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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Credelio Plus (EMEA/V/C/005325/0000)

INN: lotilaner / milbemycin oxime

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

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Introduction

The applicant Elanco GmbH submitted, on 1 November 2019, an application for a marketing authorisation to the European Medicines Agency (the Agency) for Credelio Plus through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

On 17 February 2021, the CVMP adopted an opinion and CVMP assessment report.

On <date>, the European Commission adopted a Commission Decision granting the marketing authorisation for Credelio Plus.

The eligibility to the centralised procedure was agreed upon by the CVMP on 16 April 2019 as Credelio Plus contains a combination of existing active substances (lotilaner/milbemycin oxime), one of which (lotilaner) was not authorised in a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

At the time of submission, the applicant applied for the following indications:

"For use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm.

This veterinary medicinal product is intended for use where treatment and/or prevention of two or more of the indications below is required concurrently.

Ticks and fleas

For the treatment of tick (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus* and *I. hexagonus*) and flea (*Ctenocephalides felis* and *C. canis*) infestations in dogs.

This veterinary medicinal product provides immediate and persistent killing activity for 1 month for ticks and fleas.

Ticks and fleas 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).

Gastrointestinal nematodes

Treatment of gastrointestinal nematodes: hookworm (adult and larval *Ancylostoma caninum*), roundworms (adult and larval *Toxocara canis*, adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*).

Heartworm

Prevention of heartworm disease (*Dirofilaria immitis*).

Lungworm

Prevention of angiostrongylosis by reduction of the level of infection with immature adult (L5) and adult stages of *Angiostrongylus vasorum* (lungworm) with monthly administration."

The active substance of Credelio Plus is a combination of lotilaner and milbemycin oxime, both parasiticides of the isoxazoline and milbemycins class, respectively. Lotilaner is an inhibitor of gamma–aminobutyric acid (GABA)-gated chloride channels and milbemycin oxime opens glutamate-sensitive chloride channels. Both actions result in the death of various parasites such as insects, acari and helminths. The target species is dogs.

Credelio Plus is presented as chewable tablets in strengths of (lotilaner + milbemycin oxime) 56.25 mg + 2.11 mg, 112.5 mg + 4.22 mg, 225 mg + 8.44 mg, 450 mg + 16.88 mg and 900 mg + 33.75 mg. The product is presented in packs of 1, 3, 6 and 18 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 13b of Directive 2001/82/EC – a fixed combination application.

Scientific advice

The applicant received scientific advice from the CVMP on 6 November 2015 (EMA/CVMP/SAWP/546084/2015) and 19 July 2018 (EMA/CVMP/SAWP/293418/2018). The scientific advice pertained to safety and efficacy as well as to efficacy, quality and safety issues, respectively. In most respects, the scientific advice provided by the CVMP has been followed by the applicant.

With respect to quality, a new dissolution method was introduced in line with the approach approved in scientific advice EMA/CVMP/SAWP/293418/2018.

MUMS/limited market status

Not applicable.

Part 1 – Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated October 2018), 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

Batch release of the dosage form takes place in France at Elanco France S.A.S. Huningue, France. The site has GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms.

Primary and secondary packaging takes place in the EEA. The site has GMP certification which confirms the date of the last inspection and shows that the site is authorised for the packaging of medicinal products.

A GMP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration was issued following an on-site audit of each of the sites between 2017 and 2019.

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 is in line with legal requirements.

Part 2 – Quality

Composition

The finished product is presented as a chewable, flavoured tablet containing the active substances lotilaner and milbemycin oxime in 5 tablet strengths (lotilaner/milbemycin oxime): 56.25 mg/2.11 mg, 112.5 mg/4.22 mg, 225 mg /8.44 mg, 450 mg/16.88 mg and 900 mg/33.75 mg of lotilaner and milbemycin oxime, respectively. The other ingredients are cellulose powdered, lactose monohydrate, silicified microcrystalline cellulose, meat dry flavour, crospovidone, povidone, sodium laurilsulfate, silica colloidal anhydrous and magnesium stearate.

Containers

Tablets are packaged in an Aluminium/Aluminium (Alu/Alu) perforated unit dose blister within a carton box.

The 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.

Development pharmaceutics

The qualitative and quantitative composition of the drug product was driven by the selected manufacturing process (wet granulation and tablet compression), which in turn was driven by the properties of the active substances: wet granulation was used to accommodate the drug load of lotilaner, which has a low flowability. The active substance lotilaner has one chiral centre and the *S*-isomer of lotilaner is used in the product, which is the clinically relevant isomer, along with the use of the thermodynamically more stable polymorph G. Particle size, polymorphism and enantiomeric purity are routinely controlled on the active substance specification, in line with material used in batches used in clinical studies.

Formulation development was also focussed on an 80:3 ratio of lotilaner to milbemycin oxime. As such, homogeneity of milbemycin oxime is a critical issue in manufacturing. Incorporation of the active substance intra-granularly demonstrated acceptable content uniformity and assay for milbemycin oxime.

Derivation of the formulation is logical and well described in the dossier and the formulation components are commonly used in this 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. Although different sources of milbemycin oxime were used in the bulk of the target animal studies, batches of the finished product manufactured with milbemycin oxime from the proposed manufacturer were used in at least one study each for efficacy on ectoparasites, efficacy on endoparasites, safety and pharmacokinetics, and the formulation used in these studies is the same as that intended for marketing.

Investigation of the dissolution test is described. Establishment of the dissolution limits was carried out in line with the recommendations of the "Reflection paper on the dissolution specification for generic

oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/226031/2017), using batches from clinical studies only. The dissolution limits are considered to be acceptable.

Method of manufacture

The manufacturing process is a standard wet granulation process with all intra-granulation excipients and the active substances mixed in a high shear granulator equipped with spraying nozzles. Purified water is added and granulation stopped at the appropriate instantaneous power endpoint. These granules are then dried under vacuum until the desired loss on drying is obtained. The granules are milled through a screening mill before preparation of the final blend. The extra granular excipients, except magnesium stearate (the lubricant), are then pre-mixed and subsequently screened through a sieve. The screened extra granular excipients are then mixed with the granules in a diffusion tumble blender. The lubricant is screened, added and mixing is then performed to produce the final blend for compression. The tablets are compressed into the desired weight using a rotary tablet press and packaged in bulk packaging. The final packaging is Alu/Alu blister. With respect to the proposed in-process controls, the applicant has proposed control of process parameters within specified ranges that will ensure a consistent and clinically relevant dissolution profile for both active substances based on the process parameters used for manufacture of the batches used in clinical trials.

The manufacturing process is not a standard one. Given that it contains an active substance in low content (≤ 2% of composition), acceptable justification has been provided and, in accordance with the "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 in the application dossier is not required. Thus, an acceptable validation protocol has been provided.

Control of starting materials

Active substance

Milbemycin oxime

There is a monograph of milbemycin oxime in the Ph. Eur. and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for milbemycin oxime, a copy of which has been provided with the application. The relevant information has been assessed by the EDQM before issuing the CEP. The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for residual solvents compliant with the requirements of VICH GL 18, for microbial quality in line with the requirements of Ph. Eur. general text 5.1.4, and regarding particle size in line with material used in batches used in clinical studies. All additional methods have been validated. Confirmation that the working standard has been characterised against the Ph. Eur. chemical reference substances (CRS) is provided. Stability data has been provided for milbemycin oxime from the active substance manufacturer and it is considered that the proposed re-test period of 24 months for milbemycin oxime, stored in the original tight container protected from light, is supported by the stability data provided.

Lotilaner

The active substance, lotilaner, is a member of the isoxazoline class of parasiticides. The information on the active substance is provided in the dossier. 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.

Lotilaner is manufactured in an eight-step synthetic process using four starting materials, followed by micronisation. Sufficient detail is provided on the manufacturing process, including amounts of raw materials and reaction parameters. The choice of the starting materials are justified by the following facts: they are a discrete chemical entities that can be well characterised; they are synthesised in a linear process comprising simple and well-established chemistry; the molecular structures are not complex and not chiral; potential impurities are controlled in the starting material so that they are removed in the first step of the process after introduction and are not carried over into the active substance; and there are multiple steps and chemical transformations in the active substance synthesis after their introduction. The proposed starting materials are in line with the conclusions drawn in the scientific advice given on the designation of the starting materials for lotilaner in EMA/CVMP/SAWP/230321/2015 and are considered to be acceptable. The specifications and control methods for intermediate products, starting materials and reagents have been adequately presented.

The characterisation of the active substance is in accordance with the "Guideline on the chemistry of active substances for veterinary medicinal products" (EMA/CVMP/QWP/707366/2017). 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. It includes tests for appearance, identification, 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 GL 2. Batch analysis data is provided for 11 development and production-scale batches of the active substance and all results comply with the proposed specification and were consistent from batch to batch. Satisfactory information regarding the reference standards has been presented.

Stability data are provided for 3 registration batches of the active substance manufactured in September 2012 and for 3 commercial batches manufactured in August 2016. The samples on stability were packaged in a container closure system that simulates that used for the bulk active substance. Data was provided to 60 months on long term (25 °C/60% relative humidity [RH]), intermediate (30 °C/65% RH) and cooled (5 °C/ambient humidity) conditions, to 24 months on accelerated (40 °C/75% RH) conditions for the registration batches and to 24 months on long-term stability conditions only for the additional 3 commercial batches. All results are within specification, with no trending apparent for all batches on all 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, and tested for identity, assay, related substances, and enantiomeric purity. Degradation was observed for strongly acidic conditions and under UV light and the HPLC method was shown to be stability-indicating. 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 controlled in accordance with their respective Ph. Eur. monographs, with the exception of silicified microcrystalline cellulose and the excipient meat dry flavour.

Silicified microcrystalline cellulose is not monographed in the Ph. Eur. and is therefore controlled in line with its USP/NF monograph. In addition, it has been confirmed that the components of this excipient, i.e. microcrystalline cellulose and colloidal anhydrous silica, comply with their Ph. Eur. monographs.

The meat dry flavour is controlled in line with an in-house specification. Limits for functionality-related

characteristics are included in the specifications of the excipients and justification was provided for the functionality-related characteristics that were not included. The compliance of the excipients with the requirements of Ph. Eur. general text 5.1.4 for non-sterile substances for pharmaceutical use is detailed. A satisfactory specification is provided for the meat dry flavour, along with information on its manufacture and composition.

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

The meat dry flavour is produced from porcine livers. Pigs are however not a TSE relevant species as defined in the current version of the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the above-mentioned note for guidance (EMA/410/01 rev.3). A declaration has been provided that the meat dry flavour is produced in the Netherlands from processed pork livers from European countries and that it is fit for human consumption.

Lactose monohydrate is sourced from milk from healthy animals under the same conditions 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" (EMA/410/01 rev.3).

The Ph. Eur. CEP for milbemycin oxime states that that the holder of the certificate has declared the use of material of human or animal origin in the manufacture of the active substance. However, the TSE risk will have been evaluated during the CEP procedure by EDQM, and so it is accepted that the material must have been demonstrated to comply with the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" (EMA/410/01 rev.3).

