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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Credelio (EMEA/V/C/004247/0000)

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 23 February 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Credelio chewable tablets for dogs, through the centralised procedure under Article 3(2)a of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 9 July 2015 as Credelio contains a new active substance (lotilaner) which is not yet authorised as a veterinary medicinal product in the Union.

The recommended indications are as follows:

"For the treatment of flea and tick infestations in dogs. This veterinary medicinal product provides immediate and persistent killing activity for 1 month for fleas (*Ctenocephalides felis* and *C. canis*) and ticks (*Rhipicephalus sanguineus, Ixodes ricinus, I. hexagonus, and Dermacentor reticulatus*). Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD)".

The active substance of Credelio is lotilaner, a parasiticide of the isoxazoline class. The target species is the dog. The route of administration is oral use. Lotilaner is a potent inhibitor of gamma–aminobutyric acid (GABA)-gated chloride channels and, after oral administration to affected dogs, results in the rapid death of ticks and fleas. Credelio is presented as chewable tablets in strengths of 56 mg, 112 mg, 225 mg, 450 mg and 900 mg. The product is presented in packs of 1, 3 or 6 tablets.

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

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

On 16 February 2017, the CVMP adopted an opinion and CVMP assessment report.

On 25 April 2017, 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 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 2015) 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

Manufacture of the dosage form take place within the EEA. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture of such veterinary dosage forms, has been provided.

Batch release takes place at Elanco France S.A.S, Huningue, France. The site has a manufacturing authorisation issued on 21/04/2016 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 of such veterinary dosage forms, has been provided.

Packaging (primary and secondary) takes place at sites outside the EEA and the sites are considered appropriately certified as complying with EU GMP requirements.

The active substance and its intermediate are manufactured outside the EEA. 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 on the basis of on-site audits of each of the sites. The audit of the site of manufacture of the intermediate was performed by the final active substance manufacturing site.

Overall conclusions on administrative particulars

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

The GMP statuses of all the active substance and finished product manufacturing sites have been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a chewable, flavoured tablet containing the active substance lotilaner in 5 tablet strengths, 56.25 mg (label strength 56 mg), 112.5 mg (label strength 112 mg), 225 mg, 450 mg and 900 mg.

All five tablet strengths are compressed from the same (common) final blend to form tablets of different sizes.

The other components of the formulation are cellulose powdered, lactose monohydrate, silicified microcrystalline cellulose, a meat dry flavour, 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 cardboard 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 selected manufacturing process (wet granulation and tablet compression) was driven by the properties of the active substance.

The active substance has one chiral centre and exhibits polymorphism. Particle size, polymorphism and enantiomeric purity are routinely controlled in the active substance specification, and are in line with the batches of lotilaner used in the clinical studies.

The development of the formulation is logical and well described in the dossier and the formulation components are commonly used in this type of dosage form. The function of each excipient is clearly detailed and their selection was based on experience with the development and manufacturing of other drug products. The formulation used in pivotal safety and efficacy trials was the same as that proposed for marketing. Two efficacy studies and a palatability study utilised formulations with very minor differences in the composition of active substance (less than 0.5%). These minor differences will not impact on clinical performance.

The development of the dissolution test used in the finished product specification is described and it has been demonstrated to be discriminatory with respect to changes to the tablet formulation and method of manufacture.

Method of manufacture

The manufacturing process is a standard aqueous wet granulation process. The final primary packaging is aluminium/aluminium blister. 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.

The manufacturing process has been described in sufficient detail, including specific detail on in-process controls, re-processing and intermediate specifications.

The choice of the starting materials is appropriately justified. The proposed starting materials are in line with the conclusions drawn in the scientific advice (EMA/CVMP/SAWP/230321/2015) given on the designation of the starting materials for lotilaner, and are considered to be acceptable.

The specifications and control methods for the intermediate products, starting materials and reagents have been presented, and are considered to be acceptable.

The characterisation of the active substance is in accordance with the CVMP guideline on chemistry of new active substances (EMEA/CVMP/541/03). Potential and actual impurities are well discussed with regards to their origin and characterisation.

Lotilaner is not monographed in a pharmacopoeia and the proposed in-house specification is generally considered to be 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 the VICH guideline GL2 on validation of analytical procedures: methodology (CVMP/VICH/591/98) and Ph. Eur. requirements.

Batch analysis data are provided for 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.

Stability data are provided for 3 production scale batches of the active substance. The samples on stability were packaged in a container-closure system that simulates that used for the bulk active substance. Data was provided for up to 24 months storage at 25 ºC/60% RH, at 30 °C/65% RH, at 40 ºC/75% RH and at 5 °C/ambient humidity. All results are within specification, with no trending apparent, for all batches at all storage conditions. Forced degradation studies were also carried out on a single batch of the active substance. The batch was subjected to light, thermal, oxidative, acidic and alkaline conditions. It is considered that the proposed re-test period of 3 years with no specific storage precautions is supported by the stability data provided.

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

Silicified microcrystalline cellulose is composed of intimately associated microcrystalline cellulose and colloidal silicon dioxide particles. 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 meat dry flavour. With respect to viral safety of the meat flavour, a satisfactory risk assessment in accordance with the Ph. Eur. General chapter

5.1.7 *Viral Safety* is provided.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form including : appearance, identification, water content, active substance content, degradation products, uniformity of dosage units, dissolution, enantiomeric purity, tablet weight, hardness, friability and microbiological contamination. The proposed specification for tablet dissolution has been set based on results obtained for the registration stability batches after storage and with reference to the dissolution of batches for which acceptable bioavailability (efficacy) has been demonstrated.

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 both active substances has been presented.

Batch data is provided for 4 pilot scale batches of the 56.25 mg tablets, 2 pilot scale batches each of the 112.5 mg, 225 mg and 450 mg strengths, and 5 pilot scale batches of the 900 mg strength tablets. The data demonstrates compliance with the proposed specifications.

