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ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 5 mg/50 mg tablets for dogs weighing at least 0.5 kg (BE, BG, CY, CZ, DE, EE, EL, ES, FR, HU, HR, IE, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK(NI))
Alpramil Vet 5 mg/50 mg tablets for dogs weighing at least 0.5 kg (FI, IS, NO)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:

Milbemycin oxime	5.0 mg
Praziquantel	50.0 mg

Excipients:

Qualitative composition of excipients and other constituents
Povidone
Cellulose, microcrystalline
Croscarmellose sodium
Lactose monohydrate
Silica, colloidal hydrated
Magnesium stearate
Chicken flavour
Yeast (dried)

Light brown with brown spots, round and convex 11 mm tablet with a cross-shaped break line on one side. Tablets can be divided into halves and quarters.

3. CLINICAL INFORMATION

3.1 Target species

Dogs weighing at least 0.5 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
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 "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 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

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.
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 milbemycin oxime have already been reported.

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 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 3.6 "Adverse events").

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 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 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:
This veterinary medicinal product may be harmful when ingested, particularly for children.
Avoid accidental ingestion.
Any unused tablet parts should be discarded or returned to the open blister, inserted back into the outer packaging and used at the next administration.
The veterinary medicinal 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.

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.

3.6 Adverse events

Dogs:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Hypersensitivity reaction; Systemic disorders (e.g. lethargy, anorexia); Neurological disorders (e.g. muscle tremor and ataxia); Digestive tract disorders (e.g. emesis, diarrhoea and drooling).

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 of the veterinary medicinal product and other macrocyclic lactones. Also, no such studies have been performed with reproducing animals.

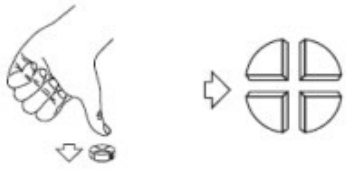
3.9 Administration routes and dosage

Oral use.
To ensure a correct dosage, body weight should be determined as accurately as possible.
Minimum recommended dose rate: 0.5 mg of milbemycin oxime and 5 mg of praziquantel per kg are given once orally.
The veterinary medicinal product should be administered with or after some food.
Depending on the bodyweight of the dog and the availability of tablet strengths, practical dosing examples are as follows:

Weight (kg)	**5 mg/50 mg tablet**	
0.5 – 2.5		¼ tablet
> 2.5 – 5		½ tablet
> 5 – 10		1 tablet
> 10 – 15		1½ tablets

The 5 mg/50 mg tablets can be divided into halves and quarters to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.
Halves: press down with your thumbs on both sides of the tablet:

Quarters: press down with your thumb in the middle of the tablet:



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).

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.

4.3 Pharmacokinetics

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%.

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 of divided tablets after first opening the immediate packaging: 7 days.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

5.4 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.

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

Alfasan Nederland B.V.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

{DD/MM/YYYY}

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 (BE, DE, EE, EL, FI, HR, IE, NO, PL, SI, UK(NI)).

Veterinary medicinal product not subject to prescription (BG, CY, CZ, ES, FR, HU, IS, IT, LT, LU, LV, NL, PT, RO, SK).

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).