In addition, a risk assessment on viral safety of the meat dry flavour was provided, which is considered to be acceptable.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form. Parameters on the specification are identification, appearance, moisture content, content of the active substances and their degradation products, uniformity of dosage units, dissolution, microbiological testing, mean tablet weight, mean tablet hardness and friability. The proposed specification for tablet dissolution has been set based on results obtained for the clinical trial batches, in line with the recommendations of the "Reflection paper on the dissolution specification for generic oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/226031/2017). Satisfactory supporting data has been provided to justify the lack of a test and limit for the enantiomeric impurity for lotilaner. The validation of the analytical methods is in accordance with the VICH GL 2 ("Validation of analytical procedures: methodology").

Batch data is provided for 1 pilot-scale batch of each strength, 6 production-scale batches each of the lowest strength tablet (lotilaner/milbemycin oxime: 56.25 mg/2.11 mg) and the highest strength tablet (lotilaner/milbemycin oxime: 900 mg/33.75 mg), and 2 production-scale batches each of the three intermediate strengths (lotilaner/milbemycin oxime: 112.5 mg/4.22 mg, 225 mg/8.44 mg and 450 mg/16.88 mg). The data demonstrate compliance with the proposed specifications and are

comparable between batches. Satisfactory information regarding the reference standards used for assay of both active substances has been presented.

Stability

The proposed specification for shelf life is the same as that for release with the following exceptions: moisture content and uniformity of dosage units are omitted from the shelf life specification and acceptable widening is proposed to the limits for unspecified degradation products of lotilaner in line with VICH GL 11 limits.

A stability study on tablets stored in the proposed bulk intermediate container (double polyethylene bags with silica gel desiccant packets in drums) was conducted. Testing was conducted on the smallest and largest tablets from two production-scale batches and samples were stored at monitored warehouse conditions before being 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 shelf life of 12 months stored in the original bulk container is considered acceptable.

A stability study on production-scale batches stored in the Alu/Alu blisters was conducted. As the tablets are compressed from a common blend, a partial bracketing approach in accordance with VICH GL 45 was used: 3 batches each of the lowest (lotilaner/milbemycin oxime: 56.25 mg/2.11 mg) and highest (lotilaner/milbemycin oxime: 900 mg/33.75 mg) strengths, and one batch each of the three intermediate strengths were included in the study. Samples were stored at 25 ºC/60% RH, 30 ºC/65% RH and 40 ºC/75% RH according to VICH GL 3 and stability data is available to 24 months. Samples were also tested following storage at 5 °C/ambient humidity to 24 months, and at 50 °C/ambient humidity for 1 month. The study is scheduled to continue up to 60 months. Photostability studies were not conducted, as the Alu/Alu blisters provide protection from light. A satisfactory post-approval stability protocol and commitment is included in the dossier.

All results are in compliance with the proposed specification. Overall, although decreases or decreasing trends were noted for most of the batches for both active substances, the magnitude of the decrease is within the tolerated range for method variation and no widening of the assay specification for shelf life compared with release is proposed. The proposed finished product shelf-life of 3 years with no special storage precautions is supported by the stability data provided.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance is generally satisfactory.

The quality of this product can be 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 the dissolution limits have been set in line with the recommendations of the "Reflection paper on the dissolution specification for generic oral immediate release products with systemic action" (EMA/CHMP/CVMP/QWP/226031/2017) using batches from clinical studies and are considered to be acceptable. Data has been presented to give reassurance on TSE and viral safety.

The active substance milbemycin oxime is monographed in the Ph. Eur. and the manufacturer of the active substance has been granted a CEP, a copy of which has been provided within the application.

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.

In addition, the applicant has committed to generate the following information post-authorisation:

- Process validation studies on at least three consecutive commercial batches.
- The first 3 batches produced for commercial release of the lowest (lotilaner/milbemycin oxime: 56.25 mg/2.11 mg) and highest (lotilaner/milbemycin oxime: 900 mg/33.75 mg) strengths to be placed in a stability study, for which the protocol has already been approved.

Although the manufacturing process is not a standard one, given that it contains an active substance in low content (≤ 2% of composition), acceptable justification has been provided and, in accordance with the "Guideline on process validation for finished products — information and data to be provided in regulatory submissions" (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), it was accepted that full-scale validation would be performed post-authorisation.

The applicant has provided an acceptable protocol for the process validation study.

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. Based on the review of the data on quality, the manufacture and control of the product are considered to be acceptable.

Part 3 – Safety

Credelio Plus chewable tablets for dogs contain a fixed combination of lotilaner and milbemycin oxime. It is indicated for use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm.

A safety file in accordance with Article 12(3)(j) has been provided.

Safety documentation

Lotilaner and milbemycin oxime have been previously assessed by the CVMP and the present assessment considers data previously provided by the applicant in the dossiers for Credelio and Trifexis, as well as studies conducted with the Credelio Plus.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

Single dose toxicity

Lotilaner

No single dose toxicity studies for the individual active substance have been provided.

Milbemycin oxime

Milbemycin oxime has been shown, after oral administration, to be of moderate general toxicity. It is reported to have an acute oral LD_{50} of 863 mg/kg in male rats and 532 mg/kg in female rats. The intraperitoneal LD_{50} was 454 mg/kg and 318 mg/kg in male and female rats, respectively.

No systemic effects after dermal application were observed in rats up to a dose of 5000 mg/kg bw.

Lotilaner and milbemycin oxime in combination

An acute toxicity study investigating the effects of a lotilaner and milbemycin-formulated tablet when administered by the oral route of administration to rats has been provided. The study was compliant with GLP principles and OECD guidelines. The acute oral LD_{50} for the formulated tablet containing lotilaner (450 mg) and milbemycin oxime (16.88 mg) in rats was greater than 2000 mg/kg of the combined active substances. No mortality, clinical findings and no adverse events were observed. No remarkable bodyweight (bw) changes were noted. At necropsy, no test-article related macroscopic findings were recorded. The tablet formulation was considered to have no significant acute toxic risk.

Repeat dose toxicity

Lotilaner

Five repeat dose oral toxicity studies have been provided. All studies were conducted in the rat. Three of these are classified as exploratory non-GLP-compliant studies. The two GLP-compliant studies were conducted in accordance with OECD GLs 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, bodyweight and food decreases were recorded when lotilaner was administered at high doses. Consequent to decreases in food intake and bodyweight, decreases in organ weights and changes in clinical pathology were recorded. 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 in the rat, that the no observed adverse effect level (NOAEL) be set at 5 mg/kg bw/day.

Milbemycin oxime

Milbemycin oxime showed haematological changes at 30 mg/kg bw/day and above, liver changes at 100 mg/kg bw/day and bodyweight loss at 300 mg/kg bw/day in a repeated dose toxicity study in rats.

Lotilaner and milbemycin oxime in combination

No repeat dose toxicity studies for lotilaner and milbemycin oxime in combination in laboratory animals (rats, mice) were provided. However, repeat dose studies were conducted with lotilaner and milbemycin oxime in the target species, investigating target animal tolerance. This is considered acceptable.

In the exploratory target animal tolerance study, 9-week old dogs were administered up to 200 mg/kg lotilaner/7.5 mg/kg milbemycin oxime orally as capsules on days 0, 24 and 52 in a fed state. The maximum desired target dose was achieved by daily administration of 40 mg/kg lotilaner/1.5 mg/kg milbemycin oxime up to a five-day period, to give 1x, 3x or 5x the recommended dose. Evidence of treatment-related adverse effects including soft faeces, mucoid faeces and diarrhoea as well as

possibly blood in faeces was observed when the early dose formulation containing lotilaner and milbemycin oxime was administered.

In the pivotal GLP-compliant target animal tolerance study, 8-week old dogs were administered 1x, 3x or 5x a dose of 30–40 mg/kg lotilaner/1.125–1.5 mg/kg milbemycin oxime at 28-day intervals for nine dose cycles. Tablets were administered once daily for up to 5 consecutive days once every 28 days to achieve the target dose. It was concluded that no clinically relevant findings attributable to the test item outside of biological variation were observed. The test item was considered to be well tolerated.

In the second pivotal GLP-compliant target animal tolerance study, 30–40 mg/kg lotilaner/1.125–1.5 mg/kg milbemycin oxime were administered to 11-month old dogs at 1x, 3x or 5x the intended therapeutic dose range once every 28 days for 7 consecutive months. Tablets were administered once daily for up to 5 consecutive days to achieve the target dose. The product was generally considered to be well tolerated, although a higher incidence of gastrointestinal disturbances (loose and mucoid stools) were observed in treated groups across all days and across dosing days when all cycles were combined. However, no dose-response was observed.

The repeat dose studies did not identify signs indicative of carcinogenicity, immunotoxicity or neurotoxicity. The available *in vivo* data with the combination administered to the target species do not indicate an altered safety profile of the fixed combination compared to the safety profile of the individual substances when administered alone.

Tolerance in the target species of animal

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

Reproductive toxicity

Lotilaner

A GLP-compliant, 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 GL 416.

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 a 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. However, 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.

A developmental toxicity study was conducted in the rat at doses of 9, 18 and 50 mg/kg bw/day. This was a GLP-compliant study conducted in accordance with OECD GL 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.

Milbemycin oxime

Milbemycin did not show teratogenic potential when examined in two species (rats and rabbits) up to doses of 30 mg/kg bw. In addition, a reproductive toxicity study using a combination product containing this substance was performed in the target animal species. Treatment was applied monthly from at least 43 days prior to mating until weaning at 42 days postpartum. Most reproductive parameters were equal in the placebo and treatment groups. Due to the small sample size, final conclusions could not be drawn, but a treatment of bitches with a mean dose of 0.87 mg/kg bw milbemycin oxime did not appear to influence fertility or pup viability.

Lotilaner and milbemycin oxime combined

No reproductive toxicity studies have been provided with lotilaner and milbemycin oxime in combination.

Based on the available data on reproductive toxicity, the applicant has included the following text in the SPC:

"The safety of the veterinary medicinal product in breeding, pregnant and lactating dogs has not been investigated."

In addition, the following text is also included:

"Laboratory studies with the active substances in rats have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity of males and females."

Genotoxicity

The genotoxic potential of lotilaner and milbemycin oxime was evaluated in a standard test battery in accordance with VICH GL 23.

Lotilaner

- Lotilaner did not induce mutations in five histidine-requiring strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537 and TA102) with or without metabolic activation in the bacterial reverse mutation assay.
- Lotilaner was negative for inducing chromosome aberrations in human lymphocytes in the *in vitro* chromosome aberration assay.
- Lotilaner was negative in the *in vivo* micronucleus assay in male rats.

Milbemycin oxime

- Milbemycin oxime did not induce mutations in *S. typhimurium* or *E. coli* strains in the presence or absence of metabolic activation in the bacterial reverse mutation assay.
- Milbemycin oxime was negative for inducing structural and numerical chromosome aberrations in CHO cells in the *in vitro* chromosome aberration assay.
- Milbemycin oxime was negative in the *in vivo* micronucleus assay in male ICR mice.

Based on the above studies, it is concluded that lotilaner and milbemycin oxime are not genotoxic.

Carcinogenicity

Lotilaner

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

Milbemycin oxime

No carcinogenicity data have been provided. The absence of genotoxic/mutagenic potential and the absence of structural alerts indicates that the likelihood of carcinogenic potential for milbemycin oxime is low.

Lotilaner and milbemycin oxime combined

No carcinogenicity studies have been provided for lotilaner or milbemycin oxime, alone or in combination. Based on the negative results in genotoxicity studies, absence of structural alerts and absence of neoplastic lesions in repeat dose studies this is acceptable.

Studies of other effects

The dermal irritation potential of the final formulation was evaluated in an *in vivo* study in New Zealand White rabbits. Lotilaner and milbemycin oxime combination tablets were found to be slightly irritating to skin.