Stability

The proposed finished product specification for shelf life is the same as that for release except that uniformity of dosage units, enantiomeric purity, tablet weight, hardness and friability are omitted from the shelf life specification. This difference is acceptable as these parameters are not stability indicating.

A stability study on tablets stored in the proposed bulk intermediate container (double low density polyethylene (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 considered acceptable.

A stability study on three pilot scale batches of the finished product stored in the proposed commercial (alu/alu) blisters was conducted. As the tablets are compressed from a common blend, a partial bracketing approach was used: 3 batches each of the lowest (56.25 mg) and highest (900 mg) strength and one batch each of the three intermediate strengths were included in the study in accordance with the VICH guideline GL45 on quality: bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products (EMA/CVMP/VICH/581467/2007). Samples were stored at 25 ºC/60% RH, 30 ºC/65% RH and 40 ºC/75% RH and tested to the release specification after up to 12 months storage in line with the VICH guideline GL3 on stability: stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/899/99-Rev.1). 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.

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

All results are in compliance with the proposed specification with no adverse trends observed.

A satisfactory post approval stability protocol and commitment is included in the dossier. As the product has been demonstrated to be extremely stable, extrapolation of the real time data is considered appropriate and based on the reported results, the proposed shelf life of 24 months with no special storage conditions when stored in the original (non-opened) primary packaging is considered acceptable.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product is 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 relevant specifications are applied. Data has been presented to give reassurance on TSE safety. A risk assessment in accordance with the Ph. Eur. General chapter 5.1.7 *Viral safety* relating to viral safety of the animal derived flavouring material is provided.

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.

Based on the review of the data on quality, the manufacture and control of Credelio chewable tablets for dogs are considered acceptable.

The applicant will generate the following information post-authorisation:

- Process validation studies on the first commercial batches, for which the protocol has already been approved.
- The first 3 batches produced for commercial release to be placed in a stability study, for which the protocol has already been approved.

The Committee considered this to be acceptable.

As the manufacturing method is a standard process and validation data on pilot-scale batches were provided, it was accepted that full scale validation would be performed post-authorisation 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).

Part 3 – Safety

The veterinary medicinal product contains the new active substance lotilaner. This application is a full stand-alone application compiled according to Article 12 (3) of Directive 2001/82/EC as amended. A full safety file in accordance with Article 12(3)(j) has been provided.

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Toxicological studies

Single dose toxicity

A study investigating the acute oral toxicity of lotilaner was carried out in the rat. This was a GLP study conducted in accordance with OECD guideline 423. There were no deaths, and no clinical signs of toxicity were noted. It is concluded that the oral LD_{50} is greater than the limit dose of 2000 mg/kg.

Two studies investigating the acute dermal toxicity of lotilaner were carried out in the rat. Both were GLP studies conducted in accordance with OECD guideline 402. No effects on mortality and no clinical signs were noted. Dermal reactions were confined to incidents of very slight erythema. It is concluded that the oral LD_{50} is greater than the limit dose of 2000 mg/kg bw.

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

Repeat dose toxicity

Five repeat dose oral toxicity studies are presented. All studies were conducted in the rat. Three of these are classed as exploratory, non-GLP studies. The two GLP studies were conducted in accordance with OECD guidelines 407 (28-day study) and 408 (13-week study) and investigated the toxicity of oral doses up to 60 mg lotilaner/kg bw/day.

Across all repeat dose toxicity studies in rats, body weight and food decreases were recorded when lotilaner was administered at high doses. Consequent to decreases in food intake and body weight, there were decreases in organ weight and changes in clinical pathology. No main target organ could be defined. The mechanisms underlying a number of observed effects (skin lesions and pathological findings in the ovaries and lungs) in the 13-week repeat dose study are unclear. Notwithstanding the absence of information on underlying mechanisms, the CVMP accepts, based on the 13-week study that the no-observed-adverse-effect-level (NOAEL) in the rat, be set at 5 mg/kg bw/day.

Tolerance in the target species of animal

The tolerance in the target animal is described under Part 4.

Reproductive toxicity

Study of the effect on reproduction

A GLP, two-generation study was performed in the rat to investigate effects of lotilaner at doses up to 40 mg/kg bw/day on reproductive performance. This study was conducted in accordance with OECD guideline 416 (two-generation reproduction toxicity study).

Daily administration of the test item was reasonably well tolerated in both males and females at dose levels of up to 40 mg/kg bw/day for 10 weeks before pairing. After pairing females at the highest

dose showed reduced pregnancy rate and low implantation rates, both associated with low bodyweight gain and low food consumption. Halving the dose level administered to the high dose animals appeared to improve the pregnancy rate of the animals which had mated later but litter sizes were still low. No F1 generation was produced at this high (40–20 mg/kg bw/day) dose level.

There were no clear adverse effects on the F1 generation at lower dose levels. None of the effects seen at 5 mg/kg bw/day were considered of toxicological significance such that a dose level of 5 mg/kg bw/day was considered to be the NOAEL from this study.

Study of developmental toxicity

A developmental toxicity study was conducted in the rat at doses of 9, 18 and 50 mg/kg bw/day. This was a GLP study conducted in accordance with the OECD guideline 414. Maternal toxicity occurred at 50 mg/kg bw/day. However, there were no findings indicating any embryotoxicity, foetotoxicity, or teratogenicity. The NOAEL for maternal toxicity and for embryofoetal toxicity was considered to be 18 mg/kg bw/day.

No studies on the effects on reproduction in the target species have been provided.

Based on available data, the following precautionary statement is included in section 4.7 of the SPC: "Laboratory studies in rats have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity of males and females. The safety of the veterinary medicinal product in breeding, pregnant and lactating dogs has not been established. Use only according to the benefit-risk assessment of the responsible veterinarian."

