conducted do not support the proposed speed of kill claim (8 hours) against new flea infestations. Accordingly, the claimed speed of kill of 8 hours against fleas is restricted to existing flea infestations; and given that adequate efficacy against fleas at 12 hours post treatment/infestation was confirmed at all timepoints in three of four studies conducted, a speed of kill of 12 hours against fleas can be accepted for new flea infestations.

Based on the pharmacokinetic data, the flea speed of kill data, noting the biology of the parasite and the supporting data of the simulated home environment studies, it is accepted that the product will kill existing and newly emerged fleas on cats before they can lay eggs. Accordingly, the statement can be accepted that the product "*kills existing and newly emerged fleas on cats before they can lay eggs. Therefore, the product breaks the flea life cycle and prevents environmental flea contamination in areas to which the cat has access*".

Two GCP confirmatory studies conducted in Europe using tick isolates that originated in Europe were provided in support of the killing effect of the product against *I. ricinus*. It is accepted that the findings of the pivotal European speed of kill study provide sufficient scientific evidence of the claimed speed of kill against ticks in accordance with the current guideline.

Field trials:

Three field studies were provided, two undertaken in Europe, and one from the USA. The data presented support the claim that the Credelio is efficacious for four weeks against fleas and *I.ricinus* ticks when administered to naturally infested cats. The data also support the proposed indication for use as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Palatability: Voluntary acceptance of the product was investigated in pre-clinical studies as well as part of an EU and a US field trial. Based on the totality of data, it is not accepted that the product will be voluntarily accepted by the majority of the target population, and reference to the tablet acceptance in the SPC and product information has been deleted.

Part 5 – Benefit-risk assessment

Introduction

Credelio chewable tablets for cats contain lotilaner as the active substance. The product is available in two different strengths of either 12 mg or 48 mg per tablet. The route of administration is oral use.

The product is a potent insecticide and acaricide, and intended for the treatment of tick and flea infestations in cats and for use as part of a treatment strategy for the control of flea allergy dermatitis.

The application for the authorisation of Credelio chewable tablets for cats is submitted as an extension to the initial community marketing authorisation of Credelio chewable tablets for dogs (Marketing Authorisation Numbers EU/2/17/206/001-015). The line extension application is made in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2c thereof (change or addition of a new strength/potency).

Benefit assessment

Direct therapeutic benefit

Lotilaner is a potent insecticide and acaracide. Laboratory and field studies showed that when administered orally to cats at the recommended dose of 6 mg/kg bw, there is a persistent killing effect against fleas (*Ctenocephalides felis*) for at least four weeks after treatment.

When administered orally at a dose of 6 mg/kg bw to cats over 5 months of age at the recommended dose, there is a persistent killing effect against ticks (*I. ricinus)* for at least four weeks after treatment.

Speed of kill studies demonstrated that for fleas (*Ctenocephalides felis* and *C. canis*), the onset of efficacy is within 8 hours for existing flea infestations, and 12 hours for new flea infestations. Speed of kill studies demonstrated that for ticks (*I. ricinus),* the onset of efficacy is within 18 hours for existing tick infestations, and 24 hours for new tick infestations.

A well conducted GCP field study supports the use of the product as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

The product kills existing and newly emerged fleas on cats before they can lay eggs. Therefore, the product will help break the flea life cycle.

Additional benefits

Credelio chewable tablets increase the range of available treatment possibilities against flea and tick infestation in cats.

Risk assessment

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.

Safety:

Risks for the target animal:

The target animal safety data presented in support of this application suggest that lotilaner, when administered orally as chewable tablets at 1X, 3X, and 5X the maximum intended clinical dose once monthly for 8 consecutive doses to 8-week old kittens is well tolerated. The product was generally well tolerated in the laboratory and clinical efficacy studies. No data were submitted on reproductive toxicity in the target species. However it is accepted that this is addressed in the product information.

To ensure comprehensive adverse event surveillance, it is recommended to re-start the periodic safety update report (PSUR) cycle for Credelio for submission of 6-monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at three-yearly intervals.

The data lock point (DLP) for the first 6-monthly PSUR of the re-started cycle would be 31 July 2018.

Risk for the user:

The risk to the user is considered acceptable noting in particular that the pharmaceutical form (chewable tablet) limits the potential for the user to be exposed to the active substance when removing the product from the packaging and administering the tablet to the animal. Adequate information has been provided to support the claim that the packaging is child-proof. The product is not expected to pose a risk for the user when used in accordance with the SPC.

Risk for the environment:

Credelio chewable tablets for cats are for the individual treatment of companion animals. The product is not expected to pose a risk for the environment when used in accordance with 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, user, and the environment, and to provide advice on how to prevent or reduce these risks.

In view of extension to a new target species as well as new presentations, the PSUR cycle should be re-started to ensure more frequent monitoring of adverse events.

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is considered positive.

The applicant applied for the following indications: "For the treatment of flea and tick infestations on cats. This veterinary medicinal product provides immediate and persistent killing activity for 1 month against fleas *(Ctenocephalides felis* and *C. canis)* and ticks *(Ixodes ricinus).* Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD)". The product has been shown to be efficacious for these claims, and the CVMP agreed with the applicant's proposed indications.

The qualitative and quantitative composition of the cat tablet formulation is based on the existing formulation of the product for use in dogs, and the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. It is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) considers that the application for Credelio chewable tablets for cats is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of this extension of the marketing authorisation for Credelio for cats.