1. NAME OF THE VETERINARY MEDICINAL PRODUCT

MILIPRAZ 12.5 mg/125 mg Chewable Tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablets contains:

Active substances:
Milbemycin oxime 12.5 mg
Praziquantel 125.0 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Propylene glycol (E 1520)	4.54 mg
Iron Oxide, Brown (E 172)	3.29 mg
Butylhydroxyanisole (E 320)	1.32 mg
Propyl Gallate (E 310)	0.46 mg
Glycerol (E 422)	
Pre-gelatinised pea starch	
Chicken flavour	
Confectioner's sugar	
Purified water	
Sodium Chloride	
Citric acid monohydrate	

Oval shaped, dark brown chewable tablet.

3. CLINICAL INFORMATION

3.1 Target species

Dogs (≥ 5kg)

3.2 Indications for use for each target species

For dogs with, or at risk from mixed infections by cestodes, gastro-intestinal 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 3.9 "Administration routes and dosage").

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 3.9 "Administration routes and dosage"),
Crenosoma vulpis (Reduction of the level of infection).

Heartworm
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 case of hypersensitivity to the active substances or to any of excipients.
See also section 3.5 "Special precautions for use".

3.4 Special warnings

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.

The possibility that other animals in the same household can be a source of re-infection with nematodes and cestodes 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.

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

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 in dogs.

It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method.

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

Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities.

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

3.5 Special precautions for use

Special precautions for safe use in the target species:
Studies with milbemycin oxime indicate that the margin of safety in certain dogs (MDR1 mutant (-/-), which may include Collies or related breeds is less than in other breeds. In these dogs, the recommended dose should be strictly observed.
See also section 3.10 "Symptoms of overdose (and where applicable, emergency procedures and antidotes)". The tolerance of the veterinary medicinal product in young puppies from these breeds has not been investigated
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, if 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, tape worm infection is unusual. Treatment of animals less than 4 weeks old with a combination veterinary medicinal 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 cause hypersensitivity reactions. People with known hypersensitivity to milbemycin oxime/praziquantel should avoid contact with the veterinary medicinal product. If contact occurs, wash hands and seek medical advice in case of hypersensitivity reactions.
The product may be harmful in case of ingestion, especially by a child.
To avoid accidental ingestion, the product should be stored out of sight and reach of children.
In the event of accidental ingestion of the tablets, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the doctor.
Unused part tablets should be discarded
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):	Digestive tract disorders (such as Diarrhoea, Drooling, Emesis) Hypersensitivity reaction Neurological disorders (such as Ataxia, Convulsions, Muscle tremors) Systemic disorders (such as Anorexia, 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.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has been established during pregnancy and lactation.

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

Fertility:
Can be used in breeding animals.

3.8 Interaction with other medicinal products and other forms of interaction

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. Although not recommended, the concomitant use of the veterinary medicinal product with a spot on containing moxidectin and imidacloprid at recommended dose rates following a single application was well tolerated in one experimental study by beagle dogs at the age 11 months or older. Transient neurological adverse reactions (poor proprioception, flaccid frontal and hind legs, incoordination, slight tremors and high stepping gait of the hind limbs only) were observed after concurrent administration of both veterinary medicinal products in another study conducted in puppies aged 8-12 weeks. Such signs were however not observed in this study after giving the veterinary medicinal product alone.
The safety and efficacy of this combination have not been investigated in field studies.
In the absence of further studies, caution should be taken in the case of concurrent use with any other macrocyclic lactone. Also, no such studies have been performed with breeding animals, Collies, related breeds and their crosses.

3.9 Administration routes and dosage

Oral use.
Minimum recommended dose rate 0.5 mg milbemycin oxime and 5 mg praziquantel per kg are given as a single dose. The veterinary medicinal product should be administered with or after some food.
To ensure a correct dosage, body weight should be determined as accurately as possible.
Underdosing could result in ineffective use and may favour resistance development.

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

Weight	**Number of Tablet**
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 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.

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

The adverse reactions observed are the same as those observed at the recommended dose (see section 3.6 “Adverse events”) but more pronounced.

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: QP54A B51

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 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 Ca2+) 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.

Avermectins and milbemycin have similar molecular targets - glutamate–gated chloride channels. These channels have multiple isoforms in nematodes which may have different susceptibilities to avermectins/milbemycin. Different mechanisms of avermectins and milbemycin resistance may be due to the multiplicity of glutamate- gated chloride channels subtypes.
The resistance mechanism for praziquantel is still unknown.

4.3 Pharmacokinetics

After oral administration of praziquantel in the dog, peak serum levels of parent are rapidly attained (Tmax approximately **0.8-3.0** hours) and decline quickly (t1/2 approximately **0.95** 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 **1.5-5** hours, and decline with a half-life of the unmetabolised milbemycin oxime of **2.2** days. Bioavailability is about 80%.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 24 months

5.3 Special precautions for storage

Do not store above 30°C.

5.4 Nature and composition of immediate packaging

Aluminium/aluminium blister (OPA/Al/PVC//Al/Heat-Seal coating)
Pack sizes:
Cardboard box containing 2 tablets. (1 blister strip of 2)
Cardboard box containing 4 tablets. (2 blister strips of 2 or 1 blister strip of 4)
Cardboard box containing 5 tablets. (1 blister strip of 5)
Cardboard box containing 10 tablets. (5 blister strips of 2 or 2 blister strips of 5)
Cardboard box containing 12 tablets. (6 blister strips of 2 or 3 blisters strips of 4)
Cardboard box containing 15 tablets. (3 blister strips of 5)
Cardboard box containing 20 tablets. (10 blisters strips of 2 or 5 blister strips of 4)
Cardboard box containing 24 tablets. (12 blister strips of 2 or 6 blisters strips of 4)
Cardboard box containing 25 tablets. (5 blister strips of 5)
Cardboard box containing 30 tablets. (6 blister strips of 5)
Cardboard box containing 35 tablets. (7 blister strips of 5)
Cardboard box containing 40 tablets. (8 blister strips of 5)
Cardboard box containing 45 tablets. (9 blister strips of 5)
Cardboard box containing 48 tablets. (24 blisters strips of 2 or 12 blister strips of 4)
Cardboard box containing 50 tablets. (10 blister strips of 5)

Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products 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 it 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

Chanelle Pharmaceuticals Manufacturing ltd.,

7. MARKETING AUTHORISATION NUMBER(S)

VPA10987/182/001

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).