Genotoxicity

Three studies investigating genotoxic potential were presented. These GLP studies investigated: gene mutations in bacterial cells (OECD guideline 471); chromosome aberrations in mammalian cells (OECD guideline 473) and gene mutations in eukaryotic cells (OECD guideline 474).

The studies represent the standard genetic toxicity test battery defined by the VICH guideline GL23 on studies to evaluate the safety of residues of veterinary drugs in human food: genotoxicity testing (EMA/CVMP/VICH/526/2000). Based on the outcome of these studies, it is accepted that lotilaner does not appear to have genotoxic potential. This finding is in keeping with what is accepted for other substances in this class.

Carcinogenicity

No carcinogenicity data have been provided. This is considered acceptable due to the lack of genotoxic potential, the lack of structural alerts, and the lack of findings relevant to neoplastic lesions in repeat dose toxicity studies.

Studies of other effects

A series of studies were conducted for the purpose of investigating potential local effects of the active substance and the final product formulation. All studies were conducted to GLP and followed the relevant OECD guidelines (guideline 404 for skin irritation, guideline 405 for ocular irritation and guideline 429 for skin sensitisation). All studies can be accepted as valid in that the stated

within study acceptance criteria, were met. These studies show that lotilaner, when formulated as Credelio tablets, is not irritant to the skin, is mildly irritant to the eyes and has no potential to induce skin sensitisation.

It is noted that the ocular irritation test was conducted with powdered tablets while in the real life scenario minimal exposure is expected from the tablet form.

No signs of immunotoxicity and neurotoxicity were observed in repeat dose toxicity studies. Therefore, no specific studies were performed.

Excipients

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. It is 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.

User safety

A user safety risk assessment has been conducted in accordance with CVMP guideline on user safety of pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

Credelio tablets for dogs will be supplied as 56 mg, 112 mg, 225 mg, 450 mg and 900 mg hard flavoured chewable tablets dispensed individually in an aluminium foil/foil blister package with 1 or 3 tablets per blister. Tablets are hard and are not divisible. It is expected that the tablet will be removed from the blister package by an adult pet owner and administered to the dog immediately.

For the adult user, the most relevant exposure route is dermal exposure at the time of product administration. While a quantitative risk assessment for this exposure scenario has not been conducted, it is accepted that the risk of user exposure to the active ingredient is likely to be very low in view of the presentation (in blister packs) and the tablet characteristics (hard and non-friable). Further, while the adult pet owner/veterinarian could potentially be exposed to trace amounts of the active substance through dermal exposure from handling the tablets and oral and ocular exposure from hand-to-mouth or hand-to-eye transfer, respectively, standard hygiene measures (washing hands after administering the product) will further minimise the potential for dermal, oral or ocular exposure. Accordingly, the risk to adults and veterinarians from dermal contact at the time of tablet administration is considered acceptable. It is proposed that the label will carry the following user warning: "Wash hands after handling the product." This is considered acceptable. The final product was shown to be slightly irritant to eyes. However given that the potential for ocular exposure is considered minimal and noting that the ocular irritation test was conducted with powdered tablets, the CVMP is of the opinion that a precautionary statement is unnecessary.

For this product, the exposure scenario that represents the most significant risk is ingestion of a tablet. Ingestion of one tablet of Credelio chewable tablets 900 mg by a 60 kg-adult results in exposure to 15 mg/kg of lotilaner. It is accepted that such a one-off exposure is not expected to be associated with significant toxicity given that doses up to 215 mg/kg were well tolerated by dog pups when administered once monthly for eight months (see target animal tolerance in Part 4). An assessment of the risk to children (associated with ingestion of a tablet) has not been presented. For a child, no accidental ingestion is expected as the tablet is contained within an aluminium foil blister with peelable lid, limiting the accessibility. Adequate information has been presented to support the claim that the packaging is child proof. Further, it is stated that appropriate warnings to keep the

tablet out of reach of children will prevent children from obtaining direct access to the tablet. In addition, the product literature includes the following statement: "In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician." Based on available information, the CVMP accepts that the product, as presented, will not pose an unacceptable risk to children or to other categories of user.

Environmental risk assessment

An environmental risk assessment was provided according to the guideline on environmental impact assessment for veterinary medicinal products – Phase I (CVMP/VICH/592/98-FINAL). Due to the fact that Credelio chewable tablets for dogs are only used in non-food producing animals, it can reasonably be concluded that the recommended use of Credelio chewable tablets for dogs will not result in significant exposure of the environment.

Overall conclusions on the safety documentation

For pharmacological properties, see Part 4.

A comprehensive safety data package has been presented. All pivotal studies were conducted to GLP standard and in accordance with relevant OECD guidelines. It is accepted that toxicity in laboratory animals has been adequately characterised. In particular, it is noted that:

- the active substance has no significant acute toxic risk;
- a NOAEL of 5 mg/kg bw/day is accepted for repeat dose and reproductive toxicity;
- the active substance is not embryotoxic or teratogenic;
- the active substance is non-mutagenic and unlikely to be carcinogenic; and
- Credelio chewable tablets for dogs are non-irritant to skin, mildly irritant to the eyes, and do not induce skin sensitization.

The data generated are adequate for the purposes of conducting a user safety assessment.

A user safety assessment in accordance with relevant guidance was presented. It is accepted that the product, when used as directed in the SPC will not pose an unacceptable risk to the user.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

Lotilaner is a member of the isoxazoline family, a class of parasiticides that are potent inhibitors of gamma-aminobutyric acid-gated chloride channels (GABACls) (Ozoe et al., 2010; Lahm et al., 2013). The GABA-mediated chloride influx leads to hyperpolarisation of the cellular membrane and generates an inhibitory postsynaptic potential, which decreases the probability of an action potential. Insects and other invertebrates possess GABACls that are expressed not only in the central nervous system, where they generate inhibitory potentials for the correct integration of neuronal signals, but also at peripheral neuromuscular sites, where they promote muscular

relaxation. In the presence of lotilaner, GABAChs are not able to open upon GABA stimulation, defining this molecule as an antagonist of GABAChs. Parasites exposed to lotilaner will endure a spastic paralysis leading to their starvation and eventually death.