In a local lymph node assay in mice, the final formulation tested at concentrations up to 25% did not show any skin sensitisation potential.

No specific studies on the immunotoxicity or neurotoxicity of lotilaner and milbemycin oxime were provided. However, the repeat dose toxicity studies and assessment of tolerance in the target species did not identify changes indicative of immunotoxicity or neurotoxicity.

Excipients

All excipients are either natural food ingredients, approved food additives, or approved for the use in food- producing animals (with a "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 substances, i.e. lotilaner and milbemycin oxime.

User safety

The applicant has presented a user safety risk assessment which is broadly in line with the recommendations of CVMP "Guideline on user safety for pharmaceutical veterinary medicinal products" (EMEA/CVMP/543/03-Rev.1). This is considered acceptable.

Credelio Plus chewable tablets for dogs will be provided in aluminium/aluminium blisters with 1, 3, 6 or 18 tablets per pack. The maximum tablet strength contains 900 mg lotilaner and 33.75 mg milbemycin oxime and is to be administered at monthly intervals.

In a number of target animal studies, gastrointestinal disturbances have been observed in individual animals following treatment with lotilaner and milbemycin oxime.

The main routes of exposure are considered to be dermal contact by the user when administering the product to dogs and accidental oral ingestion by a child. In relation to dermal exposure, it is accepted that exposure to the active substances is likely to be very low and so a quantitative risk assessment is not required. Although the product is potentially slightly irritating to the skin, when the low exposure is

taken into account, together with standard hygiene measures, the risk to the user is considered acceptable. The user warning "Wash hands after handling the product" is included in the SPC and is considered to be appropriate. The same considerations for dermal exposure are also considered to be applicable to ocular exposure.

The greatest potential exposure scenario is considered to be accidental ingestion of a tablet by a child as a single exposure. The information provided suggests a margin of exposure (MOE) of 4 for lotilaner and 4 for milbemycin oxime when the largest tablet size of 900 mg lotilaner and 33.75 mg milbemycin oxime is ingested by a child weighing 15 kg. This is based on the NOAEL for lotilaner of 240 mg/kg bw/day and for milbemycin oxime of 9 mg/kg bw/day derived from the single-dose acute target animal safety study in Beagle dogs. An MOE of less than 100 indicates that appropriate risk management measures should be proposed, e.g. child-resistant packaging. The product will be presented in child-resistant packaging, demonstrated as being in accordance with European standard EN 14375, and this mitigation measure, together with appropriate warnings on the packaging, are considered to mitigate the concerns of accidental oral ingestion by a child.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines.

The environmental risk assessment can stop in phase I and no phase II assessment is required since the veterinary medicinal product will only be used in non-food-producing animals.

Conclusions on the environmental risk assessment

An ERA was provided according to the CVMP/VICH guidelines. Based on the data provided, the ERA can stop at phase I. Credelio Plus chewable tablets are not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

For pharmacological properties, see part 4.

Lotilaner

The safety information on lotilaner is summarised below.

- Based on a 13-week study, the no observed adverse effect level (NOAEL) in the rat was set to 5 mg/kg bw/day. Bodyweight and food decreases were recorded when lotilaner was administered at high doses. Consequent to decreases in food intake and bodyweight, decreases in organ weights and changes in clinical pathology were recorded. Skin lesions and pathological findings in the ovaries and lungs were also observed.
- The NOAEL for maternal toxicity and for embryofoetal toxicity in the rat was considered to be 18 mg/kg bw/day.
- Lotilaner did not induce gene mutations in bacterial cells with or without metabolic activation in the bacterial reverse mutation assay. It did not cause chromosomal damage in human lymphocytes in the *in vitro* chromosome aberration test. The *in vivo* micronucleus test in male rat bone marrow cells was also negative. It is concluded that lotilaner is non-genotoxic and unlikely to be carcinogenic.

- No carcinogenicity studies have been provided for lotilaner. The absence of genotoxic effects indicates that the likelihood of carcinogenic potential for lotilaner is low. The observations in chronic toxicity studies provided no indication of neoplastic lesions. The absence of carcinogenicity studies is considered justified for lotilaner.
- No specific studies on the immunotoxicity or neurotoxicity of lotilaner were provided. However, the repeat dose toxicity studies and assessment of tolerance in the target species did not identify changes indicative of immunotoxicity or neurotoxicity.
- No local effect studies were provided for lotilaner. The omission of these can be accepted on the basis that studies investigating the combination of active substances have been provided.

Milbemycin oxime

Milbemycin oxime is claimed to be well-established in veterinary medicine. The safety information on milbemycin oxime is summarised below.

- An acute oral LD_{50} of 863 mg/kg bw in male rats and 532 mg/kg bw in female rats and intraperitoneal LD_{50} of 454 mg/kg bw and 318 mg/kg bw in male and female rats, respectively, have been reported in the published literature. No systemic effects after dermal application were observed in rats up to a dose of 5000 mg/kg bw.
- In a repeated dose toxicity study in rats, milbemycin oxime showed haematological changes at 30 mg/kg bw/day and above, liver changes at 100 mg/kg bw/day and bodyweight loss at 300 mg/kg bw/day.
- Milbemycin oxime did not show a teratogenic potential when examined in two species (rats and rabbits) up to doses of 30 mg/kg bw.
- Milbemycin oxime did not induce gene mutations in bacterial cells with or without metabolic activation in the bacterial reverse mutation assay. It did not cause chromosomal damage in CHO cells in the *in vitro* chromosome aberration test. The *in vivo* micronucleus test in bone marrow cells derived from male ICR mice was also negative. It is concluded that milbemycin oxime is not genotoxic and does not possess structural alerts.
- No specific studies on the immunotoxicity or neurotoxicity of milbemycin oxime were provided. However, the repeat dose toxicity studies and assessment of tolerance in the target species did not identify changes indicative of immunotoxicity or neurotoxicity.
- No local effect studies were provided for milbemycin oxime. The omission of these can be accepted on the basis that studies investigating the combination of active substances have been provided.

Lotilaner and milbemycin oxime combined

- The acute oral LD_{50} for the formulated tablet containing lotilaner (450 mg) and milbemycin oxime (16.88 mg) in rats was greater than 2000 mg/kg (combined active substances). The tablet formulation is considered to have no significant acute toxic risk.
- No repeat dose toxicity tests for lotilaner and milbemycin oxime in combination in laboratory animals (rats, mice) were provided. However, the applicant has conducted studies in the target species using the final formulation investigating target animal tolerance. These studies suggest that the combination is generally well tolerated, although the treatment does appear to be associated with gastrointestinal disturbances (loose and mucoid stools).
- No studies investigating the effect of the combination on reproduction/development have been provided.

- Studies to investigate the dermal irritation potential and skin-sensitising potential of the final formulation were provided. The combination of lotilaner and milbemycin oxime was found to be slightly irritating to skin and not considered to have skin-sensitising potential.
- The available *in vivo* data with the combination administered to both rodent and the target species do not indicate an altered safety profile of the fixed combination compared to the safety profile of the individual substances when administered alone.

Based on the available data on reproductive toxicity, the applicant has included the following text in the SPC:

"The safety of the veterinary medicinal product in breeding, pregnant and lactating dogs has not been investigated."

In addition, the following text is also included:

"Laboratory studies with the active substances in rats have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity of males and females."

The data presented are considered adequate to characterise the toxicity profile of the combined active substances.

A user safety assessment conducted broadly in accordance with relevant guidance was presented. The main routes of exposure are considered to be dermal contact by the user when administering the product to dogs and accidental oral ingestion by a child. The risk from dermal exposure is considered to be low and can be mitigated by standard hygiene measures. In the case of accidental oral ingestion by a child, a potential risk has been identified. However, the product will be presented in child-resistant packaging, demonstrated in accordance with European standard EN 14375, and this measure, together with appropriate warnings on the packaging, is considered to mitigate the concerns of accidental oral ingestion by a child.

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 the active substance of the veterinary medicinal product Credelio (EMEA/V/C/004247) authorised in 2017. Lotilaner is an acaricide and insecticide belonging to the isoxazoline family which blocks gamma amino butyric acid (GABA) and glutamate-gated chloride channels in the central nervous system of insects and acari, preventing the uptake of chloride ions by these channels and thus resulting in increased nerve stimulation and death of the target parasite.

The active substance milbemycin oxime is a well-established substance in dogs and is currently used alone or in combination in several oral veterinary medicinal products authorised throughout the EU. Milbemycin oxime is a member of the macrocyclic lactones class and contains two major forms, A3 and A4, in a ratio of 20:80, respectively. Milbemycin oxime acts by binding to chloride ion channels in invertebrate nerve and muscle cells. Increased permeability by the cell membrane to chloride ions causes hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the target parasite.

It is accepted that both of the active substances have already been authorised in veterinary medicinal products for indications similar to those being claimed for the candidate product. Whilst the documentation provided in support of the pharmacodynamic properties of both individual active substances is brief, it can be accepted that they have been adequately characterised.

Development of resistance

Lotilaner was first authorised in the EU for use in dogs in 2017 and in cats in 2018. No resistance to lotilaner has been reported to date.

It is acknowledged that there have been reports of resistance development of *A. caninum* and *D. immitis* to macrocyclic lactone use in dogs in the US. The CVMP is unaware of similar reports against *D. immitis* or *A. caninum* or against other gastrointestinal nematodes originating from within the EU. Further, it is accepted that macrocyclic lactones continue to be effective in the vast majority of situations and the appropriate use of macrocyclic lactone products as per label recommendation is the basis for effective heartworm prevention.

Given the concerns regarding resistance development, section 4.4 of the SPC includes prudent use warnings relating to the potential for resistance emergence. Further, the text in sections 4.2 and 4.9 of the SPC makes it clear that the fixed combination product is only intended for use when both active substances are required at the same time.

Pharmacokinetics

The pharmacokinetics of lotilaner and milbemycin oxime when administered alone and in combination were investigated in a series of studies in the target animal species. The findings of these pharmacokinetic studies can be summarised as follows:

Lotilaner

- After single oral dosing in adult Beagles, lotilaner was well absorbed with an absolute bioavailability value of 77% (GLP-compliant pivotal study).
- The effect of feeding on bioavailability was not determined for the combination product. That said, the results of the aforementioned study indicate that lotilaner administered concurrently with milbemycin oxime is highly bioavailable after oral administration in fed dogs. Section 4.9 of the SPC indicates that the product should be administered with or after food. This is considered appropriate.
- Following oral dosing, lotilaner reached a maximum concentration in plasma within 3–5 hours (T_{max}) after administration (GLP-compliant PK study).
- There is evidence of accumulation upon repeat dosing at the recommended therapeutic dose (RTD) at 28-day intervals, with a greater exposure observed in adult compared to 8-week old dogsnon-GLP-compliant. In adult dogs, the accumulation ratio was 1.75 and 1.4 for AUC and C_{max}, respectively. Accumulation is more pronounced in younger dogs (< 8 weeks old) with an accumulation ratio of 4 and 1.6 for AUC and C_{max}, respectively. Time to achieve steady state was estimated to be between dose cycles 4 and 5 in adults and between dose cycles 8 and 9 in juveniles. The difference in time to achieve steady state between adult and juvenile dogs was attributed to the changing physiology in juvenile dogs. Noting that in the target animal tolerance studies, steady state of lotilaner was achieved by the 4th dose in 11–12 month old dogs and by the 7th dose in 8-week old puppies, respectively, the CVMP considers that safety of lotilaner in the combination has been adequately investigated at steady state.

