ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 12 mg/30 mg film-coated tablets for cats weighing at least 3 kg (AT, 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 12 mg/30 mg film-coated tablets for cats weighing at least 3 kg (DK, FI, IS, NO, SE)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substances:

Milbemycin oxime	12.0 mg
Praziquantel	30.0 mg

Excipients:

Titanium dioxide (E171)	0.456 mg
Iron oxide (E172)	0.181 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
Oblong and convex orange coated tablet.

4. CLINICAL PARTICULARS

4.1 Target species

Cats weighing at least 3 kg

4.2 Indications for use, specifying the target species

Treatment of mixed infections by immature and adult cestodes **and** nematodes of the following species:

- Cestodes:
Dipylidium caninum
Taenia spp.
Echinococcus multilocularis

- Nematodes:
Ancylostoma tubaeforme
Toxocara cati

Prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

4.3 Contraindications

Do not use in cats weighing less than 3 kg.
Do not use in known cases of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

In order to develop an effective worm control programme local epidemiological information and the risk of exposure of the cat should be taken into account.
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.

4.5 Special precautions for use

Special precautions for use in animals
No studies have been performed with severely debilitated cats 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.

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, especially in young cats, hypersensitivity reactions, systemic signs (such as lethargy), neurological signs (such as ataxia and muscle tremors) and/or gastrointestinal signs (such as emesis and diarrhoea) have been observed after administration of the veterinary medicinal product.

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 cats including pregnant and lactating queens.

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.

Although not recommended, the concomitant use of the product with a spot on containing moxidectin and imidacloprid at recommended dose rates following a single application was well tolerated in one laboratory study in 10 kittens.
The safety and efficacy of the concurrent use have not been investigated in field studies. In the absence of further studies, caution should be taken in the case of concurrent use of the product with any other macrocyclic lactone. 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: 2 mg of milbemycin oxime and 5 mg of praziquantel per kg are given orally as a single dose.
The product should be administered with or after some food. Doing so ensures optimum protection against heartworm disease.

Animals should be weighed to ensure accurate dosing. Depending on the bodyweight of the cat and the availability of tablet strengths, practical dosing examples are as follows:

Weight (kg)	**12 mg/30 mg tablet**	
> 3 – 6		1 tablet
> 6 – 12		2 tablets

The product can be inserted into a programme for prevention of heartworm disease if at the same time treatment against tapeworms is indicated. The product has a duration of heartworm prevention of one month. For regular prevention of heartworm disease the use of a monosubstance is preferred.

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

In case of overdose, in addition to signs observed at the recommended dose (see section 4.6), drooling was observed. This sign will usually disappear spontaneously within a day.

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 Ca2+) 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, praziquantel reaches peak plasma concentrations (C_{max} 1.08 µg/ml) within 2 hours after oral administration. The half-life of elimination is around 2 hours.

After oral administration, milbemycin oxime reaches peak plasma concentrations (C_{max} 1.48 µg/ml) within 3 hours. The half-life of elimination is around 22 hours (± 10 hours).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Povidone
Cellulose, microcrystalline
Croscarmellose sodium
Lactose monohydrate
Silica, colloidal hydrated
Magnesium stearate

Coat:
Hypromellose
Lactose monohydrate
Titanium dioxide (E171)
Macrogol
Vanillin
Iron oxide yellow (E172)
Iron oxide red (E172)

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

PVC / PE / PVDC - Aluminium blisters 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(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON BOX

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 12 mg/30 mg film-coated tablets
milbemycin oxime/praziquantel

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:

Active substances:

Milbemycin oxime	12.0 mg
Praziquantel	30.0 mg

3. PHARMACEUTICAL FORM

Film-coated tablet

4. PACKAGE SIZE

1 tablet
2 tablets
4 tablets
10 tablets
20 tablets
25 tablets
40 tablets
50 tablets
100 tablets

5. TARGET SPECIES

Cats weighing at least 3 kg

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD(S)

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}

11. SPECIAL STORAGE CONDITIONS

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Dispose of waste material in accordance with local requirements.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

PVC / PE / PVDC / Aluminium blisters

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 12 mg/30 mg film-coated tablets
milbemycin oxime/praziquantel

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Alfasan Nederland B.V.

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Lot {number}

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

Alpramil 4 mg/10 mg film-coated tablets for cats weighing at least 0.5 kg
Alpramil 12 mg/30 mg film-coated tablets for cats weighing at least 3 kg
Alpramil 16 mg/40 mg film-coated tablets for cats weighing at least 4 kg

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:
Alfasan Nederland B.V.
Kuipersweg 9
3449 JA Woerden
The Netherlands

Manufacturer responsible for batch release:
LelyPharma B.V.
Zuiveringsweg 42
8243 PZ Lelystad
The Netherlands

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Alpramil 4 mg/10 mg film-coated tablets for cats weighing at least 0.5 kg
Alpramil 12 mg/30 mg film-coated tablets for cats weighing at least 3 kg
Alpramil 16 mg/40 mg film-coated tablets for cats weighing at least 4 kg
milbemycin oxime/praziquantel

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each 4 mg/10 mg tablet contains:

Active substances:

Milbemycin oxime	4.0 mg
Praziquantel	10.0 mg

Excipients:

Titanium dioxide (E171)	0.186 mg
Quinoline Yellow (E104)	0.023 mg
Sunset Yellow FCF (E110)	0.004 mg

Film-coated tablet
Round and convex yellow coated tablet with a break line on one side.
Tablets can be divided into halves.

