SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbemax 12.5 mg/125 mg tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:

Milbemycin oxime	12.5 mg
Praziquantel	125.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Round shaped, white tablet. One side bears the imprint "CCA", the other side "NA".

4. CLINICAL PARTICULARS

4.1 Target species

Dogs (>5 kg)

4.2 Indications for use, specifying the target species

For dogs with, or at risk from mixed infections of cestodes, gastrointestinal nematodes, eyeworm, lungworms and/or heartworm. This veterinary medicinal product is only indicated when use against cestodes and nematodes or prevention of heartworm disease/angiostrongylosis is indicated at the same time.

Cestodes
Treatment of tapeworms: *Dipylidium caninum, Taenia* spp*., Echinococcus* spp*., Mesocestoides* spp*.*

Gastrointestinal nematodes
Treatment of:
Hookworm: *Ancylostoma caninum*
Roundworms: *Toxocara canis, Toxascaris leonina*
Whipworm: *Trichuris vulpis*

Eyeworm
Treatment of *Thelazia callipaeda* (see specific treatment schedule under section 4.9 “Amount(s) to be administered and administration route”).

Lungworms
Treatment of:
Angiostrongylus vasorum (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment and prevention disease schedules under section 4.9 “Amount(s) to be administered and administration route”),
Crenosoma vulpis (Reduction of the level of infection).

Heartworm
Prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

4.3 Contraindications

Do not use in dogs weighing less than 5 kg
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
See also section 4.5 "Special precautions for use".

4.4 Special warnings for each target species

The possibility that other animals in the same household can be a source of re-infection should be considered, and these should be treated as necessary with an appropriate veterinary medicinal product. It is recommended to treat all the animals living in the same household concomitantly.

When infection with the cestode *D. caninum* has been confirmed, concomitant treatment against intermediate hosts, such as fleas and lice, should be discussed with a veterinarian to prevent re-infection.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.

Unnecessary use of antiparasitics or use deviating from the instructions given in the SPC may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the parasitic species and burden, or of the risk of infection based on its epidemiological features, for each individual animal.

In the absence of risk of co-infection with nematodes or cestodes, a narrow spectrum veterinary medicinal product should be used.

Resistance of *Dipylidium caninum* to praziquantel as well as cases of multi-drug resistance of *Ancylostoma caninum* to milbemycin oxime and resistance of *Dirofilaria immitis* to macrocyclic lactones have been reported.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method. Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

4.5 Special precautions for use

Special precautions for use in animals
Treatment of dogs with a high number of circulating microfilariae can sometimes lead to the appearance of hypersensitivity reactions, such as pale mucous membranes, vomiting, trembling, laboured breathing or excessive salivation. These reactions are associated with the release of proteins from dead or dying microfilariae and are not a direct toxic effect of the veterinary medicinal product. The use in dogs suffering from microfilaremia is thus not recommended.

In heartworm risk-areas, or in the case it is known that a dog has been travelling to and from heartworm risk regions, before using the veterinary medicinal product , a veterinary consultation is advised to exclude the presence of any concurrent infestation of *Dirofilaria immitis*. In the case of a positive diagnosis, adulticidal therapy is indicated before administering the veterinary medicinal product .

No studies have been performed with severely debilitated dogs or individuals with seriously compromised kidney or liver function. The veterinary medicinal product is not recommended for such animals or only according to a benefit/risk assessment by the responsible veterinarian.

In dogs less than 4 weeks old, tapeworm infection is unusual. Treatment of animals less than 4 weeks old with a combination veterinary medicinal product may therefore not be necessary.

Studies with milbemycin oxime indicate that the margin of safety in certain dogs of Collie or related breeds is less than in other breeds. In these dogs, the recommended dose should be strictly observed.
The tolerance of the veterinary medicinal product in young puppies from these breeds has not been investigated.
Clinical signs in Collies are similar to those seen in the general dog population when overdosed (see section 4.10 " Overdose (symptoms, emergency procedures, antidotes)").

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Wash hands after use.

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

Special precautions for the protection of the environment
See section 6.6

Other precautions
Echinococcosis represents a hazard for humans. As Echinococcosis is a notifiable disease to the World Organisation for Animal Health (WOAH), specific guidelines on the treatment and follow up and on the safeguard of persons need to be obtained from the relevant competent authority (e.g. experts or institutes of parasitology).

4.6 Adverse reactions (frequency and seriousness)

Dogs:

Very rare (<1 animal / 10 000 animals treated, including isolated reports):	Digestive tract disorders (such as Diarrhoea, Drooling, Emesis) Hypersensitivity reaction Neurological disorders (such as Ataxia and Muscle tremor) Systemic disorders (such as Anorexia and Lethargy)

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

4.7 Use during pregnancy, lactation or lay

Pregnancy and lactation:
Can be used during pregnancy and lactation.