- Less-than-proportional increases were observed for both C_{max} and AUC_{0-672} in adult dogs administered the test item on a single occasion at dose of 1X, 1.5X and 2X the minimum RTD (GLP-compliant pivota studyl). Less-than-proportional exposure also appeared at the upper end of the dose range for 1X, 2X and 6X the minimum RTD in the non-GLP-compliant pilot study. Given that efficacy and safety studies were conducted using the lower and upper half of the proposed dose range, respectively, the non-linear dose finding is of limited significance.
- Lotilaner appeared to have a 2-fold increase in brain concentrations in Mdr1a/b knockout mice (non-GLP-compliant study, indicating that tolerance needs to be further considered in avermectin-sensitive (i.e. carrying an MDR1 gene mutation) Collies.
- The primary route of elimination of lotilaner is biliary excretion. 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.

Milbemycin oxime

- After single oral dosing in Beagles, milbemycin oxime was well absorbed with an absolute bioavailability value of 61%.
- The effect of feeding on bioavailability was not determined. That said, the results of the aforementioned study indicate that milbemycin oxime administered concurrently with lotilaner is highly bioavailable after oral administration in fed dogs. Therefore, the SPC recommendation to administer the combination product with or after food is appropriate.
- Following oral dosing, milbemycin oxime reached a maximum concentration in plasma within 2–4 hours (T_{max}) after administration (GLP-compliant study).
- There is evidence of accumulation upon repeat dosing at the RTD on 12 occasions at 28-day intervals (non-GLP-compliant study). In adult dogs, the accumulation ratio of milbemycin oxime A3 was 1.34 and 1.24 for AUC and C_{max}, respectively, and the accumulation ratio for milbemycin oxime A4 was 1.35 and 1.36 for AUC and C_{max}, respectively. In 8-week old puppies, the accumulation ratio of milbemycin oxime A3 was 2.3 and 1 for AUC and C_{max}, respectively, and the accumulation ratio for milbemycin oxime A4 was 2.4 and 1 for AUC and C_{max}, respectively. Time to achieve steady state was estimated to be between dose cycles 4 and 5 in adults and between dose cycle 8 and 9 in juveniles. The difference in time to achieve steady state between adult and juvenile dogs was attributed to the changing physiology in juvenile dogs. Noting that in the target animal tolerance studies there was no accumulation observed for either milbemycin oxime A3 or milbemycin oxime A4 in 11–12 month old dogs and, in another study, steady state was achieved in juveniles at dose 7 for milbemycin oxime A3 and dose 6 for milbemycin oxime A4, it is considered that safety of milbemycin oxime in the combination has been adequately investigated at steady state.
- A linear increase with dose was observed for AUC_{0-672} but not C_{max} in adult dogs administered the test item on a single occasion at dose of 1X, 1.5X and 2X the minimum RTD, (GLP-compliant pivotal study). A less-than-proportional exposure also appeared at the upper end of the dose range for 1X, 2X and 6X the minimum RTD in the non-GLP-compliant pilot study. Given that efficacy and safety studies were conducted using the lower and upper half of the proposed dose range, respectively, the non-linear dose finding is of limited significance.
- Milbemycin oxime had a 4 to 5-fold increase in brain concentrations in Mdr1a/b knockout mice(non-GLP-compliant study), indicating that tolerance needs to be further considered in avermectin-sensitive (i.e. carrying an MDR1 gene mutation) Collies.

- No new studies were conducted to evaluate distribution or excretion of MO. The CVMP indicated that publicly available information relating to the metabolism and excretion of milbemycin oxime could be accepted as substantial changes in MO excretion, metabolism and/or metabolites in the presence of lotilaner are not expected. According to the proposed text in section 5.1 of the SPC, excretion of milbemycin A3 and A4 5-oxime is primarily via faeces and, to a lesser extent, via the urine.

Interaction between lotilaner and milbemycin oxime

- The results of a non-GLP-compliant pilot study using a developmental liquid formulation (in capsule) indicated that the PK profile of lotilaner when administered concomitantly with milbemycin oxime is comparable to that obtained after administration of lotilaner alone. However, a distinct decrease in C_{max}, AUC and $t_{1/2}$ of milbemycin oxime was observed after a single dose in the combination when compared to the administration of milbemycin oxime alone.

  The applicant repeated the pharmacokinetic study to investigate potential interaction using the final formulation. In this study, it was confirmed that, after a single oral dose of the final formulation at the RTD in adult dogs, the PK profile of lotilaner when administered concomitantly with milbemycin oxime is comparable to that obtained after administration of lotilaner alone (C_{max}: 10.4 x 10^3 versus 10.7 x 10^3 ng/ml, AUC_{last}: 3430 x 10^3 versus 3130 x 10^3 h*ng/ml and $t_{½}$: 568 versus 547 hours). In terms of milbemycin oxime A3, it is noted that comparing the combination product to milbemycin oxime alone, C_{max} was lower (82.2 ng/ml versus 123 ng/ml), and AUC_{last} and $t_{½}$ are considered comparable (1750 versus 2030 h*ng/ml and 25 versus 26.1 hours respectively). Similarly, for milbemycin oxime A4, comparing the combination product to milbemycin oxime alone, C_{max} was lower (445 ng/ml versus 598 ng/ml), and AUC_{last} and $t_{½}$ are considered comparable (15000 versus 15500 h*ng/ml and 49.5 versus 50.9 hours respectively).

  While it is acknowledged that there are differences in some individual parameters when comparing pharmacokinetics following administration of the combination product *versus* pharmacokinetics of the actives when administered alone, these differences are not considered substantive and, overall, it is accepted that there is no significant interaction when the actives are administered in combination. Importantly, the findings of this study are not dissimilar to the findings of the pilot pharmacokinetic (interaction) study reported above.

- The applicant conducted a pharmacokinetic study to compare bioavailability resulting from the administration of lotilaner + milbemycin oxime in a liquid capsule formulation, a clinical trial (CT) tablet made on a pilot manufacturing scale and a registration batch tablet made at commercial scale. The registration batch tablet made at commercial scale is considered the final formulation intended for marketing. As the relative bioavailability of both the capsule and registration batch tablet were close to 1 for both lotilaner and milbemycin oxime, the applicant concludes that safety and effectiveness of the capsule and registration batch tablet would be similar to that of the CT tablet. The results of this study allow bridging data from pilot pharmacokinetic, efficacy and safety studies that utilised the oral liquid formulation to data from pivotal studies that used the CT tablet. Additionally, the CT tablet made on a pilot manufacturing scale proved to be similar to the registration batch tablet that was made at commercial scale. Overall, it is accepted that the three formulations indicated similar exposure of both active substances and that these data suggest that safety and efficacy demonstrated in the development of the combination product will be reflected in the formulation that will be commercialised.

- Protein binding was high (≥ 95%) for lotilaner and milbemycin oxime components. There was no interaction between lotilaner and milbemycin oxime regarding protein binding (non-GLP-compliant study).

- A non-GLP-compliant *in vitro* study was presented for the assessment of metabolism of milbemycin oxime when administered alone or in combination with lotilaner. It appears that lotilaner and milbemycin oxime do not interact in microsomes and hepatocytes of the target species.
- There was no evidence of a drug-drug interaction in either the plasma or brain following co-administration of lotilaner and milbemycin oxime in Mdr1a/b knockout mice (non-GLP-compliant). That said, it should be noted that safety of administration of the combination product to Collies has been investigated.
- The applicant has investigated the absence of any therapeutic interaction (non-interference studies) between the active substances in three dose confirmatory studies. Two of the dose confirmation studies support non-interference of the efficacy of lotilaner by the addition of milbemycin oxime in the combination against *C. felis* and *R. sanguineus*, respectively. The third supports non-interference of the efficacy of milbemycin oxime by the addition of lotilaner in the combination against L4 and L5 stages of *A. caninum*.

The effect of different physical properties of the combination tablet on bioavailability

A study was conducted to investigate PK differences between tablet formulations containing varied lotilaner particle sizes, tablet solid fractions and granulation processes. The primary objective of the study was to evaluate, *in vivo*, the clinical relevance of observed variability in dissolution rates of tablets with varying physical properties. In conclusion, based on the data package presented, it is accepted that the pharmacokinetics of lotilaner in Beagle dogs when administered in the fixed combination formulation were comprehensively investigated and well characterised. Further, based on the totality of data presented, it is accepted that the PK profiles of lotilaner and milbemycin oxime when administered concomitantly are comparable to those obtained after administration of the active substances alone. Therefore, clinical data relating to the individual active substances can be extrapolated to the combination product, where relevant.

In terms of target animal safety, repeated administration of the combination at the RTD at 28-day intervals resulted in accumulation of both lotilaner and milbemycin oxime in adult and juvenile dogs. Time to achieve steady state was estimated to be between dose cycles 4 and 5 in adults and between dose cycles 8 and 9 in juveniles. The difference in time to achieve steady state between adult and juvenile dogs is attributed to the changing physiology in juvenile dogs. Taking into account the findings of tolerance studies, the safety of lotilaner and milbemycin oxime in the combination has been adequately investigated at steady state.

Justification of fixed combination

The justification for the fixed combination is based on the broadening of the spectrum of activity by combination of the insecticidal lotilaner with the endectocide milbemycin oxime. Credelio is authorised for the treatment of flea (*Ctenocephalides felis* and *Ctenocephalides canis*) and tick (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*) infestations. However, with the inclusion of the additional active substance milbemycin oxime in the candidate formulation, the proposed indications are extended to include gastrointestinal nematodes, heartworm and *A. vasorum*.

In support of the combination of active substances, the following additional points are noted:

- The parasites targeted by the combination product (fleas, ticks, gastrointestinal nematodes and heartworm and/or lungworm) are commonly found in dogs in Europe and can be present simultaneously on the same animal. This is illustrated by the findings of the pivotal European

nematode field study: 33% of dogs in the investigational veterinary product (IVP) group and 29.1% of dogs in the control group also showed flea infestations on day 0.

- The product, being a fixed combination, facilitates dog handling by reducing the total number of tablets given.

As it is expected that all of the active substances in a fixed combination should be indicated for use at the moment of treatment, the proposed indication highlights that the product is for use in dogs with or at risk of mixed external and internal parasitic infestations. That is, the product is only indicated for use when both active substances are required at the same time and in the absence of the risk of mixed co-infestation, a narrower spectrum parasiticide should be used.

It is accepted that the applicant has provided adequate justification of the fixed combination in accordance with the "CVMP Guideline on pharmaceutical fixed combination products" (EMEA/CVMP/83804/2005).

Target animal tolerance

The target animal tolerance for Credelio Plus has been investigated in several studies using the fixed combination product. However, safety data relating to other products containing lotilaner and milbemycin oxime as active substances are also available to the CVMP.

Lotilaner: The proposed RTD for Credelio Plus is 20–41 mg/kg bw. The RTD of Credelio (EMEA/V/C/004247/0000), which is authorised as a mono-active product in dogs, is 20–43 mg/kg bw orally at a minimum of monthly intervals. Information on the target animal tolerance of Credelio is provided in the European public assessment report (EPAR; EMA/118228/2017). Further, in the context of a recent PSUR assessment for Credelio chewable tablets for dogs, the CVMP concluded that amendment of section 4.6 of the approved SPC text was appropriate based on post-authorisation safety data. The following text has been agreed:

"Mild and transient gastrointestinal signs (vomiting; diarrhoea; anorexia) and lethargy have been reported very rarely based on post-marketing safety experience. These signs typically resolve without treatment.

