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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Credelio Plus (EMEA/V/C/005325/VRA/0005)

INN: lotilaner / milbemycin oxime

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Elanco GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 21 July 2022 an application for a variation requiring assessment for Credelio Plus.

1.2. Scope of the variation

Variation requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one

The variation is to add a new therapeutic indication for the treatment of demodicosis (caused by *Demodex canis*).

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Credelio Plus is currently authorised as chewable tablets for use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm. The product is indicated for use when treatment against ticks/fleas and gastrointestinal nematodes or the treatment against ticks/fleas and prevention of heartworm disease/angiostrongylosis is required concurrently.

The recommended dose ranges are 20 - 41 mg lotilaner/kg bodyweight and 0.75 - 1.53 mg milbemycin oxime/kg bodyweight.

This variation application has been submitted for the purpose of introducing a new indication for the treatment of demodicosis (caused by *Demodex canis*) in dogs. The proposed dose rate for the new indication is the existing recommended treatment dose (20 - 41 mg lotilaner/kg bodyweight).

2.1. Safety (tolerance, user, environment)

No new preclinical or specific target animal safety studies have been conducted by the applicant in the context of this variation application. Given that the dose rate and re-treatment interval for the newly proposed indication do not differ from those which have already been accepted for the existing target parasites, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

Further, as the product will be administered to the same target species, using the same route of administration and at the same posology that has already been accepted by the CVMP, no concerns in terms of user safety are considered to arise; that is, the user will not be exposed to a greater amount of the active substances or for a greater frequency than that which has been assessed for the existing indications approved for the product. No change to the impact on the environment is envisaged.

Therefore, no further assessment is deemed necessary in respect of target animal tolerance, user safety or safety for the environment and it can be concluded that the introduction of the proposed indication will not present an unacceptable risk for the animal, user or the environment.

2.2. Efficacy: treatment of demodicosis (caused by Demodex canis)

No new studies have been conducted with the Credelio Plus formulation. The studies submitted to support the indication are those submitted, assessed and accepted for Credelio chewable tablets for dogs (procedure no EMEA/V/C/004247/II/0019). The applicant argues that the Credelio *Demodex canis* efficacy data can be extrapolated to Credelio Plus based on available pharmacokinetic data. Specifically, a re-evaluation of the pharmacokinetic data generated in study WIL-668072 (presented in the original dossier for Credelio Plus) has been conducted for the purposes of evaluating bioequivalence of the lotilaner component between the Credelio Plus and the Credelio tablet formulations.

In this study it was confirmed that, after a single oral dose of the final formulation at the recommended therapeutic dose in adult dogs, the PK profile of lotilaner when administered concomitantly with milbemycin oxime (n=10) is comparable to that obtained after administration of lotilaner alone (n=10) (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 active substances when administered alone, these differences are not considered substantive and, overall, it is accepted that there is no significant interaction when the active substances are administered in combination.

In order to further support the *D. canis* claim for Credelio Plus based on the available efficacy data for Credelio, a re-evaluation of the data from the pivotal PK study (WIL-668072) to look at bioequivalence has been conducted, using only the oral tablet administration groups and lotilaner (active substance responsible for *D. canis* efficacy).

The bioequivalence calculations of AUC and C_{max} using the lotilaner data generated in Study WIL-668072 are shown below:

PK Parameter	Reference	Ref LSM	Test	Test LSM	Difference	Ratio %Ref	Lower CI90	Upper CI90
$Ln(AUC_{last})$	Credelio	7.9	Credelio Plus	8.1	0.16	117.8	82.7	167.6
$Ln(C_{max})$	Credelio	2.3	Credelio Plus	2.3	0.03	103.6	76.7	139.9

Abbreviations: PK: Pharmacokinetics, LSM: Least Squares Mean; CI: Confidence Interval

On average, the results of this study show that Credelio Plus provides greater AUC and at least similar C_{max} compared to Credelio as the ratios are greater than 100% (ratios of 118 and 104%, respectively). At 83%, the lower bound of the confidence interval on AUC is above 80%; thus, one-sided (lower level - efficacy) bioequivalence for AUC was demonstrated in this study. However, at 77%, the lower confidence interval on C_{max} is not greater than 80%; thus, bioequivalence for efficacy for C_{max} is not achieved. On this point, the applicant argues that efficacy for *D. canis* is not driven by C_{max}, but more likely by AUC or C_{last}. In contrast to fleas and ticks which take blood meals, mites feed on cellular debris and skin secretions. Therefore, blood concentrations are only important to allow distribution (over time) into the skin. Killing the mites likely requires multiple feedings and exposure. For this reason, the applicant considers AUC and C_{last} to be a more appropriate parameters for concluding on efficacy.

