1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Milbemycin oxime Praziquantel Chew Alfamed 2.5 mg / 25.0 mg chewable tablets for small dogs and puppies.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:
Milbemycin oxime 2.5 mg
Praziquantel 25.0 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Meat flavour	
Maize Starch	
Glycerol	
Croscarmellose Sodium	
Microcrystalline Cellulose	
Macrogols 3350	32.90 mg
Confectioner's Sugar	
Soya-bean oil, refined	26.32 mg
Purified Water	
Sodium Chloride	
Ferric oxide (E172)	0.66 mg
Butylhydroxyanisole (E320)	0.26 mg

Brown to dark brown rounded rectangular chewable tablet.

3. CLINICAL INFORMATION

3.1 Target species

Dog (puppies and small dogs).

3.2 Indications for use for each target species

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
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 veterinary medicinal 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 1 kg.
Do not use in cases of hypersensitivity to the active substances, or to any of the excipient(s).
See also section 3.5 "Special precautions for use”.

3.4 Special warnings

The possibility that other animals in the same household can be a source of re-infection with cestodes and nematodes should be considered, and these should be treated as necessary with an appropriate veterinary medicinal product.

The use of the veterinary medicinal 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 veterinary medicinal 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.

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.
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.
In third countries (USA), resistance of *Dipylidium caninum* to praziquantel as well as cases of multiple-drug resistance of *Ancylostoma caninum* and resistance of *Dirofilaria immitis* to macrocyclic lactones have already been reported.

The use of this veterinary medicinal product should take into account local information about susceptibility of the target parasites, where available.
In the absence of risk of co-infection with the indicated parasites, a narrow spectrum veterinary medicinal product should be used, when available.
It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method. Confirmed resistance should be reported to the marketing holder or to the competent authority.

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 than in other breeds. In these dogs, the minimum recommended dose should be strictly observed (see section 3.9).
The tolerance of the veterinary medicinal 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”).
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 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 butylhydroxyanisole, macrogols or soya (bean) oil should avoid contact with the veterinary medicinal product. If contact occurs, wash hands and seek medical advice in case of hypersensitivity reactions.
This veterinary medicinal product may be harmful after accidental ingestion. To avoid accidental ingestion, particularly by a child, blister carts should be inserted back into the carton and kept out of 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.
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

Dog:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction Systemic disorders (e.g. lethargy, anorexia) Neurological disorders (e.g. ataxia, convulsion, muscle tremor) 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 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:

Can be used during pregnancy.

Lactation:

Can be used during 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 combination praziquantel/milbemycin oxime with selamectin is well tolerated. No interactions were observed when the recommended dose of the macrocyclic lactone selamectin was administered during treatment with the combination at the recommended dose. In the absence of further studies, caution should be taken in the case of concurrent use of the veterinary medicinal product 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. The veterinary medicinal 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
1 – 5 kg	1 tablet

>5 - 10 kg	2 tablets

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

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.

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.

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.

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 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.

The avermectins and therefore milbemycin anthelmintics have similar molecular targets which are the glutamate–gated chloride channels. These channels have multiple forms between nematodes which explains different susceptibilities of the worms to avermectins/milbemycin. The mechanisms of avermectins and milbemycin resistance would be due to the multiplicity of glutamate- gated chloride channels subtypes. Hence, there might be cross-resistance between the different compounds of the avermectin family.
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 0.5-12 hours) and decline quickly ($t_{1/2}$ approximately 1.85 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 2-6 hours, and decline with a half-life of the unmetabolised milbemycin oxime of 2.5 days. Bioavailability is about 80%.
In the rat, metabolism appears to be complete although slow, since unchanged milbemycin oxime has not been found in urine or faeces. Main metabolites in the rat are monohydroxylated derivatives, attributable to hepatic biotransformation. 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: 21 months.

5.3 Special precautions for storage

Do not store above 25°C.
Store in the original package to protect from light.

5.4 Nature and composition of immediate packaging

Aluminum/aluminum blister (OPA/Alu/PVC, sealed with Alu/Paper film) in cardboard box.

Available pack sizes:
1 box with 1 blister, each blister contains 2 chewable tablets
1 box with 2 blisters, each blister contains 2 chewable tablets
1 box with 12 blisters, each blister contains 2 chewable tablets

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 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

Alfamed

7. MARKETING AUTHORISATION NUMBER(S)

VPA25201/001/001

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*).