Each 12 mg/30 mg tablet contains:

Active substances:

Milbemycin oxime	12.0 mg
Praziquantel	30.0 mg

Excipients:

Titanium dioxide (E171)	0.456 mg

Iron oxide (E172) 0.181 mg

Film-coated tablet
Oblong and convex orange coated tablet.

Each 16 mg/40 mg tablet contains:

Active substances:
Milbemycin oxime 16.0 mg
Praziquantel 40.0 mg

Excipients:
Titanium dioxide (E171) 0.711 mg
Iron oxide (E172) 0.139 mg

Film-coated tablet
Oblong and convex purple-brown coated tablet.

4. INDICATION(S)

Treatment of mixed infections by immature and adult cestodes **and** nematodes of the following species:

- Cestodes:
Dipylidium caninum
Taenia spp.
Echinococcus multilocularis

- Nematodes:
Ancylostoma tubaeforme
Toxocara cati

Prevention of heartworm disease (*Dirofilaria immitis*) if concomitant treatment against cestodes is indicated.

5. CONTRAINDICATIONS

4 mg/10 mg tablet: Do not use in cats of less than 6 weeks of age and/or weighing less than 0.5 kg.
12 mg/30 mg tablet: Do not use in cats weighing less than 3 kg.
16 mg/40 mg tablet: Do not use in cats weighing less than 4 kg.
Do not use in known cases of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

On very rare occasions, especially in young cats, hypersensitivity reactions, systemic signs (such as lethargy), neurological signs (such as ataxia and muscle tremors) and/or gastrointestinal signs (such as emesis and diarrhoea) have been observed after administration of the veterinary medicinal product.

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).

If you notice any side effects, even those not already listed in this package leaflet or you think that the medicine has not worked, please inform your veterinary surgeon.
Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

4 mg/10 mg tablet: Cats weighing at least 0.5 kg
12 mg/30 mg tablet: Cats weighing at least 3 kg
16 mg/40 mg tablet: Cats weighing at least 4 kg

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

Oral use.
Minimum recommended dose rate: 2 mg of milbemycin oxime and 5 mg of praziquantel per kg are given orally as a single dose.
Animals should be weighed to ensure accurate dosing. Depending on the bodyweight of the cat and the availability of tablet sizes, practical dosing examples are as follows:

4 mg/10 mg tablet:

Weight (kg)	**4 mg/10 mg tablet**	
0.5 – 1		½ tablet
> 1 – 2		1 tablet
> 2 – 3		1½ tablets
> 3 – 4		2 tablets

12 mg/30 mg tablet:

Weight (kg)	**12 mg/30 mg tablet**	
> 3 – 6		1 tablet
> 6 – 12		2 tablets

16 mg/40 mg tablet:

Weight (kg)	**16 mg/40 mg tablet**	
> 4 – 8		1 tablet
> 8 – 16		2 tablets

9. ADVICE ON CORRECT ADMINISTRATION

The product should be administered with or after some food. Doing so ensures optimum protection against heartworm disease.

The product can be inserted into a programme for prevention of heartworm disease if at the same time treatment against tapeworms is indicated. The product has a duration of heartworm prevention of one month. For regular prevention of heartworm disease the use of a monosubstance is preferred.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
This veterinary medicinal product does not require any special storage conditions.
Do not use this veterinary medicinal product after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
4 mg/10 mg tablet: Shelf life of divided tablets after first opening the immediate packaging: 7 days

12. SPECIAL WARNING(S)

Special warnings for each target species:
In order to develop an effective worm control programme local epidemiological information and the risk of exposure of the cat 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.

Special precautions for use in animals:
No studies have been performed with severely debilitated cats 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.

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 of 4 mg/10 mg tablets should be discarded or returned to the open blister, inserted back into the outer packaging and used at the next administration. 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.

Pregnancy and lactation:
The product can be used in breeding cats including pregnant and lactating queens.

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.

Although not recommended, the concomitant use of the product with a spot on containing moxidectin and imidacloprid at recommended dose rates following a single application was well tolerated in one laboratory study in 10 kittens.
The safety and efficacy of the concurrent use have not been investigated in field studies. In the absence of further studies, caution should be taken in the case of concurrent use of the product with any other macrocyclic lactone. Also, no such studies have been performed with reproducing animals.

Overdose (symptoms, emergency procedures, antidotes):
In case of overdose, in addition to signs observed at the recommended dose (see Adverse Reactions), drooling was observed. This sign will usually disappear spontaneously within a day.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste. The product should not enter water courses as this may be dangerous for fish and other aquatic organisms. Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

15. OTHER INFORMATION

PVC/PE/PVDC - Aluminium blisters 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.