A bioequivalence calculation was performed comparing C_{last} concentrations (28 days after dosing). Lotilaner concentrations achieved at 672 hours were very similar for both products. On average, Credelio Plus provided greater C_{last} concentrations versus Credelio as the ratios are greater than 100% (ratio of 108%). At 82%, the lower bound of the confidence interval for C_{last} was above 80%; thus, one-sided (lower level - efficacy) bioequivalence for C_{last} was demonstrated in this study.

PK Parameter	Reference	Ref LSM	Test	Test LSM	Difference	Ratio %Ref	Lower CI90	Upper CI90
$Ln(Conc_{672})$	Credelio	1.1	Credelio Plus	1.2	0.08	108.1	82.0	142.6

Abbreviations: PK: Pharmacokinetics, LSM: Least Squares Mean; CI: Confidence Interval

In relation to the re-analysis of study WIL-668072 and the applicant's overall approach to support the *D. canis* claim for Credelio Plus based on the available efficacy data for Credelio, the CVMP has the following comments:

- While acknowledging that study WIL-668072 was never intended to be a bioequivalence study, and was not powered to be so, a re-evaluation of the data from this study is still appropriate, noting in particular previous conclusions of the CVMP in respect of comparability of the lotilaner pharmacokinetic profile between Credelio and Credelio Plus.
- It is accepted that AUC and C_{last} are the most appropriate parameters to evaluate for concluding on efficacy against *D. canis* (for the reasons presented by the applicant).
- It is accepted that, in order to conclude on adequate efficacy, it is necessary to demonstrate that the one-sided (lower) 95% confidence limit is greater than 80% for relevant pharmacokinetic parameters.
- It is accepted that breaching of the upper confidence interval for relevant pharmacokinetic parameters is not relevant to the efficacy claim and does not reflect a safety concern knowing that a full safety package already exists for Credelio Plus at the recommended dosages to treat *D. canis*.

While the re-analysis of the bioequivalence study does not allow one to conclude that Credelio and Credelio Plus are bioequivalent, it does provide further support for comparable efficacy between products noting in particular the comparability of mean data for AUC and C_{last} and the fact that, for both parameters, the one-sided (lower) 95% confidence limit is greater than 80%.

When the findings of the re-analysis are taken together with the previous conclusions of the CVMP in respect of Credelio Plus (that there was no significant pharmacokinetic interaction when the active ingredients are administered in combination and that clinical data relating to the individual active substances can be extrapolated to the combination product, where relevant), it is accepted that the data generated, submitted, assessed and accepted for the Credelio *Demodex* indication are applicable to Credelio Plus; these studies are presented below.

In support of the *Demodex canis* indication, the applicant has provided the results of one dose confirmation study and one field study, both conducted using Credelio tablets.

The dose confirmation study was GCP-compliant and investigated the efficacy of the final formulation of Credelio chewable tablets against generalised demodicosis in naturally infested client-owned dogs in South Africa. Previous scientific advice had been received by the applicant in respect of this study and, in general, the advice has been followed.

This was a single-arm study conducted at one site and therefore was neither blinded nor randomised. The CVMP previously noted that in the absence of a control group, the possibility for spontaneous improvement cannot be excluded (for example, inclusion of dogs with juvenile demodicosis) and therefore further reassurances were provided by the applicant to justify that the presentation of animals with demodicosis in the study is unlikely to have altered significantly over the course of the follow-up period in the absence of treatment.

Eleven privately owned dogs naturally infested with *Demodex* spp. mites and displaying signs of generalised demodectic mange were acclimatised to the study site for at least seven days. Dogs were housed in individual cages for the duration of the study to prevent physical contact.