Neurological disorders such as tremor, ataxia or convulsion may occur in very rare cases. In most cases these signs are transient."

Milbemycin oxime: The proposed RTD for Credelio Plus is 0.75–1.53 mg/kg bw. Milbemycin oxime has been already authorised in EU countries either in combination with the cestocidal active praziquantel or with the insect growth regulator lufenuron at a minimum recommended oral dose of 0.5 mg milbemycin oxime/kg bw in dogs. Trifexis (EMEA/V/C/002635/0000) was previously authorised as a fixed combination product containing milbemycin oxime (0.75–1.18 mg/kg bw) and spinosad (45–75 mg/kg bw) to be given orally at a minimum of monthly intervals. Based on information in the EPAR for Trifexis (EMA/481078/2013), lethargy, neurological and gastrointestinal symptoms occur in very rare cases following treatment with 0.75 to 1.18 mg milbemycin oxime/kg bw. Massive overdose may lead to signs of avermectin toxicosis.

Fixed combination product (combination of lotilaner + milbemycin oxime): The safety of lotilaner in combination with milbemycin oxime was investigated in 4 studies using Beagle dogs.

A pilot target animal safety (TAS) study was conducted in 9-week old Beagle puppies using an early developmental liquid formulation (in capsule). Three treatment groups were given the non-final formulation containing lotilaner and milbemycin oxime in a fed state at 1X, 3X and 5X the maximum RTD over a five-day period for 3 doses at monthly intervals. Clinical observations considered test

article-related were soft faeces, mucoid faeces and diarrhoea in all test article-treated groups, with an incidence generally increasing with increasing dosage level. Clinical observations considered possibly test article-related were red material in faeces and red mucoid faeces (5X RTD group), yellow mucoid faeces (3X and 5X RTD groups) and influence on bodyweights. A number of alterations in clinicopathological parameters were considered possibly test article-related, however the changes detected were not considered to be clinically relevant. Based on the results of this study, it is accepted that the product was generally well tolerated when administered orally to 9-week old Beagle puppies at 1X, 3X, and 5X the maximum intended clinical dose at monthly intervals for 3 consecutive doses. However, treatment-related adverse effects including soft faeces, mucoid faeces and diarrhoea and possibly blood in faeces were observed.

The pivotal TAS study was GLP-compliant and conducted in accordance with VICH GL 43. There were 4 treatment groups including 8 puppies (≥ 8 weeks of age) per group. Treatment group 1 was a non-treated control (sham-dosed). Treatment groups 2, 3 and 4 were given the intended final formulation in a fed state at doses of (lotilaner + milbemycin oxime) 36.3 mg/kg bw + 1.36 mg/kg bw, 109.2 mg/kg bw + 4.10 mg/kg bw and 179.9 mg/kg bw + 6.75 mg/kg bw (equates to 0.9, 2.7 and 4.4-fold the maximum RTD) administered over a five-day period at monthly intervals for 9 months. The approach using the dose regime of repeated daily administration on 3 and 5 consecutive days (instead of a single daily dose of 3X and 5X) to achieve 3X and 5X dose multiples of the maximum RTD to maximise total exposure (AUC) of lotilaner was also used in two other TAS studies and can be accepted. The product was generally well tolerated at doses up to 5 times the maximum recommended treatment dose in this study, with no evidence of adverse effects on clinical, clinicopathological or pathological parameters. Blood loss, diarrhoea, emesis, gingival erythema, increased salivation, lacrimation, loose stool, mucoid stool, pinnal erythema, swollen vulva, and vaginal haemorrhage were the most common observations across all groups. Given that the majority of these observations occurred with similar incidence in the control group, were limited to single animals, were not noted to occur in a dose-related manner and/or were common findings for laboratory dogs of this age and breed, they were not considered by the applicant to be related to treatment. Some statistical differences in clinical pathology and pathology parameters were observed between the control group and test item-treated groups. However, again, due to differences between sexes, the absence of dose trend, persistence of the values within historical controls and detection at isolated time points, they were not considered to be test-article related or clinically relevant. Based on concentrations of lotilaner and milbemycin oxime (A3 and A4) measured 24 hours after each five-day dosing cycle, accumulation of the three analytes was observed in all study groups administered the test item with steady state concentrations achieved at dose 7 for lotilaner and milbemycin oxime A3 and dose 6 for milbemycin oxime A4. Based on the results of this study, the fixed combination product containing lotilaner and milbemycin oxime was well tolerated when administered orally at 1X, 3X, and 5X the maximum intended clinical dose divided over a five-day period monthly for 9 consecutive doses to 8-week old Beagle puppies. Further, it is accepted that the safety of lotilaner and milbemycin oxime in the combination has been adequately investigated in juvenile dogs at steady state (noting that the safety of 9 consecutive monthly doses has been evaluated, the safety evaluation extends beyond the time to steady state).

It is noted that section 4.5 of the SPC states: "All safety and efficacy data have been acquired from dogs and puppies 8 weeks of age and older and 1.4 kg of bodyweight and greater. Use of this veterinary medicinal product in puppies younger than 8 weeks of age or less than 1.4 kg of body weight should be based on a benefit-risk assessment by the responsible veterinarian". The animals included in this study were ≥ 8 weeks of age and, therefore, the CVMP is of the opinion that the age of the study animals is appropriate for the purpose of supporting target animal tolerance in animals ≥ 8 weeks of age. Animals weighed ≥ 1.8 kg bw, which is slightly higher than the minimum bodyweight (1.4 kg) of animals to which it is proposed to recommend product administration. On the basis that

Credelio (mono-product containing lotilaner only) is authorised for dogs as small as 1.3 kg and milbemycin oxime has well-established use and safety in puppies, as demonstrated by products such as Milbemax (minimum body weight 1 kg), the CVMP is of the opinion that the administration of the product to dogs with a minimum weight of 1.4 kg is appropriate.

Another GLP-compliant TAS study was conducted according to a similar design. The animals included in this study were 11–12-month-old Beagles. Three treatment groups were given the intended final formulation containing lotilaner and milbemycin oxime in a fed state at mean treatment doses of (lotilaner + milbemycin oxime) 35.7 mg/kg bw + 1.34 mg/kg bw, 108.2 mg/kg bw + 4.06 mg/kg bw and 180.3 mg/kg bw + 6.76 mg/kg bw, respectively (equates to 0.9, 2.6 and 4.4-fold the maximum RTD), over a five-day period at monthly intervals for 7 months. The most common observations across all groups were similar to those observed in the TAS study in 8-week old dogs. Loose stool was observed at a higher incident rate in treated groups across all days and across dosing days when all cycles were combined. Given that there was no dose-response and the higher incidence in the 1X group was attributed to males only, they were not considered by the applicant to be related to treatment. Mucoid stool was also observed at a higher incident rate in treated groups across all days and across dosing days when all cycles were combined. Given that there was no dose-response, they were considered by the applicant to be unrelated to treatment. Some statistical differences in clinical pathology and pathology parameters were observed between the control group and test item-treated groups. Due to differences between sexes, the absence of dose trend, persistence of the values within historical controls and detection at isolated time points, they were not considered to be test-article related or clinically relevant. Based on concentrations of lotilaner and milbemycin oxime (A3 and A4) measured 24 hours after each five-day dosing cycle, the applicant concludes that steady state of lotilaner was achieved by the 4th dose and that there was no accumulation observed for either milbemycin oxime A3 or milbemycin oxime A4. Based on the results of this study, the fixed combination product containing lotilaner and milbemycin oxime was well tolerated when administered orally at 1X, 3X, and 5X the maximum intended clinical dose over a five-day period monthly for 7 consecutive doses to 11–12-month-old Beagle dogs. That said, a relationship between the gastrointestinal disturbances (loose and mucoid stools) and treatment cannot be excluded. Further, it is accepted that the safety of lotilaner and milbemycin oxime in the combination has been adequately investigated in adult dogs at steady state (noting that the safety of 7 consecutive monthly doses has been evaluated, the safety evaluation extends beyond the time to steady state).

A fourth GLP-compliant TAS study was conducted in 1-year-old Beagles. Treatment group 1 was a non-treated control group (sham-dosed). Treatment groups 2, 3 and 4 were given the intended final formulation containing lotilaner and milbemycin oxime in a fed state at mean treatment doses of 1X RTD (lotilaner + milbemycin oxime: 40.5 mg/kg bw + 1.52 mg/kg bw), 3X RTD (lotilaner + milbemycin oxime: 119.9 mg/kg bw + 4.5 mg/kg bw) and 6X RTD (lotilaner + milbemycin oxime: 240.9 mg/kg bw + 9.03 mg/kg bw), respectively, as a single dose. Decreased bowel movements and loose stool were noted more frequently in the control group and test item groups after dose administration than during the acclimation period; however, the frequencies of these findings were similar across all groups. Based on the results of this study, the fixed combination product containing lotilaner + milbemycin oxime was well tolerated when administered orally at 1X, 3X, and 6X the maximum intended clinical dose on a single occasion in 1-year-old Beagles.

Two GCP-compliant target animal tolerance studies were conducted in Collies.

The first study demonstrated avermectin sensitivity in 30 Collies with the homozygous genetic mutation of the multidrug resistance protein 1 (MDR1) gene following oral dosing with 120 µg/kg bw of ivermectin. Twenty-four of these animals were selected for inclusion in the subsequent study.

The 24 sensitive Collies were randomly allocated to four treatment groups and the final commercial formulation of Credelio Plus was used. Animals were administered the test item in a fed state at mean doses of (lotilaner + milbemycin oxime) 38.99 mg/kg bw + 1.46 mg/kg bw (T02), 117.54 mg/kg bw + 4.41 mg/kg bw (T03) and 195.86 mg/kg bw + 7.35 mg/kg bw (T04) (equates to 1, 2.9 and 4.8-fold the maximum RTD) at monthly intervals for 3 months. The test item was administered to animals in groups T02, T03 and T04 over one, three and five-day periods, respectively. The approach using the dose regime of repeated daily administration on 3 and 5 consecutive days (instead of a single daily dose of 3X and 5X) to achieve 3X and 5X dose multiples of the maximum RTD was also used in three other TAS studies and can be accepted.

Neurological signs associated with avermectin sensitivity in MDR1-negative Collies (including depression, ataxia, mydriasis, salivation/drooling/vomiting and muscle tremors) were observed in animals in all four study groups on observation days 0–4, 28–32 and 56–60. The cumulative overall scores for signs of avermectin sensitivity were 20.7 ± 22.9 in dogs administered the placebo (T01), 7.9 ± 8.0 in dogs administered the test item at 1X the RTD (T02), 13.9 ± 7.6 in dogs administered the test item at 3X the RTD (T03) and 35.3 ± 31.2 in dogs administered the test item at 5X the RTD (T04).

Additional adverse events included occasional signs of diarrhoea, digestive tract haemorrhage, emesis, lameness, metritis and trauma which were transient and resolved without treatment. It is noted that gastrointestinal signs (diarrhoea and vomiting) are currently included in section 4.6 of the SPC. The digestive tract haemorrhage reported as a single event in a dog in T04 during the second dose cycle was not subsequently observed during the third dose cycle and was not considered to be related to treatment.