Based on the pharmacodynamics data presented, it is accepted that:

- Lotilaner is a potent inhibitor of gamma-aminobutyric acid (GABA)-gated chloride channels, resulting in rapid death of ticks and fleas.
- The activity of lotilaner is not affected by resistance to organochlorines (cyclodienes, e.g. dieldrin), phenylpyrazoles (e.g. fipronil), neonicotinoids (e.g. imidacloprid), formamidines (e.g. amitraz) and pyrethroids (e.g. cypermethrin).
- Lotilaner is the enantiomer of clinical relevance for the efficacy against fleas and ticks. Its opposite enantiomer has limited efficacy.
- Adult ticks were shown to be the least susceptible tick stage. Accordingly, all effectiveness studies with ticks were conducted with adults. This is considered acceptable.
- The findings of an in vitro study comparing the susceptibility of *C. felis* and *C. canis* fleas to lotilaner suggests that *C. felis* is the least sensitive (susceptible) of the two flea species.

The pharmacodynamics effects of lotilaner have been adequately described and characterised.

Development of resistance

Lotilaner is a new chemical entity. Since lotilaner 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

A number of studies investigating blood pharmacokinetics and ADME profile have been presented. The pivotal pharmacokinetic studies were conducted to GLP standard. Validated methods were used for sample analysis.

Following oral administration to the dog, lotilaner is rapidly absorbed, but is slowly eliminated. In fed conditions, the mean maximum blood concentration (Cmax) was 3584 ng/mL at 2 hours (Tmax) after a 20 mg/kg dose. The half-life was estimated to be 30.7 days. 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, food enhances the absorption and lotilaner displays high systemic absorption in fed dogs (this effect is consistent over a number of studies reported). The absolute bioavailability was 82% in fed dogs and 24% in fasted dogs. Therefore, lotilaner should be administered at or around the time of feeding. It is noted that these recommendations (i.e. ensuring fed state with a time limit of 30 minutes between feeding and administration) were implemented in the protocols of the pivotal efficacy and safety studies.

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 and liver, followed by kidney. The major route of elimination is biliary excretion. Renal clearance is the minor route of elimination (less than 10% of the dose). Although unchanged lotilaner is the largely predominant form in blood and tissues and is still the major form in faeces, a number of slightly more hydrophilic metabolites were identified in faeces as well. The ADME profile in the rat was similar to that described for the dog.

Based on the analysis of pharmacokinetic data reported in target animal safety studies, it was noted that:

- Following monthly administration of lotilaner, mean systemic exposure ($AUC_{0\text{-}672hr}$) and Cmax values of lotilaner generally increased with increasing dose; however, both Cmax and AUC increased in a less than proportional manner with increasing dose.
- Half-life (T½) was shorter in puppies than in adult dogs. In the pivotal eight month target animal safety study, the mean T½ values calculated across all dose groups for months 1, 5 and 8 were 10.0, 18.2 and 29.5 days, respectively.
- Systemic exposure to lotilaner, as indicated by $AUC_{0\text{-}672hr}$, increased following repeated administration of lotilaner. 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. The resulting mean accumulation ratios did not appear to change with increasing dose and were 1.67, 1.57, and 1.58 for month 5, and were 3.33, 2.41, and 3.24 for month 8 at 43, 129 and 215 mg/kg, respectively. The accumulation ratio may be an overestimate of drug accumulation in adult dogs as the $AUC_{0\text{-}672hr}$ calculated for month 1 was determined in puppies (puppies displayed lower exposure due to shorter T½).

- The change in pharmacokinetics as animals grew from puppies to young dogs was attributed to expected growth rather than to any specific changes induced by the repeated administration of lotilaner. Elimination was faster and elimination half-life was shorter in very young animals, as compared to adults. Consequently there was less accumulation compared to what may be expected if the study had been conducted in adult dogs. However the difference in pharmacokinetic profile between adults and pups was not considered to have implications for safety evaluation in adult dogs or for efficacy evaluation in pups that is, the between dose interval of 28 days is considered satisfactory for pups for the following reasons:
  - The target animal safety study design with an extended treatment duration of 8 months covered the period of pups growing to young adults and the period of expected drug accumulation in adult dogs. Further, the results of the pivotal target animal safety study indicate a margin of safety 5-fold above the maximum therapeutic dose. Therefore, the target animal safety data generated in pups can be considered adequate to support safety in adult dogs. See TAS section below.
  - The mean observed concentration at day 28 post-treatment and mean predicted concentration at day 30 post-treatment, when normalized to the minimum dose of 20 mg/kg, in 8-week old puppies, resulted in predicted efficacy above 90% for all ticks species of interest in Europe. Therefore, the faster elimination of the active substance in pups (compared to adult dogs) is unlikely to adversely impact efficacy in pups (that is, adequate efficacy over the proposed between treatment interval is anticipated). Further comment on dose justification is presented below.

Dose justification

The minimum recommended dose rate was determined first by pharmacokinetic/pharmacodynamic modelling using early development studies. 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. Using the information from this modelling exercise, a pivotal dose determination study was conducted.

The objective of the modelling and simulation activity was to characterize the dose concentration-response relationship of lotilaner in dogs, integrating data from numerous studies conducted under different experimental conditions (e.g. discovery, dose ranging, and pilot efficacy studies). Data from 16 single-dose studies were pooled, including concentration measurements and efficacy assessments at several time points. Based on the concentration-response analysis, it appears that *A. americanum* was the least susceptible tick species of the spectrum tested followed by *I. ricinus* and *R. sanguineus*, followed at some distance by *I. hexagonus* and then the other parasites tested. It is accepted that fleas are more susceptible to lotilaner than ticks.

