1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbepar 25 mg / 250 mg chewable tablets for large dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Active substances:
Milbemycin oxime 25 mg
Praziquantel 250 mg

Excipients:

Qualitative composition of excipients and other constituents
Povidone
Croscarmellose sodium
Lactose monohydrate
Chicken flavour*
Yeast
Cellulose microcrystalline
Silica, colloidal anhydrous
Magnesium stearate

**Artificial origin*

Round tablet, beige to light brown, scored on one side. The tablet can be divided into two equal parts.

3. CLINICAL INFORMATION

3.1 Target species

Dogs weighing at least 5 kg

3.2 Indications for use for each target species

In dogs: treatment of mixed infections by adult cestodes and nematodes of the following species:

- Cestodes:
Dipylidium caninum
Taenia spp.
Echinococcus spp.
Mesocestoides spp.

- Nematodes:
Ancylostoma caninum
Toxocara canis
Toxascaris leonina
Trichuris vulpis
Crenosoma vulpis (Reduction of the level of infection)

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 3.9 "Administration routes and dosage")

Thelazia callipaeda (see specific treatment schedule under section 3.9 "Administration routes and dosage")

The product can also be used in the prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

3.3 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 3.5 "Special precautions for use".

3.4 Special warnings

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.

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 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.

Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.
In third countries (USA), 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 already 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.
In the absence of risk of co-infection with nematodes or cestodes, a narrow spectrum product should be used.
The use of this product should take into account local information about susceptibility of the target parasites, where available.

3.5 Special precautions for use

Special precautions for safe use in the target species:
In heartworm risk-areas, or if it is known that a dog has been travelling to and from heartworm risk regions, before using the 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 product.

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 product. The use in dogs suffering from microfilaremia is thus not recommended.

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

Studies with milbemycin oxime indicate that the margin of safety in MDR1 mutant (-/-) dogs of Collie or related breeds is lower compared to the non-mutant population. In these dogs, the recommended dose should be strictly observed. The tolerance of the 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 3.10 “Symptoms of overdose”).

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

The tablets are flavoured. In order to avoid any accidental ingestion, store tablets out of reach of the animals.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
This veterinary medicinal product may be harmful when ingested, particularly for children. To avoid accidental ingestion, the product should be stored out of sight and reach of children. Any unused tablet parts should be returned to the opened blister, inserted back into the outer packaging and used at the next administration or securely discarded (see section 5.5).
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.
The product may cause a weak skin sensitisation. Do not handle this product in case of known hypersensitivity to the active substances or to any of the excipients.
If symptoms such as skin rash persist, seek medical advice and show the package leaflet or the label to the physician.
Wash hands after use.

Special precautions for the protection of the environment:
Not applicable.

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).

3.6 Adverse events

Dogs:

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

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 the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation
The safety of the veterinary medicinal product has been established during pregnancy and lactation. Can be used during pregnancy and lactation.

Fertility
Can be used in breeding dogs.

3.8 Interaction with other medicinal products and other forms of interaction

The concurrent use of a tablet containing milbemycin oxime and praziquantel with selamectin is well tolerated. No interactions were observed when the recommended dose of the macrocyclic lactone selamectin was administered during treatment with a tablet containing milbemycin oxime and praziquantel at the recommended dose. In the absence of further studies, caution should be taken in the case of concurrent use of a tablet containing milbemycin oxime and praziquantel and other macrocyclic lactones. Also, no such studies have been performed with reproducing animals.

3.9 Administration routes and dosage

Oral use.
Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once orally.
Animals should be weighed to ensure accurate dosing. Depending on the bodyweight of the dog, the practical dosing is as follows:

Body Weight (kg)	25 mg /250 mg chewable tablets
5-25	1/2 tablet
>25-50	1 tablet
>50-100	2 tablets

The veterinary medicinal product should be administered with or after some food.
In cases when heartworm disease prevention is used and at the same time treatment against tapeworm is required, the product can replace the monovalent 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 product and continue with the monovalent product containing milbemycin oxime alone, for the remaining three weekly treatments.
In endemic areas administration of the 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 product can replace the monovalent product containing milbemycin oxime alone.
Underdosing could result in ineffective use and may favour resistance development.
The need for and frequency of re-treatment(s) should be based on professional advice and should take into account the local epidemiological situation and the animal's lifestyle.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No other signs than those observed at the recommended dose have been observed (see section 3.6 "Adverse events").

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QP54AB51

4.2 Pharmacodynamics

Milbemycin oxime belongs to the group of macrocyclic lactones, isolated from the fermentation of *Streptomyces hygroscopicus* var. *aureolacrimosus*. It is active 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 $GABA_A$ 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. It modifies the permeability for calcium (influx of Ca2+) in the membranes of the parasite inducing an imbalance in the membrane structures, leading to membrane depolarization 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.

4.3 Pharmacokinetics

After oral administration of praziquantel in the dog, peak plasma levels of the parent drug (1918 µg/L) are rapidly reached. T_{max} is about 30 min and ranged between 15 min and 10 hours. Plasma concentrations decline quickly ($t_{1/2}$ around 1.72 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 reach 773 µg/L and occur at about 1.25 hours. T_{max} ranged between 45 min and 10 hours, plasma concentrations decline with a half-life of the unmetabolised milbemycin oxime of 1-5 days. Bioavailability is about 80%. In addition to relatively high liver concentrations, there is some concentration in fat, reflecting its lipophilicity.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life for halved tablet after first opening the blister: 6 months

5.3 Special precautions for storage

Any unused tablet parts should be returned to the opened blister, inserted back into the outer packaging and used at the next administration or securely discarded (see section 5.5)
Protect from light.

5.4 Nature and composition of immediate packaging

Polyamide-Aluminium-Polyvinyl chloride / aluminium heat sealed blisters.
Cardboard box with 1 blister of 2 tablets (2 tablets).
Cardboard box with 2 blisters of 2 tablets (4 tablets).
Cardboard box with 5 blisters of 2 tablets (10 tablets).
Cardboard box with 12 blisters of 2 tablets (24 tablets).
Cardboard box with 24 blisters of 2 tablets (48 tablets).
Cardboard box with 50 blisters of 2 tablets (100 tablets).

Not all pack sizes may be marketed.

5.5 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 or household waste.
The veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms.
Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ceva Santé Animale

7. MARKETING AUTHORISATION NUMBER(S)

VPA10815/069/003

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).