1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbemycin oxime / Praziquantel Alfamed 2.5 mg/25 mg film-coated tablets for small dogs and puppies

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:

Active substances:

Milbemycin oxime	2.5 mg
Praziquantel	25.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Core:
Cellulose microcrystalline
Croscarmellose sodium
Lactose monohydrate
Starch, pregelatinised
Povidone
Magnesium stearate
Silica hydrophobic colloidal
Coat:
Poultry liver flavour
Hypromellose
Cellulose microcrystalline
Macrogol stearate

Film-coated tablet.
Oval shaped, beige to pale brown, tablets with a score on both sides.
The tablets can be divided into halves.

3. CLINICAL INFORMATION

3.1 Target species

Dogs (weighing more than 0.5 kg).

3.2 Indications for use for each target species

For dogs with, or at risk from mixed infections of cestodes, gastrointestinal nematodes, eyeworm, lungworms and/or heartworm. The veterinary medicinal product is only indicated when the use against cestodes and nematodes is required 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 "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.

3.3 Contraindications

Do not use in puppies of less than 2 weeks of age and/or weighing less than 0.5 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

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 animal.

In the absence of risk of co-infection, 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/or cestodes should be considered, and these should be treated as necessary with an appropriate veterinary medicinal product.

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

Resistance of Dypilidium caninum to praziquantel and, an imported case of resistance of Dirofilaria immitis to milbemycin oxime, a macrocyclic lactone, have been reported in Europe.
The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.

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.

When *Dipylidium caninum* infection is present, concomitant treatment against intermediate hosts, such as fleas and lice, should be considered to prevent re-infection.

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 minimum recommended dose should be strictly observed.
See also section 3.10 “Symptoms of overdose”.
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, or if it is known that a dog has been travelling to and from heartworm risk regions, before preventive use of 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.

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:
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.
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.

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.

Wash hands after use.

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

Other precautions:
Echinococcosis represents a hazard for humans and is a notifiable disease to the World Organisation for Animal Health (WOAH). In case of echinococcosis, specific guidelines on the treatment and follow up and on the safeguard of persons have to be followed (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 and anorexia) Neurological disorders (e.g. muscle tremor, ataxia and convulsion) Digestive tract disorders (e.g. emesis, drooling, and 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 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

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

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.

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 of bodyweight are given once 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:

Bodyweight	**Tablets**
0.5 - 1 kg	½ tablet
> 1 – 5 kg	1 tablet
> 5 – 10 kg	2 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 and can be administered every 30 days.

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.

For infections with cestodes and nematodes, 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 reactions").

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 broth 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: increasing the cell membrane permeability to chloride ions that results in the hyperpolarization of the neuromuscular membrane and flaccid paralysis and 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.

Praziquantel is an acylated pyrazino-isoquinoline derivative. Praziquantel is active against cestodes and trematodes. It acts primarily by changing the calcium permeability of the parasite membranes 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.

The resistance mechanism for praziquantel is still unknown.

4.3 Pharmacokinetics

After oral administration of praziquantel in the dog, peak serum levels of the parent drug 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%.

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 after first opening the immediate packaging: 6 months.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special temperature storage conditions.
Half tablets should be stored in the original blister and be used for the next administration.

5.4 Nature and composition of immediate packaging

Oriented polyamide/Aluminium/Polyvinyl chloride-Aluminium blister with 2 tablets/blister in a cardboard box.
Pack sizes:
1 box containing 12 blister (24 tablets).

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 milbemycin oxime and praziquantel 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

Alfamed

7. MARKETING AUTHORISATION NUMBER(S)

VPA25201/003/001

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).