The conclusion of this modelling activity is that, in dogs, a monthly lotilaner dose (formulated as tablet) of 23.75 mg/kg (*Ixodes ricinus*) and 18.75 mg/kg (*Rhipicephalus sanguineus*) is expected to provide 90% efficacy against the least susceptible tick species in Europe, in at least 75% of the host population throughout the entire dosing period (i.e. one month). Given the susceptibility of fleas to lotilaner, a dose of 4.50 mg/kg is expected to provide 95% efficacy in at least 75% of the dog population. In effect, a minimum dose rate of around 20 mg/kg results in satisfactory efficacy against the parasite spectrum tested for up to 30 days after treatment.

The CVMP is prepared to accept the approach to dose determination used by the applicant and can agree, based on the information presented, that a minimum dose of 20 mg lotilaner/kg should ensure satisfactory efficacy against all claimed target parasites for the duration of the proposed between treatment interval (1 month). The adequacy of this dose has been further investigated in pivotal dose determination and dose confirmation studies.

Target animal tolerance

Four target species tolerance studies were conducted. Three of these studies were classed as exploratory, non-GLP studies, whereas the pivotal study was conducted to GLP standard in accordance with the requirements of the guideline on target animal safety for veterinary pharmaceutical products -VICH GL 43 (CVMP/VICH/393388/2006).

The pivotal study was designed to evaluate the safety of the test article, lotilaner tablets, in eight-week old Beagle dogs (pups) when administered orally as tablets one day every four weeks for eight months. The final formulation was administered at doses of 0, 43 (1x), 129 (3x) and 215 (5x) mg lotilaner/kg. Animals were fed within 30 minutes prior to dosing.

The type and timing of observations/sampling were appropriate for a comprehensive safety evaluation.

Based on the results of this study, it can be concluded that lotilaner was generally well tolerated in pups at doses up to 5X the maximum intended clinical dose. There were no treatment-related (toxicologically relevant) changes in the daily clinical observations; body weights and food consumption data; electrocardiograms; ophthalmoscopy, physical and neurological examinations; and clinical chemistry, haematology, coagulation, and urinalysis parameters. There were no test article-related macroscopic findings at terminal necropsy.

No effects attributable to treatment were detected in this study.

In the exploratory tolerance studies, some statistical changes in various clinical pathology parameters (notably, BUN and blood glucose) were observed. For these changes a relationship with treatment is unclear; however, it is notable that such effects were not detected in the pivotal study (conducted over 8 months).

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 and diarrhoea) were observed in a number of dogs within a short period of time following treatment. Given their proximity to treatment administration, these events may be treatment-related. However, the number of observations of gastrointestinal disorder in the various clinical studies is very low and, while numerically greater in the lotilaner treated animals than in control animals, a statistically significant difference between groups was not detected. Further, it is acknowledged that mild gastrointestinal upset is not an uncommon event in otherwise healthy animals. In the absence of a clear association between treatment and these observed effects, the wording 'none known' can be accepted for section 4.6 of the SPC. The occurrence of all adverse events, including gastrointestinal effects, will be monitored post-authorisation. In the event that a signal is detected and that a clear association with treatment is established, the applicant will be requested to update the product information accordingly.

Dose confirmation

A large number of laboratory dose confirmation studies, with at least 2 studies per parasite for most parasite species were conducted in the EU, US and/or other regions. All confirmation studies were conducted according to the standards of Good Clinical Practices - VICH GL9 (EMA/CVMP/VICH/526/2000) using the same basic design as detailed in the CVMP guideline on testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2): parallel group design, blinded, randomized, negatively controlled.

Group allocation was by ranking the dogs by descending parasite infestation rates and random allocation to the study groups, including at least 8 dogs (adults, usually Beagle dogs or purpose-bred cross-breeds) in each treatment group. Dogs received either a single oral dose of 20 mg lotilaner/kg bw or no treatment (negative control). Given the effect of feeding on systemic exposure (see pharmacokinetic section), the test item was administered within 30 minutes after feeding. In most studies, persistence of effect was investigated up to, at least, 35 days after treatment.

Ticks:

A number of laboratory dose confirmation studies in ticks investigated efficacy against the following tick species: *Dermacentor reticulatus, D. variabilis, Rhipicephalus sanguineus, Ixodes ricinus, I. scapularis, I. holocyclus* and *Amblyomma americanum.* Typically, tick infestations were conducted 48 hours before treatment started and continued weekly by placing approximately 50 viable, adult unfed ticks of the respective species directly on each dog. All tick isolates originated from the field and were multiplied in vivo (i.e. on host animals) in the laboratory. The ticks were applied to the dorsal area of the dog. Up to 48 hours following treatment administration (on Day 0) or infestations, tick counts were conducted that covered the entire body surface of the animals. All ticks recovered were removed from the animals.

The assessment of efficacy was based on the percent reduction in the arithmetic mean (live parasite counts relative to control) using the recommended Abbott's formula as recommended in the recently revised CVMP guideline (EMEA/CVMP/EWP/005/2000 Rev.3). Further, for similarly acting active substances, given that parasites must attach to the host and commence feeding in order to be exposed to the active substance, the CVMP agreed that the SPC (section 4.2) and package leaflet (section 4) would clearly state that the use of the product is for treatment only (not preventive use). In addition, the product information (sections 4.2 and 4 of the SPC and package leaflet respectively)

includes a statement that fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. Further, the product information (sections 4.4 and 12 of the SPC and package leaflet respectively) includes a statement to the effect that the risk of the transmission of parasite-borne diseases cannot be excluded.