Whilst the toxicity profile of Credelio Plus when administered to avermectin-sensitive Collies has been investigated, the conclusions that can be drawn from the findings of this study are considered to be somewhat limited given that the cumulative avermectin sensitivity scores observed in the placebo group was higher than that observed in the 1X group (T02) and the 3X group (T03). Given that dogs were randomised to treatment groups based on avermectin-sensitive scores obtained in the ivermectin screening study, and given that clinical evaluation was conducted for all animals at all time points blinded by the same trained investigator, it can be concluded that variation between groups is minimised when assigning scoring values for nervous behaviours in study animals. Further, no dosing holiday or veterinary intervention with a rescue therapy was required during the study due to signs of avermectin toxicity. In the opinion of the CVMP, despite the attempts of minimising variability in this study, the results for this group do not appear to support the 5X margin of safety (the highest cumulative avermectin sensitivity score was observed in this group). Safety precautions in section 4.5 and warnings in case of overdose in section 4.10 of the SPC are included in order to ensure animal safety in dogs with a deficient MDR1 gene when administering the product.

In the various confirmatory and field efficacy studies conducted, the test item was generally well tolerated. However, in a number of studies, there were reports of gastrointestinal disturbance in individual animals after treatment. It is considered that these adverse events are possibly treatment-related.

No target animal safety study was conducted using Credelio Plus in heartworm-positive dogs. Given that the overall findings of PK studies indicate that the PK profile of milbemycin oxime when administered concomitantly with lotilaner is comparable to that obtained after administration of milbemycin oxime alone and that there is no evidence to suggest pharmacological interference of milbemycin oxime and lotilaner which could have an impact on milbemycin oxime safety in Credelio Plus, it is considered acceptable, in line with the CVMP scientific advice (EMA/CVMP/SAWP/546084/2015), to reference the heartworm-positive safety study performed in the

frame of the marketing authorisation application for Trifexis instead of performing a new safety study for Credelio Plus in heartworm-positive dogs. The heartworm-positive safety study for Trifexis evaluated doses of spinosad + milbemycin oxime at multiple dose levels (0.75–1 mg/kg, 2.25–3 mg/kg and 3.75–5 mg/kg) for a duration of three consecutive months in heartworm-positive dogs. The only adverse reaction being observed within this study was emesis, which is a known adverse effect of the Trifexis component spinosad, but not of milbemycin oxime. Apart from the observed emesis, the product was well tolerated by dogs with patent adult heartworm infections. That said, the applicant has included the safety warning "Administration of products containing milbemycin oxime (such as this product) to dogs with a high number of circulating microfilariae, in order to avoid hypersensitivity reactions associated with the release of proteins from dead or dying microfilariae" in section 4.5 of the SPC.

Based on the target animal safety data submitted in support of this application, the following text has been included and accepted in the SPC:

4.5 Special precautions for use in animals

The recommended dose should be strictly observed in MDR1 mutant ($^{-/-}$) dogs with a non-functional P-glycoprotein, which may include Collies and related breeds.

4.6 Adverse reactions (frequency and seriousness)

Gastrointestinal signs (diarrhoea and vomiting), anorexia, muscle tremors, lethargy, pruritus and changes in behaviour were uncommonly reported. These occurrences were generally self-limiting and of short duration.

Neurological signs (convulsion, muscle tremor, and ataxia) have been recorded rarely in post-marketing safety experience for the active substance lotilaner used as a mono-active (Credelio) at the same dose as in this product. These signs typically resolve without treatment.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No adverse reactions, other than those listed in section 4.6, were observed in puppies (starting at 8–9 weeks of age) after administering up to 5 times the maximum recommended dose over 1–5 days (consecutive daily dosing) at monthly intervals on 9 occasions; or in adult dogs (starting at 11 months of age) after administering up to 5 times the maximum recommended dose over 1–5 days (consecutive daily dosing) at monthly intervals on 7 occasions; or in adult dogs (approximately 12 months old) after administration up to 6 times the maximum recommended dose as a bolus on a single occasion

After administration of 5 times the maximum recommended dose to MDR1 mutant ($^{-/-}$) dogs with a non-functional P-glycoprotein, transient depression, ataxia, tremors, mydriasis, and/or excessive salivation were observed.

Dose justification

Lotilaner is included in the fixed combination as an ectoparasiticide. The applicant justifies the omission of a dose determination study investigating the minimum treatment dose of 20 mg/kg bw for lotilaner in the combination product with reference to dose titration studies that have already been conducted in the lotilaner-only development programme for Credelio. In order to justify the extrapolation of the recommended treatment dose of lotilaner in Credelio to Credelio Plus, the applicant conducted pharmacokinetic studies and non-interference studies to demonstrate that the pharmacokinetic profile of lotilaner is not changed by the concomitant administration of milbemycin oxime.

Based on the findings of the pivotal GLP-compliant PK study using the final formulation, it is accepted that there is sufficient evidence to conclude that the PK profile of lotilaner when administered concomitantly with milbemycin oxime is comparable to that obtained after administration of lotilaner alone. Further, dose confirmation studies support non-interference of the efficacy of lotilaner by the addition of milbemycin oxime in the combination against *C. felis* and *R. sanguineus*, respectively.

Based on the totality of data provided (pharmacodynamic, pharmacokinetic and preliminary clinical efficacy studies [including the non-interference studies that follow]), it is accepted that the minimum proposed treatment doses of 20 mg/kg bw for lotilaner is reasonable to be taken forward for confirmation in dose-confirmatory and clinical field studies.

Milbemycin oxime is included in the fixed combination as an anthelmintic. The proposed treatment dose of milbemycin oxime in Credelio Plus is 0.75 to 1.53 mg/kg bw. The applicant justifies the dose of 0.75 mg/kg bw for milbemycin oxime in the combination product with reference to the minimum recommended treatment dose previously accepted by the CVMP for the fixed combination product Trifexis. Milbemycin oxime was included in Trifexis for efficacy against the L4, L5 and adult stages of *A. caninum*, the L5 and adult stages of *Toxocara canis*, the adult stages of *Toxascaris leonina* and *Trichuris vulpis*, the L3 and L4 stages of *Dirofilaria immitis* and immature adult (L5) and adult stages of *Angiostrongylus vasorum*.

In order to further justify the extrapolation of the recommended treatment dose of milbemycin oxime in Trifexis to Credelio Plus, the applicant conducted pharmacokinetic studies and non-interference studies to demonstrate that the pharmacokinetic profile of milbemycin oxime is not changed by the concomitant administration of lotilaner. Based on the findings of the pivotal GLP-compliant PK study using the final formulation, it is accepted that there is sufficient evidence to conclude that the PK profile of milbemycin oxime, when administered concomitantly with lotilaner, is comparable to that obtained after administration of milbemycin oxime alone. Further, a dose confirmation study supports non-interference of the efficacy of milbemycin oxime by the addition of lotilaner in the combination against the L4 and L5 stages of *A. caninum*.

Based on the totality of data provided (pharmacodynamic, pharmacokinetic and preliminary clinical efficacy studies [including the non-interference studies that follow]), it is accepted that the minimum proposed treatment dose of 0.75 mg/kg bw for milbemycin oxime is reasonable to be taken forward for confirmation in dose-confirmatory and clinical field studies. It should be noted that the approach to dose determination for the milbemycin oxime component was accepted by the CVMP in the context of a scientific advice procedure (EMA/CVMP/SAWP/546084/2015).

Dose confirmation

Ticks

All pivotal studies were conducted in accordance with GCP principles and, in general terms, the design of each study was in line with guideline requirements. Adequate data have been submitted to support efficacy against the claimed tick species.

R. sanguineus: One supportive dose confirmation study, three pivotal laboratory dose confirmation studies and one pivotal laboratory dose confirmation and non-interference study were provided. The results of two of the pivotal laboratory dose confirmation studies provide some, limited support for the proposed claim against *R. sanguineus* given that one study only demonstrated satisfactory immediate efficacy and persistent efficacy (≥ 90%) for up to 23 days and the control animals in the other study did not maintain adequate tick infestations at a number of time points. However, the third pivotal dose confirmation study (European isolate of *R. sanguineus*) demonstrated satisfactory immediate efficacy

and persistent efficacy for up to 32 days (≥ 96.79% efficacy) and the non-interference study (US isolate) demonstrated satisfactory efficacy immediately after treatment, with a persistent effect up to 30 days (≥ 99% efficacy). Based on the findings of the study, it is accepted that non-interference of the efficacy of lotilaner by the addition of milbemycin oxime in the treatment of *R. sanguineus* has been demonstrated and supports the inclusion of lotilaner in the combination formulation.

Based on the data submitted in the current application, it is accepted that the dose confirmation data are adequate to support a claim against *R. sanguineus* ticks. No dose confirmation studies against *I. ricinus, I. hexagonus* and *D. reticulatus* were submitted. While it is noted that guideline 7AE17a ("Demonstration of efficacy of ectoparasiticides") recommends two dose confirmation studies per claimed target parasite, the following is noted:

- the pharmacokinetic profile of lotilaner when administered concomitantly with milbemycin oxime is comparable to that observed when lotilaner is administration alone;
- a minimum dose of 20 mg lotilaner/kg bw against all claimed target ectoparasites for the duration of the proposed between treatment interval (1 month) had been adequately justified;
- lotilaner is a systemically-acting insecticide and non-interference using the final formulation against the least susceptible tick species (*R. sanguineus*) has been confirmed.

Therefore, in line with the recommendation of the CVMP scientific advice (EMA/CVMP/SAWP/293418/2018), it is accepted that reference to the tick dose confirmation studies undertaken for the Credelio application has been adequately justified.

In line with the CVMP's conclusions in relation to the applicant's mono-active product Credelio, the CVMP accepts a claim for immediate and persistent killing activity for 1 month for ticks (*R. sanguineus, I. ricinus, I. hexagonus* and *D. reticulatus*). As a consequence, the omission of additional dose confirmation data for *D. reticulatus, I. ricinus* and *I. hexagonus* can be accepted.

In relation to speed of kill, in line with the CVMP's conclusions on the applicant's mono-active product Credelio, the CVMP accepts that the onset of efficacy is within 48 hours of attachment of ticks for one month after product administration and, for existing *I. ricinus* ticks present on the dog prior to administration, these are killed within 8 hours. Consequently, and again noting that confirmatory efficacy data have been provided for the dose-limiting tick species, the information proposed for inclusion in SPC section 5.1 of Credelio Plus (the same information already accepted for the lotilaner-only product Credelio) is considered acceptable.

Fleas

All pivotal studies were conducted in accordance with GCP principles and, in general terms, the design of each study was in line with guideline requirements. Adequate data have been submitted to support efficacy against the claimed flea species.

One dose confirmation and one non-interference study, which used a flea isolate (*C. felis*) that originated in the US and the final formulation intended for marketing, demonstrated satisfactory immediate efficacy and persistent efficacy for up to 30 days (100% efficacy). Based on the findings of this study, it is accepted that non-interference of the efficacy of lotilaner by the addition of milbemycin oxime in the treatment of *C. felis* fleas has been demonstrated.

No dose confirmation studies against *C. canis* were provided. While it is noted that guideline 7AE17a ("Demonstration of efficacy of ectoparasiticides") recommends two dose confirmation studies per claimed target parasite, the following is noted:

- the pharmacokinetic profile of lotilaner when administered concomitantly with milbemycin oxime is comparable to that observed when lotilaner is administration alone;

- a minimum dose of 20 mg lotilaner/kg bw against all claimed target ectoparasites for the duration of the proposed between treatment interval (1 month) had been adequately justified;
- lotilaner is a systemically-acting insecticide and non-interference using the final formulation against the least susceptible flea species (*C. felis*) has been confirmed.