Dogs were mongrels aged >6 months and in the bodyweight range 9.59 – 17.65 kg. Clinical examinations and assessments, a skin biopsy and deep skin scrapings were performed to confirm the presence of natural infestation with *Demodex* mites and to assess the extent of demodectic mange. The ten dogs (7 male; 3 female) with the highest mite counts and clinical signs of demodectic mange were included in the study. The number of study animals is considered adequate for the purpose of the study. Dogs were healthy except for clinical signs and symptoms of generalised *Demodex canis* mite infestations. The inclusion criteria can be accepted as being appropriate and resulted in a study sample that is considered to be suitably representative of the intended target population.

Credelio was administered to study animals in the fed state on study days 0, 28 and 56. The dose of lotilaner administered in this study ranged from 20.1 to 24.2 mg/kg bw and can be accepted as being sufficiently representative of the lower end of the dose rate recommended in the currently approved SPC (20 to 43 mg lotilaner/kg bw). Antibiotic therapy for pyoderma was initiated in all dogs on day -7 and continued fortnightly until study day 34.

Mite counts were performed on study days 28, 42 and 56 for all dogs, and on days 70 and 84 for one of the dogs. Skin scrapings were stopped on day 56 for dogs which had demonstrated negative live mite counts on days 42 and 56. Mite counts were performed using deep skin scrapings which were taken from five sites. Skin scraping sites were recorded and these sites and/or sites of new lesions were scraped at each subsequent examination.

Skin biopsies were collected on days -7 and 27 and clinical assessments were performed on days -7, -2, 14, 28, 42, 56, 70 and 84. Bodyweight was measured on days -1, 13, 27, 41 and 55. Efficacy

evaluation was based on the decrease in *Demodex* spp. mites and the resolution of clinical symptoms compared to their baseline pre-treatment assessments.

Deep skin scrapings were taken from five sites and numbers of live *Demodex* spp. mites (immature and adult) were counted and served as primary variable for the efficacy evaluation, namely, percentage decrease in live mite counts per time point. This can be accepted as being an appropriate outcome parameter for demonstrating efficacy. The guideline 7AE17a "Demonstration of Efficacy of Ectoparasiticides" recommends an overall efficacy of ectoparasiticides of >90% for mange mites other than *Sarcoptes scabiei*.

Efficacy was based on geometric mean live mite counts using Abbott's formula. According to guideline 7AE17a, the arithmetic mean, geometric mean or other suitably transformed mean may be used, however, such transformation must be justified. The percentage of efficacy was calculated using geometric mean counts as, according to the applicant, as zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution.

Secondary efficacy parameters were the individual percentage decrease from the pre-administration mite count to the post-administration mite count in each individual dog and the proportion of animals cured (proportion of mite-free dogs after two consecutive post-treatment zero mite counts).

The results showed that mite counts determined by skin scrapings were reduced by 100% on days 28, 42, 70 and 84 and by >99.9% at day 56. On day 56, all dogs were negative for *Demodex* spp. except for one dog where 10 mites were found. Day 27 skin biopsies revealed *Demodex* spp. mites for two of the 10 dogs assessed. Mite counts determined by skin scrapings were statistically significantly lower at days 28, 42 and 56 compared to pre-treatment mite counts ($p<0.0001$).

The proportion of dogs cured based on absence of mites on two consecutive skin scrapings was 100% at the end of the study on day 84.

All dogs showed marked improvement in the clinical signs of demodicosis including hair regrowth and no adverse events were observed that were considered to be related to treatment with lotilaner.

In conclusion, it can be accepted that the results of this study demonstrate that following monthly administration of lotilaner at the lower end of the currently approved dose rate on three consecutive monthly occasions (study days 0, 28 and 56), all ten study animals had zero mite counts detected in two consecutive monthly skin scrapings.

According to guideline 7AE17a, at least two controlled dose confirmation studies in addition to EU clinical field trials should be provided to demonstrate efficacy. Although the applicant has only provided one dose confirmation study conducted with Credelio chewable tablets, a controlled field study has also been conducted and which included an acceptable number of animals in each treatment group with efficacy based upon objective parameters – reduction in live mite counts and parasitological cure (two negative skin scrapings one month apart). The approach used by the applicant in terms of number and type of studies is consistent with previous scientific advice provided by the CVMP for Credelio and, consequently, the CVMP accepts the omission of a second dose confirmation study for the proposed indication in this instance.