The comprehensive package of confirmatory laboratory studies showed an immediate (on day 2) acaricidal efficacy of lotilaner against all tick species of at least 94.6% and a persistent efficacy of at least 93.4% for 4 weeks after treatment.

For each specific tick species investigated, the following is concluded:

- *Amblyomma americanum*: three dose confirmation studies are presented. All demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 30 days (>96.8% efficacy) in two studies and of 37 days in one study (94.9% efficacy). All studies were conducted using US isolates. This parasite does not occur in Europe.
- *Dermacentor reticulatus*: two dose confirmation studies are presented. Both demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 30 days (94.9% efficacy) in one study and of 37 days for the other study (100% efficacy). Both studies used tick isolates that originated in Europe.
- *Dermacentor variabilis:* three dose confirmation studies are presented. All demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 37 days (≥97.4% efficacy). All studies were conducted using US isolates.
- *Ixodes holocyclus:* two dose confirmation studies are presented. Both were conducted in Australia and satisfactory efficacy was achieved immediately after treatment, with a persistent effect of 72 days (95.6% efficacy) in one study, and of 44 days (95.3% efficacy) in the other study. However, it would appear that the same tick isolate was used in both studies. Given the absence of two confirmatory studies using different tick isolates, a claim for efficacy against this tick species cannot be accepted.
- *Ixodes ricinus:* two dose confirmation studies are presented. Both demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 37 days (≥95% efficacy). Both studies used tick isolates that originated in Europe.
- *Ixodes scapularis:* two dose confirmation studies are presented. Both demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 37 days (≥99.1% efficacy). Both studies were conducted using US isolates.
- *Rhipicephalus sanguineus:* four dose confirmation studies are presented. All demonstrated satisfactory efficacy immediately after treatment, with a persistent effect of 37 days (≥99.6% efficacy). One of these studies used a tick isolate that originated in Europe, whereas the other three used tick isolates originating in the US. (Note: the pivotal dose determination study used a *R. sanguineus* isolate that originated in Europe).

In addition to the standard dose confirmation laboratory studies, 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 reinfestations for 5 weeks after treatment against *I. ricinus* and *R. sanguineus.* In these studies, ticks were counted at three time points (4, 8 and 12 hours) following treatment on Day 0, and after subsequent weekly tick infestations. In both studies, lotilaner started killing ticks as early as 4 hours following treatment administration. In one study, there was greater than 90% reduction in live *I.*

ricinus count within 8 hours for existing tick infestations (Day 0); however, following re-infestation at 7, 22, 28 and 35 days, efficacy at the 8 hour time point was less than the accepted threshold of 90%. On Day 7 following treatment, *I. ricinus* ticks were killed (> 90% reduction in live tick count) within 12 hours; however, this speed of effect was not maintained at subsequent time points. In the same study, efficacy against *R. sanguineus* ticks did not reach the required efficacy threshold within 12 hours of reinfestation on any of the count days post treatment (Day 7, 22, 28 or 35). The findings of this study suggest that efficacy of lotilaner against *I. ricinus* is superior to efficacy against *R. sanguineus.* In a second study, greater than 90% efficacy was achieved on Day 0 at the 8 hour time point and on days 21 and 28 at the 12 hour time point. However, although close to 90%, the required efficacy threshold was not consistently achieved on other count days (days 7, 14 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 8 hours against existing ticks (*I. ricinus*) on the animal prior to administration and 48 hours against new tick infestations. Accordingly, the information relating to speed of kill against ticks has been included in the SPC.

Fleas:

In the pivotal dose confirmation studies for fleas (*C. felis, C. canis)*, infestations 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 dog. Dogs were kept still for several minutes to allow fleas to disperse and settle. Typically, flea comb counts that covered the entire body surface of the animals were conducted either 24 or 48 hours after treatment administration (on day 0) and after each subsequent weekly infestation. The flea isolates originated from the field and were multiplied *in vivo* (i.e. on host animals) in the laboratory.

The studies confirmed that a single oral dose of the tested product administered at 20 mg/kg is effective (>95%) in removing an existing adult *C. felis* and adult *C. canis* infestation and that an acceptable level of efficacy (>95%) persists for up to 35 days.

In addition to the standard dose confirmation laboratory studies, four studies were performed to investigate the onset of effect against existing flea infestations *(C. felis)* at time points up to 12 hours. Three of these studies also investigated onset of effect against new infestations for up to 35 days after treatment administration. Based on the findings of these studies:

- The test product was efficacious against existing and new flea *C. felis* infestations at 6, 8 and 12 hours after administration or flea infestation until day 35.
- On day 0, the % efficacy at 4 hours is below the required threshold of 95%; however, a satisfactory level of efficacy is achieved by 4 hours following reinfestation on days 7, 14, 21, 28 and 35 of the study.

For speed of kill information to be included in the SPC, it is expected that this will be based on the time point at which 95% efficacy (standard efficacy threshold for fleas) is achieved. Further, given that a persistent effect against fleas of up to at least one month is claimed, any information provided to users with respect to speed of kill should be relevant to the whole period of claimed persistent effect. Therefore, based on these data, the following text is accepted: "*For fleas, the onset of efficacy is within 4 hours of attachment for one month after product administration. Fleas on the animal prior to administration are killed within 6 hours*".

For *C. felis,* the dose confirmation study, together with the speed of kill studies, are accepted as adequate confirmation of efficacy against this flea species. While efficacy against *C. canis* was evaluated in only one of the dose confirmation studies, it is not expected that there will be a marked difference in sensitivity between the two flea species. Indeed, *in vitro* data suggest that *C. canis* is more susceptible to the effects of lotilaner than *C. felis.* In addition, it is acknowledged that the predominant flea species is *C. felis.*

An additional study investigating the efficacy of repeated monthly oral administrations of a minimum dose of 20 mg lotilaner/kg bw to adult Beagle dogs demonstrated efficacy in the treatment of pre-existing environmental flea infestations under simulated home environmental conditions.