Therefore, in line with the recommendation of the CVMP scientific advice (EMA/CVMP/SAWP/293418/2018), reference to the flea dose confirmation studies undertaken for the Credelio application has been adequately justified. In line with the CVMP's conclusions on the applicant's mono-active product Credelio, the CVMP accepted a claim for immediate and persistent killing activity for 1 month for fleas (*C. felis* and *C. canis*). On that basis, the omission of a second dose confirmation study with the combination product for *C. felis* and dose confirmatory studies for *C. canis* is accepted.

Gastrointestinal nematodes

The applicant provided five dose confirmation studies against gastrointestinal (GI) nematodes.

All pivotal studies were conducted in accordance with GCP principles and, in general terms, the design of each study was in line with guideline requirements.

A. caninum (L4 and L5 stages): Two dose confirmation studies against the L4 and L5 stages of *A. caninum* are presented. It is accepted that test animals in both studies were adequately infected. The studies demonstrated satisfactory efficacy against L4 (99.6% and 97.3%, respectively) and L5 (99.7% and 98.7%, respectively) stages of *A. caninum* using a single oral dose of the test product administered at 20–30 mg lotilaner/kg bw + 0.75 to 1.1 mg milbemycin oxime/kg bw. Based on the findings of on of the studies, non-interference of the efficacy of milbemycin oxime by the addition of lotilaner in the treatment of *A. caninum* has been demonstrated and supports the inclusion of milbemycin oxime in the combination formulation. Adequate EU field data (94.5% reduction in faecal egg output) is available to support the indication against adult *A. caninum*.

T. canis (L4 and L5 stages): Two dose confirmation studies against the L4 and L5 stages of *T. canis* are presented. The studies demonstrated satisfactory efficacy against L4 (100% and 96.8% respectively) and L5 (98.6% and 98.3% respectively) stages of *T. canis* using a single oral dose of the test product administered at 20–30 mg lotilaner/kg bw + 0.75 to 1.1 mg milbemycin oxime/kg bw. EU field data (88.9% reduction in faecal egg output) is available to support the indication against adult *T. canis*.

A. caninum, T. canis, T. leonina and *T. vulpis* (adult stages): One dose confirmation study against adult *A. caninum* was presented. The study demonstrated satisfactory efficacy (100%) against adult *A. caninum.* No dose confirmation studies against adult *Toxocara canis*, *Toxascaris leonina* or *Trichuris vulpis* were provided.

VICH GL 7 recommends that two dose confirmation studies with the dose-limiting parasite species should be conducted, of which at least one should be conducted in the geographic region where the authorisation is being pursued.

In line with CVMP's conclusions relating to Trifexis, it is accepted that late L4, L5 of *A. caninum* are the dose limiting parasite for milbemycin oxime. Taking into account the findings of *A. caninum* studies and in line with the recommendation of the scientific advice (EMA/CVMP/SAWP/546084/2015), the applicant's proposal to refer to existing data of milbemycin oxime for other nematode species is accepted. Similarly, as for the marketing authorisation of Trifexis containing spinosad and milbemycin oxime, the CVMP accepts a claim for the treatment of gastrointestinal nematode infections caused by hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (immature adult L5 and adult *Toxocara canis;* adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*). As a

consequence, the omission of a second dose confirmation study for adult *A. caninum* and dose confirmation data for adult *Toxocara canis, Toxascaris leonina* and *Trichuris vulpis* can be accepted.

The efficacy data obtained in the three *A. caninum* dose confirmation studies have all originated in the US. The applicant has considered the relevance of these data to larval and adult *A. caninum* circulating in Europe and argues that there is no plausible reason to consider EU isolates of this hookworm to be resistant or less susceptible to milbemycin oxime than for US isolates, for the following reasons:

- Until 2019, no naturally-occurring nor laboratory strains resistant to benzimidazoles (BZ) or macrocyclic lactones have been extensively described or reported. The existence of a naturally occurring *A. caninum* strain resistant to BZs and ivermectin in the US has recently been described. This strain was isolated from a retired racing greyhound who was subjected to repeated doses of anthelmintics that likely selected for mutations conferring resistance to both parasiticide classes. Until very recently, there was no information in the scientific literature suggesting that *A. caninum* populations resistant to milbemycin oxime were present in Europe or elsewhere. The existence of multi-drug (i.e. fenbendazole, pyrantel and milbemycin oxime)-resistant (MDR) *A. caninum* populations in the USA were shown in 2019 through *in vitro*/*in vivo* and molecular data. Although these data are a concern, at the moment they are single reports and no similar cases are described in the scientific literature in other geographical regions.
- It is to be noted that the minimum dose of milbemycin oxime in all US products is 0.5 mg/kg bw. Thus, given that the proposed dose of milbemycin oxime is 50% higher in Credelio Plus, and considering the absence of any data of resistant hookworm in Europe, it is the applicant's opinion that multi-drug resistance in *A. caninum* is not an actual threat in Europe, at least at the moment.
- In the past years, the efficacy of milbemycin oxime against *A. caninum* in natural conditions from various countries in Europe has been shown.
- The field study demonstrated the efficacy of Credelio Plus against canine intestinal nematodes (including *A. caninum*) in various sites from three European countries (study summarised and reported on below).

In view of the argumentation presented, the results of the three dose confirmation studies showing that Credelio Plus is efficacious against US strains of *A. caninum* can be considered relevant to the European situation.

No data are provided to support larval stages younger than L4 of *A. caninum* or *T. canis*. Therefore, the claim against the larval stages of the GI nematodes *A. caninum* and *T. canis* is restricted to "hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (L4, immature adult (L5) and adult *Toxocara canis*, and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*)".

Angiostrongylus vasorum

VICH GL 7 recommends that two dose confirmation studies with the dose-limiting parasite species should be conducted. However, the applicant proposes to replace dose confirmation studies supporting the claim against *A. vasorum* with PK data comparing the PK profile of Credelio Plus with the PK profile of other milbemycin oxime-containing products authorised for the same claim, namely Milbemax, Nexgard Spectra and Interceptor.

Milbemax and NexGard Spectra are both authorised in the EU for the prevention of angiostrongylosis by reducing immature adult (L5) and adult parasite burden with monthly administration at a dose rate of 0.5 mg/kg bw of milbemycin oxime. Comparative pharmacokinetic data show that exposure to milbemycin oxime A4 in Credelio Plus at the minimum dose rate of 0.75 mg milbemycin oxime/kg bw is higher than milbemycin oxime in Milbemax and Nexgard Spectra at the minimum dose rate of

0.5 mg milbemycin oxime/kg bw in terms of C_{max} (301 ± 124 *versus* 189 ± 61.3 *versus* 246 ± 71 ng/ml, respectively) and AUC_{last} (8970 ± 1840 *versus* 4920 ± 1805 *versus* 6192 ± 2016 h*ng/ml, respectively), whilst T_{max} is similar (2.25 ± 0.71 *versus* 2.4 *versus* 2 hours, respectively). Data on $t_{1/2}$ of milbemycin oxime in Milbemax is not available. However, $t_{1/2}$ of milbemycin oxime A4 in Credelio Plus is shorter than that of milbemycin oxime in Nexgard Spectra (55.8 ± 16.2 *versus* 79.2 ± 33.6 hours). In conclusion, the comparative PK data presented against Milbemax and Nexgard Spectra administered at 0.5 mg milbemycin oxime/kg bw provide supportive evidence of the efficacy of milbemycin oxime in Credelio Plus administered at 0.75 mg/kg against *A. vasorum*.

Further, in order to justify the extrapolation of the recommended treatment dose of milbemycin oxime in Trifexis to Credelio Plus, the applicant conducted pharmacokinetic and non-interference studies to demonstrate that the pharmacokinetic profile and therapeutic effect of milbemycin oxime is not changed by the concomitant administration of lotilaner. While it is acknowledged that there are differences in some individual parameters when comparing pharmacokinetics following administration of the combination product versus pharmacokinetics of the actives when administered alone (pivotal GLP-compliant PK study), these differences are not considered substantive and, overall, it is accepted that there is no significant pharmacokinetic interaction when the actives are administered in combination. Further, one of the *A. caninum* dose confirmation studies supports non-interference of the efficacy of milbemycin oxime by the addition of lotilaner in the combination against L4 and L5 stages of *A. caninum*, or at least the absence of any clinically relevant interference from an efficacy perspective.

In conclusion, it is accepted that the total PK data provided is sufficient to conclude that plasma levels of milbemycin oxime following the administration of Credelio Plus will be sufficient to ensure persistent efficacy against angiostrongylosis when the product is administered at the minimum proposed treatment doses of 0.75 mg/kg bw for milbemycin oxime.

Dirofilaria immitis

Four dose confirmation studies to support prevention of heartworm disease are provided. All studies were designed and conducted in accordance with VICH GLs 7 and 19. Satisfactory efficacy (100%) against *D. immitis* was demonstratedusing the "Georgia II" isolate, after a single administration of the test product. Similarly, 100% efficacy was demonstrated using the "Berkeley" isolate after single administration of the test product using milbemycin oxime in the final formulation. Inadequate efficacy was observed in two studies using the "WildCat" isolate, with efficacy rates ranging from 81.7 to 90%.

The applicant suggests that the inadequate efficacy results obtained in the “WildCat” studies are due to the reduced susceptibility of this isolate to the effects of milbemycin rather than to a general lack of efficacy of the IVP in the prevention of *D. immitis* in dogs. To support this, the applicant provided genotyping of individual *D. immitis* worms at seven polymorphic sites. By investigating single nucleotide polymorphisms (SNP) of the "WildCat" isolate, the applicant concluded that the strain showed more consistency with the known resistant/loss-of-efficacy pools compared to susceptible samples, indicating that the "WildCat" isolate is not representative for a susceptible heartworm isolate.

In addition, the applicant has provided another study whose objective was to compare the allele frequency of 10 SNP markers of macrocyclic lactone (ML) susceptibility between three US *D. immitis* isolates ("Berkeley", "Georgia II", and "WildCat" isolates) and eleven European *D. immitis* isolates from Italy (n = 4), Hungary (n = 3), and Spain (n = 4). The CVMP notes that, for the US isolates (Berkeley and Georgia II) and for all European isolates, the allele frequency for the 10 SNP markers investigated are compatible with ML-susceptible parasites. On the contrary, for the "WildCat" isolate, the allele frequency for the 10 SNP markers investigated varied from 0.39 and 0.78 compared to the reference base, suggesting that each SNP marker fell within the category of "ML-resistant". Based upon the applicant's explanation and the results described in the published literature, the CVMP acknowledges

the genotypic differences between the "WildCat" isolate and the rest of the US ("Berkeley" and "Georgia II") and European isolates. Hence, the resistance status of the *D. immitis* "WildCat" strain has been further corroborated. In the opinion of the CVMP, the studies submitted are adequate to support the claim of prevention of heartworm disease (*D. immitis*).

Clinical studies

Ticks

The applicant provided one field study conducted in the EU against ticks.