The GCP-compliant field study investigated the efficacy and safety of the final formulation of Credelio chewable tablets in the treatment of *Demodex canis* in naturally infested dogs. Animals were recruited from 11 study sites in four countries (Albania, Hungary, Portugal, Italy). One hundred and forty-nine (124 mixed breed & 25 pure-bred) privately owned dogs in the bodyweight range 2 to 44.3 kg and in the age range 2-132 months were enrolled in the study. Dogs remained with their owners who observed general health on a daily basis. The study can be considered representative of the European situation in terms of the geographical distribution of study sites and the age/breed of study animals.

Animals were included in the study if they were diagnosed with clinical signs consistent with generalised demodicosis, including alopecia, papules, pustules, erythema, comedones, casts and/or crusts, involving one or more of the following: an entire body region (e.g. facial area); five or more separate affected areas, each with a diameter greater than 2.5 cm; pododemodicosis involving two or more feet. In addition, study animals needed to have a total of at least four live *D. canis* mites (immature or adult) from five deep skin scrapings. Where there was more than one dog in a household meeting the inclusion criteria, the dog with the most severe clinical manifestations of demodicosis was considered the primary case.

A positive control group was used in this study and animals were administered the control product NexGard (afoxolaner) chewable tablets. Animals were randomised to either treatment (n=100) or control (n=49) group using a 2:1 (Credelio:NexGard) ratio with all animals in the same household allocated to the same treatment group.

According to the Guideline 7AE17a "…When treatment of groups is intended, preferably 25-50% of the groups under trial should be left untreated. Where this cannot be justified, 25-50% of the groups should be treated with a product established according to Directive 81/852/EEC which is indicated for control of the ecto-parasite or groups of ecto-parasites claimed...". Due to the potentially debilitating nature of the disease and therefore on ethical grounds, the absence of an untreated control group and the use of a positive control group (NexGard) can be accepted. NexGard chewable tablets can be accepted as a valid control product as it is authorised in the EU with a claim for the treatment of *D. canis* in dogs.

Treatments were administered at monthly intervals on at least two occasions (days 0, 30), with need for further administration dependent upon results of monthly skin scrapings. Doses of lotilaner administered ranged between 20.3 and 43.1 mg/kg bodyweight and doses of afoxolaner administered ranged from 2.8-6.1 mg/kg bodyweight. Treatments were administered with or after food. Deep skin scrapings were performed on study days 0, 30 and 60 with need for additional subsequent skin scrapings dependent upon achieving two negative monthly skin scrapings. Unlike in the dose confirmation study, antibiotic treatment was not routinely administered to all study animals; however, some individual animals (6 in total) received antibiotic therapy when clinically indicated.

The pivotal efficacy parameter was the percentage reduction in live mite counts at each study visit compared to baseline. Percent efficacy was calculated for both groups and all time points using arithmetic mean live mite counts and Abbott's formula. Efficacy was compared between groups using a generalised linear mixed model analyses approach to test for non-inferiority (using a non-inferiority margin of 15%) and all tests were performed using a one-sided test with a significance level of $\alpha = 0.025$.

Although a non-inferiority approach was used to compare percentage reduction in live mite counts between treatment groups, the CVMP considered the approach used to have been inadequately justified in terms of compatibility with the minimum threshold required to demonstrate efficacy. That said, the deficiency noted in terms of investigating non-inferiority only has implications for the assessment of efficacy at study day 30, given that at subsequent time points, no live mites were observed in either treatment group and therefore non-inferiority between Credelio and NexGard could be accepted after day 30.

Results of this study demonstrated that at day 30 (following one treatment administration), mean number of live mite counts was 0.3 in dogs administered Credelio (equivalent to 98.9% reduction compared to baseline) and no mites were detected in the control group. At all subsequent time points (days 60, 90) no live mites were detected in either group (equivalent to 100% reduction compared to baseline).

Secondary efficacy parameters included: average efficacy of Credelio compared to the control product

for the entire treatment period compared to baseline based on live mite counts; parasitological cure (percentage of dogs with a zero mite count); frequency distribution of skin lesions associated with generalised demodectic mange. Signs of generalised demodectic mange (alopecia, papules, pustules, erythema, comedones, casts and crusts scores) were scored as absent, mild, moderate, and severe with numerical values 0, 1, 2 and 3 assigned, respectively. A total generalised demodectic mange severity score was calculated for each animal at each time point as the sum of the clinical sign scores. Change in the respective signs as well as the total clinical score was calculated for each treatment group. Total scores were analysed within each treatment group over time and/or at each time point and were compared between the two treatment groups.