In this series of laboratory studies, the test product (administered at a dose of 20 mg/kg) appears to have been well tolerated. Occasional adverse events were reported. Most can be considered unrelated to treatment (skin lesions - not uncommon in dogs repeatedly exposed to ectoparasites). Regarding a possible association between treatment and isolated gastrointestinal events (vomiting, loose faeces and diarrhoea), see target animal tolerance section above.

Clinical studies

The applicant conducted three field studies in Europe to evaluate the efficacy and safety of lotilaner chewable tablets at the recommended dosage of 20 to 43 mg/kg, administered orally to dogs at monthly intervals for either one or three months, in the treatment and control of natural infestations of fleas and ticks (one study investigating efficacy against fleas and two investigating efficacy against ticks). All three studies were conducted in accordance with the VICH GL9 guideline on Good Clinical Practices (CVMP/VICH/595/1998) and were designed as randomised, single blinded, multi-centre studies where efficacy was evaluated against an appropriate positive control. For all studies, the test population is considered representative of the target population.

Ticks:

Regarding those tick species for which satisfactory laboratory dose confirmation data have been provided, EU field data are only available for *Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*.

A small scale GCP study was conducted at multiple sites in Spain. Among 82 dogs, 47 received the test product and 35 dogs the positive control product, a spot-on containing fipronil and (s)-methoprene. The efficacy and safety of lotilaner tablets was investigated at the recommended dosage (20–43 mg/kg) when administered on a single occasion for the treatment of ticks (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus* and *Ixodes hexagonus*) on naturally infested dogs. The test item was confirmed to be non-inferior to the control product. The tick counts over the whole observation period (days 7–28) after treatment were significantly lower than in the controls. The efficacy rate versus baseline and using arithmetic mean tick counts, at all times was at least 99.7% for Credelio while for the control product the efficacy was below 92.6%. While the numbers of animals enrolled in the study were adequate for the purposes of investigating non-inferiority, the relatively low numbers of animals included in the test product group, together with the fact that the product was administered on a single occasion only, do not allow for a comprehensive safety evaluation.

A second, larger European field study was provided investigating the efficacy and safety of lotilaner chewable tablets in the treatment and control of natural infestations of ticks on dogs presented as veterinary patients to practices in Germany, Hungary and Portugal. Dogs of various breeds ranging

in age (0.18 to 16.6 years) and weight (2.2 to 73.9 kg bw) and infested with at least 3 live attached ticks (*Rhipicephalus sanguineus, Dermacentor reticulatus, Ixodes ricinus* or *I. hexagonus*) received either lotilaner at the recommended dose of 20 to 43 mg/kg, orally at monthly intervals for 3 months (for efficacy evaluation: n=127), or an authorised positive control, a spot-on containing fipronil and (s)-methoprene (for efficacy evaluation: n=68). Dogs were checked for ticks at day 0, 7, 14, 21, 28, 42, 56, 70 and 84. The primary efficacy end point 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 live, attached ticks (the percentage reduction in live tick counts from baseline at the post-treatment time points, average of all visits, over all tick species combined).

The average percent efficacy over all study visits was 98.6% (arithmetic mean) and 99.3% (geometric mean) for the test product group and 97.4% (arithmetic mean) and 98.3% (geometric mean) for the control product group. Tick counts of the test product treated group were compared to those of the control product group for non-inferiority, with a 15% margin, for each time point during the study. Over all visits, non-inferiority was confirmed.

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 (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus* and *Ixodes hexagonus*) under natural conditions. In addition, the test item is generally well tolerated.

Fleas:

The findings of the dose confirmation studies were confirmed by a European multicentre field study conducted in the Germany, Hungary and Portugal. The primary objective was to evaluate the efficacy and safety of lotilaner tablets for dogs administered three times, every 4 weeks, at the minimum dose rate of 20 mg/kg body weight for the treatment and control of fleas (*C. felis* and *C. canis*) in naturally infested dogs under field conditions in Europe, compared to an authorised reference product, a spot-on containing fipronil. The effect of the product on clinical signs (pruritus, erythema, scaling, papules, alopecia, and pyoderma) associated with Flea Allergy Dermatitis (FAD) as well as the palatability of the product, were also evaluated. The primary efficacy end point 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 (the percentage reduction in flea counts from baseline at the post-treatment time points, average of all visits). Secondary objectives were to evaluate the efficacy of lotilaner in the reduction of clinical signs associated with flea allergy dermatitis (FAD), and the palatability of Credelio chewable tablets.

Credelio chewable tablets were administered by the animal owner under fed conditions (last meal taken less than 30 minutes before treatment), and the voluntary consumption of the tablets was assessed by the owner. A total number of 192 primary dogs were included in the study on day 0. One dog in each household that was infested with more than 5 live fleas at enrolment, was selected as primary patient. All other dogs in the same household (up to two), regardless of whether they were infested with fleas or not, were enrolled as supplementary dogs which were only monitored for safety evaluation. Dogs (127 purebred and 144 crossbreeds, 133 females and 138 males, 0.17–15.0 years of age, 2.4 to 62.1 kilograms body weight at enrolment) that were infested with at least 5 live fleas were enrolled, and treated either with the recommended dose of 20 to 43 mg/kg bw lotilaner (for efficacy evaluation: n=128) administered orally at monthly intervals for three months, or an authorised positive control (for efficacy evaluation: n=64). Flea counts and clinical signs were monitored at Day 0, 14, 28, 56 and 84.

In terms of efficacy, the overall conclusions of the study are accepted: the product when administered to dogs under field conditions of use was effective against the claimed flea species (*C. felis* and *C. canis*). At all times (day 14–84 after treatment), the mean efficacy compared to baseline was above 99% when using the arithmetic or the geometric mean counts of the test product group; and above 58% (arithmetic mean) and 91.2% (geometric mean) with the control product group. Non-inferiority of the test product as compared to the control product was shown at all time points.

