SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Credelio Plus 56.25 mg/2.11 mg chewable tablets for dogs (1.4–2.8 kg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Each chewable tablet contains:

Credelio Plus tablets	lotilaner	milbemycin oxime
Dogs (1.4–2.8 kg)	56.25 mg	2.11 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.

White to beige round biconvex chewable tablet with brownish spots and bevelled edges with letter “I” debossed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

For use in dogs with, or at risk from, mixed infestations/infections of ticks, fleas, mites, gastrointestinal nematodes, heartworm and/or lungworm.
This veterinary medicinal product is indicated for use when treatment against ticks/fleas/mites and gastrointestinal nematodes or the treatment against ticks/fleas/mites and prevention of heartworm disease/angiostrongylosis is required concurrently.

Ectoparasites
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).

For the treatment of demodicosis (caused by *Demodex canis*).

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*).

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.

4.3 Contraindications

Do not use in cases of known hypersensitivity to the active substances, or to any of the excipients.

4.4 Special warnings for each target species

All dogs within the household should be treated with a suitable product.

Ticks and fleas must attach to the host and commence feeding in order to be exposed to the active substance; therefore the risk of the transmission of tick/flea- borne diseases cannot be excluded.

Parasite resistance to any particular class of anthelmintic may develop following the frequent, repeated use of an anthelmintic of that class. Therefore, the use of this veterinary medicinal product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

For the treatment of infections with gastrointestinal nematodes the need for, and the frequency of, re-treatment as well as the choice of the treatment (monosubstance or combination product) should be evaluated by the prescribing veterinarian.

Maintenance of the efficacy of macrocyclic lactones is critical for *Dirofilaria immitis* prevention, therefore, to minimise the risk of resistance selection, it is

recommended that dogs should be checked for both circulating antigens and blood microfilariae at the beginning of each heartworm season prior to starting monthly preventive treatments.The product is not effective against adult *D. immitis* and is not indicated for microfilariae clearance.

4.5 Special precautions for use

Special precautions for use in animals

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 bodyweight should be based on a benefit-risk assessment by the responsible veterinarian.

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

Prior to first administration, dogs in heartworm endemic areas or who have visited heartworm endemic areas must be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to kill adult heartworms.

Administration of products containing milbemycin oxime (such as this product) to dogs with a high number of circulating microfilariae is not recommended in order to avoid hypersensitivity reactions associated with the release of proteins from dead or dying microfilariae.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Accidental ingestion may cause gastrointestinal disturbances. In order to prevent access by children, keep the tablets in the blister packs until required and keep the blister packs in the outer carton out of the reach of children.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or label to the physician.

Wash hands after handling the tablets.

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.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

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

Use only according to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Lotilaner and milbemycin oxime have been shown to be a substrate for P-glycoprotein (P-gp) and therefore could interact with other P-gp substrates (e.g. digoxin, doxorubicin) or other macrocyclic lactones. Therefore, concomitant treatment with other P-gp substrates could lead to enhanced toxicity.

4.9 Amounts to be administered and administration route

Oral use.

The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 20 to 41 mg lotilaner/kg bodyweight and 0.75 to 1.53 mg milbemycin oxime/kg bodyweight.

Dog bodyweight	**Strength and number of Credelio Plus tablets to be administered**				
	56.25 mg/ 2.11 mg	**112.5 mg/ 4.22 mg**	**225 mg/ 8.44 mg**	**450 mg/ 16.88 mg**	**900 mg/ 33.75 mg**
1.4–2.8 kg	1				
> 2.8–5.5 kg		1			
> 5.5–11 kg			1		
> 11–22 kg				1	
> 22–45 kg					1
> 45 kg	Appropriate combination of tablets				

Use an appropriate combination of available strengths to achieve the recommended dose of 20–41 mg lotilaner/kg and 0.75–1.53 mg milbemycin oxime/kg for animals > 45 kg bodyweight.

The treatment schedule should be based on the individual risk assessment of the dog, the local epidemiological situation and/or the epidemiological situation of other areas the dog has visited or is going to visit. If based on the veterinarian's opinion the dog requires re-administration(s) of the product, any subsequent administration(s) must follow the 1 month interval schedule.
The product should be used in dogs with, or at risk from, mixed infestations of ectoparasites (ticks, fleas or mites) and endoparasites (gastrointestinal nematodes and/or for prevention of heartworm/lungworm). Otherwise, a narrower spectrum parasiticide should be used.

Method of administration:
The veterinary medicinal product is a palatable chewable flavoured tablet.
Administer the chewable tablet(s) with or after food.

Dogs living in non-heartworm endemic areas:
The veterinary medicinal product can be used as part of the seasonal treatment of ticks and/or fleas in dogs with diagnosed, or at risk from, concurrent gastrointestinal nematode infections or at risk of lungworm. A single treatment is effective for the treatment of gastrointestinal nematodes.

Dogs living in heartworm endemic areas:
Prior to treatment with the veterinary medicinal product the advice in sections 4.4 and 4.5 should be considered.

For the prevention of heartworm disease and the concurrent treatment of tick and/or flea infestations, the veterinary medicinal product must be given at regular monthly intervals during the time of the year when mosquitoes, ticks and/or fleas are present. The first dose of the veterinary medicinal product may be given after first possible exposure to mosquitoes, but not more than one month after this exposure.

When the veterinary medicinal product is used to replace another heartworm preventive product, the first dose of the product must be given within a month of the last dose of the former medication.
Dogs travelling to a heartworm region should start medication within a month after arrival there.
Heartworm prevention treatment should be continued monthly, with the last administration being given 1 month after the dog has left the region.

Lungworm:
In endemic areas, monthly administration of the veterinary medicinal product will reduce the level of infection with immature adults (L5) and adults of *Angiostrongylus vasorum* in the heart and lungs. It is recommended that lungworm prevention should be continued until at least 1 month after the last exposure to slugs and snails.