In this GCP-compliant multicentre field study, the test product was administered to dogs under field conditions at monthly intervals on three occasions. Study animals were treated either with the test item (n = 149) or a positive control containing afoxolaner/milbemycin oxime (n = 75). In this study, the test product was demonstrated to be non-inferior to a positive control product in the treatment of *I. ricinus* and *R. sanguineus* (reduction > 96%). Based on the results of this study, it is accepted that there is adequate field data to support a claim for the treatment of *I. ricinus* and *R. sanguineus* tick infestations for 4 weeks under natural conditions. Not enough field data against *D. reticulatus* and *I. hexagonus* were provided for analysis. That said, it is evident from a field study conducted with the applicant's mono-active product Credelio, administered on a monthly basis, that Credelio is efficacious for the treatment of tick infestations (*Ixodes ricinus*, *Rhipicephalus sanguineus, Dermacentor reticulatus* and *Ixodes hexagonus*) under natural conditions. On that basis, and noting that efficacy against the dose-limiting tick species (*R. sanguineus*) has been confirmed in laboratory and field studies, the omission of field data for *D. reticulatus* and *I. hexagonus* is considered acceptable.

Based on the data submitted in the current application and the efficacy data also assessed in the context of the marketing authorisation application for Credelio, the proposed claim against *R. sanguineus, D. reticulatus, I. ricinus* and *I. hexagonus* for Credelio Plus can be accepted.

Fleas

The applicant provided one field study conducted in the EU against fleas.

In this GCP-compliant multicentre field study, the test product administered to dogs (n = 138) under field conditions was efficacious in the treatment of flea infestations caused by both *C. felis* and *C. canis* on dogs for 30 days. The product used was the final formulation intended for marketing. A positive control containing afoxolaner/milbemycin oxime (n = 67) was included. In this study, the majority of fleas identified during this study correspond to the species for which a claim is sought (*C. felis* and *C. canis*). Percentage reductions on study days 14, 28, 56 and 84 were significantly lower than baseline counts in both treatment groups ($p < 0.001$) and the reduction in counts post-treatment, based on arithmetic and geometric means, was ≥ 95% for both Credelio Plus and the control product. Non-inferiority was concluded for flea efficacy. Analysis of efficacy against *C. canis* and *C. felis*, specifically, demonstrated reduction of > 98% for both Credelio Plus and the control product. The product, when administered to dogs under field conditions of use, was effective against the claimed flea species (*C. felis* and *C. canis*), with a duration of pulicidal effect of up to 28 days having been supported in this study and the test product was confirmed to be non-inferior to the control product. Over the course of the study, there was a reduction in the total flea allergy dermatitis (FAD) scores in both study groups.

Based on the data submitted in the current application and the efficacy data also assessed in the context of the Credelio marketing authorisation, the proposed claim against *C. felis and C. canis* can be accepted. In addition, it can be accepted that efficacy will persist for one month after treatment, with the onset of efficacy within 4 hours of being infested for one month after product administration and fleas present on the dog prior to administration being killed within 6 hours. Further, it can be accepted

that the product can be used as part of a treatment strategy for the control of FAD and that the product kills existing and newly emerged flea infestations on dogs before the female can lay eggs and, therefore, the product breaks the flea life cycle and prevents environmental flea contamination in areas to which the dog has access.

Gastrointestinal nematodes

The applicant provided one field study conducted in the EU against gastrointestinal (GI) nematodes.

The GCP-compliant positive-controlled multicentre field study was performed in France, Hungary and Germany and involved 510 client-owned dogs of different ages, genders and breeds. Study animals were treated with a single dose of either the test item (n = 278) or a positive control containing afoxolaner/milbemycin oxime (n = 117). Based on the primary efficacy parameter the test item was confirmed to be non-inferior to the control product in the treatment of gastrointestinal roundworm *Toxocara canis* (88.9% reduction in faecal egg output), *A. caninum* (94.5% reduction in faecal egg output) and *Trichuris vulpis* (91.5% reduction in faecal egg output).

Angiostrongylus vasorum

The applicant did not submit any field data on the efficacy of Credelio Plus against *A. vasorum*. Considering the PK data submitted and the scientific advice provided by the CVMP (EMA/CVMP/SAWP/293418/2018), the absence of field data to support the *A. vasorum* claim can be accepted.

Dirofilaria immitis

The GCP-compliant positive-controlled field study conducted in the US involved 238 client-owned dogs of different ages, genders and breeds. The test product was administered to dogs under field conditions at monthly intervals on eleven occasions. Study animals were treated either with the test item (n = 112) or a positive control containing lufenuron/milbemycin oxime (n = 126). Heartworm tests, both antigen and microfilarial tests, were conducted at day -1 and at days 120, 240 and 330. The results of this study suggest that administration of the test product prevented heartworm infection in the study animals (100% efficacy against *D. immitis* infection). The applicant has justified the absence of an untreated control group on the grounds of animal welfare. In order to demonstrate that the study was conducted under a suitable level of exposure to *D. immitis*, the applicant has indicated that the field study was conducted within the period of the peak transmission months, and that the local prevalence of six of the eight counties where the animals were located varied from 1.56–6.34%, which is above the national prevalence for *D. immitis* (1.28%). In light of the above, the CVMP can accept that animals included in the study were adequately exposed to a *D. immitis* challenge.

Other studies – Palatability claim

In the GCP-compliant GI nematode field study, the test product was voluntarily consumed within two minutes on 82.3% of all 355 occasions offered, which meets the minimum threshold to permit a palatability claim. In the *D. immitis* field study, the test product was voluntarily consumed (accepted either free choice or in food) on 81.8% of all 1562 occasions offered to the safety population of dogs. While it is not stated if the tablets were voluntarily and fully consumed within two minutes as indicated in the relevant guideline, these data can be accepted as supportive of the "palatability" claim.

Given the findings of the pivotal field study against GI nematodes, it is accepted that a palatability claim has been adequately supported and, consequently, the wording proposed for inclusion in SPC section 4.9 can be accepted.

Overall conclusion on efficacy

Pharmacodynamics: It is accepted that the product is an ecto- and endoparasiticide.

Resistance: No resistance to lotilaner has been reported to date. Macrocyclic lactone resistance in *A. caninum* has been reported in the US; however, no resistance to macrocyclic lactones has been reported to date in the EU or against other gastrointestinal nematodes. Lack of efficacy of macrocyclic lactones in the prevention of heartworm disease in dogs has been reported outside Europe. Given the concerns regarding resistance development, section 4.4 of the SPC includes warnings relating to the potential for resistance emergence.

Pharmacokinetics: The PK profiles of lotilaner and milbemycin oxime when administered concomitantly are comparable to those obtained after administration of the active substances alone.

Dose determination: Based on the totality of data provided (pharmacodynamic, pharmacokinetic and preliminary clinical efficacy studies, including the non-interference studies that follow), the CVMP accepts that the minimum proposed treatment doses of 20 mg/kg bw for lotilaner and 0.75 mg/kg bw for milbemycin oxime are reasonable to be taken forward for confirmation in dose confirmatory and clinical field studies.

Tolerance: The target animal tolerance for Credelio Plus has been investigated in several studies using the fixed combination product formulation in Beagles. The adverse reactions observed in these studies are reflected in the SPC. A margin of safety of 5X has not been achieved in avermectin-sensitive Collies (i.e. carrying and MDR1 gene mutation).

Efficacy: Based on the efficacy data package presented, the following indications can be accepted:

Ticks and fleas

For the treatment of tick (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus* and *I. hexagonus*) and flea (*Ctenocephalides felis* and *C. canis*) infestations in dogs.

This veterinary medicinal product provides immediate and persistent killing activity for 1 month for ticks and fleas.

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

Gastrointestinal nematodes

Treatment of gastrointestinal nematodes: hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (L4, immature adult (L5) and adult *Toxocara canis*, and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*).

Lungworm

Prevention of angiostrongylosis by reduction of the level of infection with immature adult (L5) and adult stages of *Angiostrongylus vasorum* (lungworm) with monthly administration.

Heartworm

Prevention of heartworm disease (*Dirofilaria immitis*).

Palatability: Given the findings of the pivotal field study against GI nematodes, it is accepted that a palatability claim has been adequately supported.

Part 5 – Benefit-risk assessment

Introduction

Credelio Plus chewable tablets for dogs contain a fixed combination of two active substances: lotilaner and milbemycin oxime. The product is intended for oral administration and available in five different strengths of (lotilaner + milbemycin oxime per tablet) 56.25 mg + 2.11 mg, 112.5 mg + 4.22 mg, 225 mg + 8.44 mg, 450 mg + 16.88 mg or 900 mg + 33.75 mg, presented in packs of 1, 3, 6 and 18 tablets.

The product is a parasiticide intended for the treatment of dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm.

The application has been submitted in accordance with Article 13b of Directive 2001/82/EC – fixed combination application.

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Credelio Plus is its efficacy against:

Ticks and fleas

For the treatment of tick (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus* and *I. hexagonus*) and flea (*Ctenocephalides felis* and *C. canis*) infestations in dogs.

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

Gastrointestinal nematodes

For the treatment of the following gastrointestinal nematodes: hookworm (L4, immature adult [L5] and adult *Ancylostoma caninum*), roundworms (L4, immature adult [L5], and adult *Toxocara canis* and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*).

Heartworm

Prevention of heartworm disease (*Dirofilaria immitis*).

Lungworm

Prevention of angiostrongylosis by reduction of the level of infection with immature adult (L5) and adult stages of *Angiostrongylus vasorum* (lungworm) with monthly administration.

Additional benefits

Credelio Plus 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

Quality:

Information on the development, manufacture and control of the active substance and the finished product is satisfactory.

Safety:

Risks for the target animal:

The target animal tolerance for Credelio Plus has been investigated in several studies using the fixed combination product formulation. In the various confirmatory and field efficacy studies conducted, the test item was generally well tolerated. However, in a number of studies, there were reports of gastrointestinal disturbance and neurological signs in individual animals after treatment.

Risk for the user:

The risk to the user is considered acceptable when used in accordance with the SPC. Adequate information has been provided to support the claim that the packaging is child-resistant.

Risk for the environment:

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

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 user and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

"For use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm.

This veterinary medicinal product is intended for use where treatment and/or prevention of two or more of the indications below is required concurrently.

Ticks and fleas

For the treatment of tick (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus* and *I. hexagonus*) and flea (*Ctenocephalides felis* and *C. canis*) infestations in dogs.

This veterinary medicinal product provides immediate and persistent killing activity for 1 month for ticks and fleas.

Ticks and fleas 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).

Gastrointestinal nematodes

Treatment of gastrointestinal nematodes: hookworm (adult and larval *Ancylostoma caninum*), roundworms (adult and larval *Toxocara canis*, adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*).

Heartworm

Prevention of heartworm disease (*Dirofilaria immitis*).

Lungworm

Prevention of angiostrongylosis by reduction of the level of infection with immature adult (L5) and adult stages of *Angiostrongylus vasorum* (lungworm) with monthly administration."

The product has been shown to be efficacious for ticks and fleas, heartworm and lungworm as proposed by the applicant and the CVMP accepted these indications. The CVMP also accepted that the statement "Ticks and fleas must attach to the host and commence feeding in order to be exposed to the active substance" be moved under the section 4.4 of the SPC (Special warnings for each target species). Regarding gastrointestinal nematodes, the CVMP agreed to the following indications:

"Treatment of gastrointestinal nematodes: hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (L4, immature adult (L5) and adult *Toxocara canis*, and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*)".

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. Precautionary measures have been included in the SPC and other product information.

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