SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 12.5 mg/125 mg tablets for dogs weighing at least 5 kg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:

Milbemycin oxime	12.5 mg
Praziquantel	125.0 mg

Excipients:

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet
Light brown with brown spots, round and convex 15 mm tablet.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs weighing at least 5 kg

4.2 Indications for use, specifying the 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
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 disease prevention schedules under section “4.9 Amounts to be administered and administration route”)
Thelazia callipaeda (see specific treatment schedule under section 4.9 “Amounts to be administered and administration route”)

The product can also be used in the 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 known 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 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.
In order to develop an effective worm control programme local epidemiological information and the risk of exposure of the dog should be taken into account, and it is recommended to seek professional advice.
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 may increase the resistance selection pressure and lead to reduced efficacy. In third countries (USA), resistance of *Dipylidium caninum* to praziquantel as well as cases of multiple-drug resistance of *Ancylostoma caninum* to milbemycine oxime have already been reported.

4.5 Special precautions for use

<u>Special precautions for use in animals</u>
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 veterinary medicinal 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 (see section 4.6 “Adverse reactions (frequency and seriousness)”).

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.

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 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 product may therefore not be necessary.

As the tablets are flavoured, they should be stored in a safe place out of the reach of 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.
Avoid accidental ingestion.
The product should be stored in a safe place.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after use.

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.

4.6 Adverse reactions (frequency and seriousness)

On very rare occasions, hypersensitivity reactions, systemic signs (such as lethargy), neurological signs (such as muscle tremors and ataxia) and/or gastrointestinal signs (such as emesis, diarrhoea, anorexia and drooling) have been observed in dogs after administration of the combination of milbemycin oxime and praziquantel.

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 in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The product can be used in breeding dogs including pregnant and lactating bitches.

4.8 Interaction with other medicinal products and other forms of interaction

The concurrent use of the 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 product at the recommended dose. In the absence of further studies, caution should be taken in the case of concurrent use of the product and other macrocyclic lactones. Also, no such studies have been performed with reproducing animals.

4.9 Amounts to be administered and administration route

Oral use.
Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once orally.
The product should be administered with or after some food.
Animals should be weighed to ensure accurate dosing. Depending on the bodyweight of the dog and the availability of tablet strengths, practical dosing examples are as follows:

Weight (kg)	**12.5 mg/125 mg tablet**	
> 5 – 25	◯	1 tablet
> 25 – 50	◯◯	2 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*, milbemcyin 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.

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).

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocides, macrocyclic lactones (milbemycin oxime, combinations)
ATC vet code: QP54AB51

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 $GABA_A$ 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 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, after a small amount of food, peak serum levels of parent drug are rapidly attained (T_{max} approximately 0.5-2 hours) and decline quickly ($t_{1/2}$ approximately 1.7 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, after a small amount of food, peak plasma levels occur at about 1-3 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 1-3 days. Bioavailability is about 80%.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Povidone
Cellulose, microcrystalline
Croscarmellose sodium
Lactose monohydrate
Silica, colloidal hydrated
Magnesium stearate
Chicken flavour
Yeast (dried)

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 30 months

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

OPA/Aluminium/PVC-Aluminium blister containing 1, 2 or 4 tablets.

Box with 1 blister containing 1 tablet.
Box with 1 blister containing 2 tablets.
Box with 1 blister containing 4 tablets.
Box with 10 blisters each containing 1 tablet.
Box with 10 blisters each containing 2 tablets.
Box with 10 blisters each containing 4 tablets.
Box with 25 blisters each containing 1 tablet.
Box with 25 blisters each containing 2 tablets.
Box with 25 blisters each containing 4 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.
The product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

7. MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V.
Kuipersweg 9
3449 JA Woerden
The Netherlands

8. MARKETING AUTHORISATION NUMBER

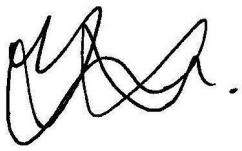
Vm 36408/5005

9. DATE OF FIRST AUTHORISATION

06 May 2022

10. DATE OF REVISION OF THE TEXT

May 2022



Approved: 06 May 2022