Seek veterinary advice regarding information on the optimal time to start treatment with this veterinary medicinal product.

For the treatment of demodicosis (caused by *Demodex canis*):
Monthly administration of the product for two consecutive months is efficacious and leads to a marked improvement of clinical signs. Treatment should be continued until two negative skin scrapings are obtained one month apart. Severe cases may require prolonged monthly treatments. As demodicosis is a multi-factorial disease, where possible, it is advisable to also treat any underlying disease appropriately.

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.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antiparasitic products, ectoparasiticides, endectocides for systemic use (milbemycin combinations)
ATC vet code: QP54AB51

5.1 Pharmacodynamic properties

Lotilaner:

Lotilaner is an insecticide and acaricide of the isoxazoline family. It is a pure enantiomer that is active against adult ticks such as *Dermacentor reticulatus, Ixodes hexagonus, I. ricinus, Rhipicephalus sanguineus,* adult fleas such as *Ctenocephalides felis* and *C. canis* as well as *Demodex canis* mites.

Lotilaner is a potent inhibitor of gamma–aminobutyric acid (GABA)-gated chloride channels and to a lesser extent of glutamate-gated chloride ion channels of insects and ticks, resulting in rapid death of ticks and fleas. The

activity of lotilaner has not been found to be affected by resistance to organochlorines (cyclodienes, e.g. dieldrin), phenylpyrazoles (e.g. fipronil), neonicotinoids (e.g. imidacloprid), formamidines (e.g. amitraz) and pyrethroids (e.g. cypermethrin).

For ticks, the onset of efficacy is within 48 hours of attachment for one month after product administration. Existing *I. ricinus* ticks present on the dog prior to administration are killed within 8 hours.

For fleas, the onset of efficacy is within 4 hours of being infested for one month after product administration. Fleas present on the dog prior to administration are killed within 6 hours.

The veterinary medicinal product kills existing and newly emerged flea infestations on dogs before the female can lay eggs. Therefore, the product breaks the flea life cycle and prevents environmental flea contamination in areas to which the dog has access.

Milbemycin oxime:

Milbemycin oxime is a systemically active macrocyclic lactone isolated from the fermentation of *Streptomyces hygroscopicus* var. aureolacrimosus. It contains two major factors, A3 and A4 (ratio of A3:A4 is 20:80). Milbemycin oxime is an antiparasitic endectocide with activity against mites, larval and adult stages of nematodes as well as larvae (L3/L4) of *Dirofilaria immitis*.

The activity of milbemycin oxime is related to its action on invertebrate neurotransmission. Milbemycin oxime, like avermectins and other milbemycins, increases nematode and insect membrane permeability to chloride ions via glutamate-gated chloride ion channels. This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.

5.2 Pharmacokinetic particulars

Absorption
Lotilaner is readily absorbed following oral administration and peak plasma concentration is reached within 3–5 hours. Milbemycin A3 5-oxime and milbemycin A4 5-oxime are also rapidly absorbed following oral administration with a T_{max} of approximately 2–4 hours for each drug substance. Food enhances the absorption of both lotilaner and milbemycin oxime. The bioavailability of lotilaner is 75% and that of milbemycin (A_3 and A_4 5-oximes) is approximately 60%.

Distribution
Lotilaner and milbemycin A3 and A4 5-oximes are extensively distributed in dogs where volume of distribution after intravenous administration is 3–4 L/kg.

Plasma protein binding is high for both lotilaner and milbemycin oxime (> 95%).

Metabolism and Excretion
Lotilaner is metabolized to a small extent into more hydrophilic compounds which are observed in faeces and urine.

The major route of elimination for lotilaner is biliary excretion, with renal excretion being the minor route of elimination (less than 10% of the dose). The terminal half- life is approximately 24 days. This long terminal half-life provides effective blood concentrations for the entire duration of the inter-dosing interval. With repeated monthly doses, slight accumulation is observed with steady state being reached after the fourth monthly dose.

The primary faecal and urinary metabolites of milbemycin oxime in dog were identified as glucuronide conjugates of milbemycin A3 or A4 5-oximes, dealkylated milbemycin A3 or A4 5-oximes, and hydroxylated milbemycin A4 5-oxime.
Hydroxymilbemycin A4 5-oxime was detected only in plasma, but not in urine or faeces, suggesting predominant excretion of conjugated metabolites in the dog.

Milbemycin A4 5-oxime eliminates more slowly than milbemycin A3 5-oxime (clearance after intravenous administration was 47.0 and 106.8 mL/h/kg, respectively) resulting in exposure (AUC) to milbemycin A4 that is higher than to milbemycin A3 5-oxime. The mean elimination half-lives were 27 hours for A3 and 57 hours for A4. Excretion of milbemycin A3 and A4 5-oxime is primarily via faeces, and also to a lesser extent in the urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, powdered
Lactose monohydrate
Silicified microcrystalline cellulose
Meat dry flavour
Crospovidone
Povidone K30
Sodium laurilsulfate
Silica, colloidal anhydrous
Magnesium stearate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years

6.4 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Aluminium/aluminium blisters packaged into an outer cardboard box.
Pack sizes of 1, 3, 6 or 18 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

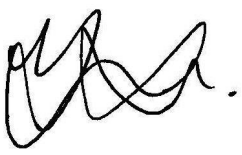
Elanco GmbH
Heinz-Lohmann Strasse 4
Groden
D-27472 Cuxhaven
Germany

8. MARKETING AUTHORISATION NUMBER

Vm 52127/5033

9. DATE OF FIRST AUTHORISATION

29 March 2021



10. DATE OF REVISION OF THE TEXT

February 2023

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