SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewable tablet contains:

Active substances:

Milbemycin oxime	2.5 mg
Praziquantel	25.0 mg

Excipients:
Macrogol 3350 (E1520) 32.90 mg,
Ferric oxide (E172) 0.66 mg,
Butylhydroxyanisole (E320) 0.26 mg,
Soya-bean oil, refined 26.32 mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Chewable tablets
Brown to dark brown rounded rectangular tablets.

4. CLINICAL PARTICULARS

4.1 Target species

Dog

4.2 Indications for use, specifying the target species

In dogs: 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 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 1 kg.
Do not use in cases of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

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.

4.5 Special precautions for use

Special precautions for use in animals

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 recommended dose should be strictly observed.
The tolerance of the 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 4.10 “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 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 if it is known that a dog has been travelling to and from heartworm risk regions, before using the 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, tapeworm infection is unusual. Treatment of animals less than 4 weeks old with a combination product may therefore not be necessary.
Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.

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 cards should be inserted back into the carton and kept out of sight and reach of children. In case of accidental ingestion of the tablets, 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).

4.6 Adverse reactions (frequency and seriousness)

Dog:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction Systemic disorders (such as lethargy and anorexia) Neurological disorders (such as ataxia, convulsion and muscle tremor) Digestive tract disorders (such as 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 also section 16 of the package leaflet for contact details.

4.7 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.

4.8 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 product and other macrocyclic lactones. Also no such studies have been performed with reproducing animals.

4.9 Amount(s) to be administered and administration route

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.
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 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.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

The adverse reactions observed are the same as those observed at the recommended dose (see section 4.6 “Adverse reactions”) but more pronounced.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Endectocides

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, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Meat flavour
Maize starch
Croscarmellose sodium
Microcrystalline cellulose
Confectioner’s sugar
Sodium Chloride
Ferric oxide
Butylhydroxyanisole

Macrogols 3350

Glycerol
Soya-bean oil, refined
Purified Water

6.2 Major Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 21 months.

6.4 Special precautions for storage

Store below 25 °C.
Store in the original package to protect from light.

6.5 Nature and composition of immediate packaging

Aluminium/Aluminium 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.

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 veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Medicines should not be disposed of via wastewater.

7. MARKETING AUTHORISATION HOLDER

Alfamed
13ème rue – L.I.D
Carros Cedex
06517
France

8. MARKETING AUTHORISATION NUMBER

Vm 17902/5000

9. DATE OF FIRST AUTHORISATION

12 June 2024

10. DATE OF REVISION OF THE TEXT

June 2024

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

11. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.
Find more product information by searching for the 'Product Information Database' or 'PID' on www.gov.uk.

Approved: 12 June 2024

Gavin Hall