Results of this study demonstrated that the average percentage efficacy for the entire treatment period compared to baseline based on mean percentage reduction of counts at the last visit for dogs that had received at least two treatments was 100% for both groups and therefore non-inferiority to the control group was concluded.

On day 30 the proportion of dogs considered to be parasitologically cured was 96.5% in the Credelio group and 100% in the control group. On day 60 the proportion of dogs considered to be parasitologically cured was 100% in the Credelio group and 100% in the control group and therefore non-inferiority to the control group was concluded. By day 90 all dogs in both treatment groups had demonstrated 2 successive negative monthly skin scrapings.

Based upon the findings from this study, it can be accepted that administration of Credelio at the currently approved treatment dose for two consecutive months results in 100% reduction in live *Demodex canis* mites in dogs under field conditions in Europe. Furthermore, study results indicate that all study animals were considered to be parasitologically cured (no live mites) from study day 60 onwards.

Taking into account the results of the two studies conducted with Credelio and the pharmacokinetic data generated in the bioequivalence study, the indication against *Demodex canis* in dogs can be accepted for Credelio Plus, along with the amendments proposed to the product information to reflect the new indication.

3. Benefit-risk assessment of the proposed change

Credelio Plus is authorised for use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, gastrointestinal nematodes, heartworm and/or lungworm. The product is indicated when use against ticks/fleas and gastrointestinal nematodes or the treatment against ticks/fleas and prevention of heartworm disease/angiostrongylosis is required concurrently. The product can also be used as part of a treatment strategy for the control of flea allergy dermatitis.

The product contains a fixed combination of two active substances: lotilaner and milbemycin oxime. Lotilaner is a systemically acting acaricide and insecticide belonging to the isoxazoline family, whilst milbemycin oxime, a macrocyclic lactone, acts against endoparasites (gastrointestinal and vascular).

The product is presented as chewable tablets of five different strengths, and is administered at a dose range of 20 to 41 mg lotilaner/kg bodyweight and 0.75 to 1.53 mg milbemycin oxime/kg bodyweight.

The proposed variation is to add a new therapeutic indication for the treatment of demodicosis (caused by *Demodex canis*).

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce an additional indication to existing presentations of the product Credelio Plus chewable tablets for dogs, the benefit will arise from the inclusion of the new indication. The indication against *D. canis* in dogs is considered as being of benefit for the user/prescriber and patient. The direct therapeutic benefit of Credelio Plus is its efficacy in the treatment of demodicosis in dogs, which was established in one dose confirmation study and one field study conducted to acceptable standards.

Additional benefits

No additional benefits foreseen.

3.2. Risk assessment

As this is a variation to introduce an additional indication to existing presentations of the product Credelio Plus chewable tablets for dogs, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indication. As the product will be administered to the same target species at the same dose rate and at the same frequency as already approved for existing indications, no new risk is considered to arise in terms of user safety, target animal tolerance, potential for resistance development or for the environment.

Quality

Quality remains unaffected by this variation.

Safety

Risks for the target animal:

The dose rate and frequency of treatment administration does not differ for the proposed indication in the target species when compared to that already approved for the existing indications. Consequently, no additional risk for the target species is foreseen.

Administration of Credelio Plus in accordance with SPC recommendations is generally well-tolerated. The main reported adverse reactions are appropriately included in the SPC and no new adverse reactions arise from the studies performed in support of the proposed new indication.

Risk for the user:

The dose rate and frequency of treatment does not change due to the addition of the new indication against *D. canis* in dogs. Therefore, no additional risk for the user arises.

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

Risk for the environment:

Credelio Plus is not expected to pose a risk for the environment when used according to the SPC recommendations.

3.3. Risk management or mitigation measures

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

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, target animal safety.

The product has been shown to be efficacious for the treatment of demodicosis (caused by *Demodex canis*).

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Credelio Plus can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: to add a new therapeutic indication for the treatment of demodicosis (caused by *Demodex canis*).

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of this variation, sections 4.2, 4.9 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.