Fertility:
Can be used in breeding animals.

4.8 Interaction with other medicinal products and other forms of interaction

The concurrent use of the veterinary medicinal product with selamectin is well tolerated. No interactions were observed when the recommended dose of the macrocyclic lactone selamectin was administered during treatment with the veterinary medicinal product at the recommended dose. In the absence of further studies, caution should be taken in the case of concurrent use with other macrocyclic lactones. Also, no such studies have been performed with breeding animals.

4.9 Amount(s) to be administered and administration route

Oral use.

Underdosing could result in ineffective use and may favour resistance development.

To ensure a correct dosage, body weight should be determined as accurately as possible.

Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once. The veterinary medicinal product should be administered with or after some food.

Depending on the bodyweight of the dog, the practical dosing is as follows:

Weight	**Tablets**
5-25 kg	1 tablet
>25 - 50 kg	2 tablets
>50- 75 kg	3 tablets

In cases when heartworm disease prevention is used and at the same time treatment against tapeworm is required, the veterinary medicinal product can replace the monovalent veterinary medicinal product for the prevention of heartworm disease.

For treatment of *Angiostrongylus vasorum* infections, milbemycin oxime should be given four times at weekly intervals. It is recommended, where concomitant treatment against cestodes is indicated, to treat once with the veterinary medicinal product and continue with the monovalent veterinary medicinal product containing milbemycin oxime alone, for the remaining three weekly treatments.

In endemic areas administration of the veterinary medicinal product every four weeks will prevent angiostrongylosis by reducing immature adult (L5) and adult parasite burden, where concomitant treatment against cestodes is indicated.

For the treatment of *Thelazia callipaeda,* milbemycin oxime should be given in 2 treatments, seven days apart. Where concomitant treatment against cestodes is indicated, the veterinary medicinal product can replace the monovalent veterinary medicinal product containing milbemycin oxime alone.

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

No other signs than those observed at the recommended dose have been observed (see section 4.6 “Adverse reactions”).

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocides

ATCvet code: QP54AB51 (milbemycin oxime, combinations)

5.1 Pharmacodynamic properties

Milbemycin oxime belongs to the group of macrocyclic lactones, isolated from the fermentation of *Streptomyces hygroscopicus* var. *aureolacrimosus.* It is active against mites, against larval and adult stages of nematodes as well as against larvae of *Dirofilaria immitis.*

The activity of milbemycin 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 (related to vertebrate GABAA and glycine receptors). This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.

Praziquantel is an acylated pyrazino-isoquinoline derivative. Praziquantel is active against cestodes and trematodes. It modifies the permeability for calcium (influx of Ca^{2+}) in the membranes of the parasite inducing an imbalance in the membrane structures, leading to membrane depolarisation and almost instantaneous contraction of the musculature (tetany), rapid vacuolization of the syncytial tegument and subsequent tegumental disintegration (blebbing), resulting in easier expulsion from the gastrointestinal tract or death of the parasite.

5.2 Pharmacokinetic particulars

After oral administration of praziquantel in the dog, peak serum levels of parent are rapidly attained (T_{max} approximately 0.5-4 hours) and decline quickly ($t_{1/2}$ approximately 1.5 hours). There is a substantial hepatic first-pass effect, with very rapid and almost complete hepatic biotransformation, principally to monohydroxylated (also some di- and tri-hydroxylated) derivatives, which are mostly glucuronide and/or sulfate conjugated before excretion. Plasma binding is about 80%. Excretion is fast and complete (about 90% in 2 days); the principal route of elimination is renal.

After oral administration of milbemycin oxime in dogs, peak plasma levels occur at about 2-4 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 1-4 days. Bioavailability is about 80%.

In the rat, metabolism appears to be complete although slow, since unchanged milbemycin oxime has not been found in urine or feces. Main metabolites in the rat are monohydroxylated derivatives, attributable to hepatic biotransformation. In addition to relatively high liver concentrations, there is some concentration in fat, reflecting its lipophilicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, microcrystalline
Croscarmellose sodium
Povidone
Lactose monohydrate
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: 2 years

6.4 Special precautions for storage

Do not store above 30 °C
Keep the blister in the outer carton in order to protect from light.

6.5 Nature and composition of immediate packaging

PVC/PE/PVdC/aluminium blisters in an outer cardboard box.

Cardboard box with 1 blister of 2 tablets.
Cardboard box with 1 blister of 4 tablets.
Cardboard box with 1, 2, 5 or 10 blisters of 10 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

Medicines should not be disposed of via wastewater.

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

The veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

Elanco Europe Ltd
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA

8. MARKETING AUTHORISATION NUMBER

Vm 00879/5030

9. DATE OF FIRST AUTHORISATION

17 April 2003

10. DATE OF REVISION OF THE TEXT

May 2024

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCT

Veterinary medicinal product subject to prescription.

Approved 04 May 2024