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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbenin 12.5 mg/125 mg chewable tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One chewable tablet contains:

Active substances:

Milbemycin oxime	12.5 mg
Praziquantel	125.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Cellulose, microcrystalline
Lactose monohydrate
Povidone
Silica, colloidal anhydrous
Magnesium stearate
Pork flavour
Talc
Pregelatinised starch

Round, white or almost white, evenly distributed brownish-pigmented chewable tablets.

3. CLINICAL INFORMATION

3.1 Target species

Dogs (weighing at least 5 kg)

3.2 Indications for use for each target species

Treatment of mixed infections by adult cestodes and nematodes of the following species susceptible to praziquantel and milbemycin oxime:

- Cestodes:

Dipylidium caninum
Taenia spp.
Echinococcus spp.
Mesocestoides spp.

- Nematodes:

Ancylostoma caninum
Toxocara canis
Toxascaris leonina

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Trichuris vulpis

Crenosoma vulpis

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

The use of the product should follow the implementation of appropriate diagnostic measures towards mixed infections by nematodes and cestodes with consideration of animal history and characteristics (e.g. age, health status), environment (e.g. kennelled dogs, hunting dogs), feeding (e.g. access to raw meat), geographical location and travel. Judgement of the administration of the product in dogs at risk from mixed re-infections or in specific at risk situations (such as zoonotic risks), should be made by the veterinarian responsible. The use of this product should take into account local information about susceptibility of the target parasites, where available.

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.

Resistance of *Dipylidium caninum* to praziquantel as well as cases of multiple-drug resistance of *Ancylostoma caninum* to milbemycin oxime have been reported in US.

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 MDR1 mutant (-/-) dogs of Collie or related breeds is lower compared to the normal 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 these dogs are similar to those seen in the general dog population when overdosed (see section 3.10 “Overdose”).

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

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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.

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 product.

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.

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:

Wash hands after use.

This veterinary medicinal product may be harmful when ingested, particularly for children. Avoid accidental ingestion. The product should be administered and stored in a safe place out of the sight and reach of children. 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.

People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.

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 (OIE), 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 reactions - lethargy - muscle tremors, ataxia and convulsions - emesis, drooling, diarrhoea and anorexia
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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

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authorisation holder or the national competent authority via the national reporting system. See section "Contact details" of the package leaflet..

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 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 product at the recommended dose.

Although not recommended, the concomitant use of the tablet containing the combination praziquantel / milbemycin oxime 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 products in another study conducted in puppies aged 8-12 weeks. Such signs were however not observed in this study after giving the 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 of the product and any other macrocyclic lactone. Also, no such studies have been performed with reproducing animals, Collies, related breeds and their crosses.

3.9 Administration routes and dosage

For oral use.

Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once.

The product should be administered with or after some food.

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

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

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

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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: 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 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 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 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). The rapid vacuolization of the syncytial tegument and subsequent tegumental disintegration (blebbing), results in easier expulsion from the gastrointestinal tract or death of the parasite.

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4.3 Pharmacokinetics

After oral administration of praziquantel in the dog, peak serum levels of parent are rapidly attained (T_{max} approximately 0.5 - 8 hours) and decline quickly ($t_{1/2}$ approximately 2.6 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 - 8 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 1 - 5 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: 2 years.

5.3 Special precautions for storage

Store in the original package.

5.4 Nature and composition of immediate packaging

2 or 4 tablets in OPA-Al-PVC/AL blisters.
1 blister of 2 chewable tablets introduced in carton box.
1 blister of 4 chewable tablets introduced in carton box.
12 blisters of 4 chewable tablets introduced in carton box.

Not all pack size 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>.
This veterinary medicinal product should not enter water courses as milbemycin oxime 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

Pharma VIM Korlátolt Felelősségű Társaság, 1029 Budapest, Pipitér street no. 5., Hungary

Part I. Administrative information	Date: 11.2022.
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7. MARKETING AUTHORISATION NUMBER(S)

NNNN

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD. month YYYY.

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

DD month YYYY

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription except for some pack sizes.

Detailed information on this veterinary medicinal product is available in the Union Product Database.