Over the course of the study, there was a reduction in the numbers of animals with clinical signs of FAD in both study groups. Given that the product is clearly effective 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.

Lotilaner chewable tablets were voluntarily and fully consumed within two minutes on 80% of all 539 occasions offered to primary and supplementary dogs; therefore, it is accepted that the product is palatable. The assessment of palatability was in line with the CVMP guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011).

Regarding safety, the test product appears to have been well tolerated.

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 flea infestation (*Ctenocephalides canis*, *C. felis*) under natural conditions and may support the treatment of the FAD. The test item is generally well tolerated.

Overall conclusion on efficacy

A comprehensive efficacy dataset has been provided.

Pharmacodynamics:

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

Pharmacokinetics:

Following oral administration to the dog, lotilaner is rapidly absorbed, but is slowly eliminated. In fed conditions, the mean maximum blood concentration (Cmax) was 3584 ng/ml at 2 hours (Tmax) after a 20 mg/kg dose. The half-life was estimated to be 30.7 days. Food enhances the absorption and lotilaner displays high systemic absorption in fed dogs (this effect is consistent over a number of studies reported). Therefore, lotilaner should be administered at or around the time of feeding. The major route of elimination is biliary excretion.

It is noted that elimination was faster and elimination half-life was shorter in very young animals, as compared to adults.

Dose finding:

Based on pharmacodynamics/pharmacokinetic modelling and a comprehensive suite of dose finding studies in fleas and ticks, a single oral dose of 20 mg/kg of lotilaner was chosen as the minimal efficacious dose over a period of one month.

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 Beagle puppies, is well tolerated. In the pivotal study conducted in accordance with OECD principles of Good Laboratory Practices and in line with the guideline on target animal safety for veterinary pharmaceutical products (VICH GL 43), there were no treatment-related (toxicologically relevant) findings. In the exploratory tolerance studies, some statistical changes in various clinical pathology parameters (notably, blood urea nitrogen and blood glucose) were observed. For these changes a relationship with treatment is unclear; however, it is notable that such effects were not detected in the pivotal study (conducted over 8 months).

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 and diarrhoea) were observed in a number of dogs within a short period of time following treatment. Given their proximity to product administration these events may be treatment-related. However, the number of observations of gastrointestinal disorder in the various clinical studies is very low and, while numerically greater in the lotilaner treated animals than in control animals, a statistically significant difference between groups was not detected. Further, it is acknowledged that mild gastrointestinal upset is not an uncommon event in otherwise healthy animals. In the absence of a clear association between treatment and these observed effects, the wording 'none known' can be accepted for section 4.6 of the SPC. The occurrence of all adverse events, including gastro-intestinal effects, will be monitored post-authorisation. In the event that a signal is detected and that a clear association with treatment is established, the applicant will be requested to update the product information accordingly.

Palatability:

Palatability of the product was investigated and confirmed as part of the EU field trials.

Efficacy:

A single dose of lotilaner (20–43 mg/kg bw) showed efficacy up to 5 weeks after treatment for fleas (*C. felis*, *C. canis*) and the tick species investigated. When the available data are viewed against the proposed indication, the CVMP concludes as follows:

- The claim for efficacy against both *Ctenocephalides felis* and *C. canis* can be accepted.
- The tick claim should be limited to those tick species for which two dose confirmation studies, supported by appropriate field studies, have been provided and which are relevant to the European situation (detected on test animals in field studies). Accordingly, the following tick species can be included as part of the indication: *Rhipicephalus sanguineus, Ixodes ricinus, I. hexagonus* and *Dermacentor reticulatus*.
- Information on speed of kill should be moved to section 5.1 of the SPC. Based on the data presented, the CVMP is prepared to accept an onset of efficacy of 6 hours for existing flea infestations (that is, speed of effect measured on the day of treatment) and 4 hours for new flea infestations (that is, speed of effect measured at subsequent time points for up to one month after treatment). However, it is the opinion of the CVMP that the data for ticks do not support a speed of effect less than 48 hours.
- The data presented support the proposed indication for use as part of a treatment strategy for the control of flea allergy dermatitis (FAD).
- Based on the flea speed of kill data, and noting the biology of the parasite, it is accepted that the product will kill existing and newly emerged fleas on dogs before they can lay eggs. Therefore, the product will help break the flea life-cycle.

Part 5 – Benefit-risk assessment

Introduction

Credelio chewable tablets for dogs contain lotilaner as the active substance. The product is available in 5 different strengths of either 56 mg, 112 mg, 225 mg, 450 mg or 900 mg per tablet. The route of administration is oral use.

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

The application was submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The benefit of Credelio is its efficacy in the treatment of tick (*Dermacentor reticulatus*, *Ixodes hexagonus, Ixodes ricinus and Rhipicephalus sanguineus)* and flea *(Ctenocephalides felis and Ctenocephalides canis*) infestations in dogs and its use as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Additional benefits

Credelio chewable tablets increase the range of available treatment possibilities against flea and tick infestation in dogs. It will help to reduce the risk of infestation of other animals in contact with infested dogs. The product is easy to apply by the owner at home as it is palatable for most dogs.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Based on the presented information on the development, manufacture and control of the active substance and finished product, the product is of appropriate quality and the information 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 Beagle puppies, is well tolerated. Similarly, in the various laboratory and clinical efficacy studies conducted, the product was generally well tolerated.

No data were submitted on reproductive toxicity in the target species and this is addressed in the product information.

Risk for the user:

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

Risk for the environment:

Credelio tablets for dogs 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 environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

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

The benefit-risk balance of the application is positive.

Conclusion

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 for Credelio 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 the marketing authorisation for the above mentioned medicinal product.