ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortis 140 mg chewable tablets for dogs and cats
Comfortis 180 mg chewable tablets for dogs and cats
Comfortis 270 mg chewable tablets for dogs and cats
Comfortis 425 mg chewable tablets for dogs and cats
Comfortis 665 mg chewable tablets for dogs
Comfortis 1040 mg chewable tablets for dogs
Comfortis 1620 mg chewable tablets for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:

Comfortis 140 mg	spinosad 140 mg
Comfortis 180 mg	spinosad 180 mg
Comfortis 270 mg	spinosad 270 mg
Comfortis 425 mg	spinosad 425 mg
Comfortis 665 mg	spinosad 665 mg
Comfortis 1040 mg	spinosad 1040 mg
Comfortis 1620 mg	spinosad 1620 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablets.

Tan to brown, or speckled with embedded darker particles, round, flat, bevelled edge tablets plain on one side and debossed with a letter and a line above on the other side:

140 mg: C
180 mg: L
270 mg: J
425 mg: C
665 mg: J
1040 mg: L
1620 mg: J

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

Treatment and prevention of flea infestations (*Ctenocephalides felis*).

The preventive effect against re-infestations is a result of the adulticidal activity and the reduction in egg production and persists for up to 4 weeks after a single administration of the product.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

4.3 Contraindications

Do not use in dogs or cats under 14 weeks of age.
Do not use in cases of known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings for each target species

The veterinary medicinal product should be administered with food or immediately after feeding. The duration of efficacy may be reduced if the dose is administered on an empty stomach.

All dogs and cats within the household should be treated.

Fleas from pets often infest the animal's basket, bedding and regular resting areas such as carpets and soft furnishings, which should be treated in case of massive infestation and at the beginning of the treatment with a suitable insecticide and vacuumed regularly.

Fleas may persist for a period of time after administration of the product due to the emergence of adult fleas from pupae already in the environment. Regular monthly treatments with Comfortis break the fleas' life cycle and may be needed to control the flea population in contaminated households.

4.5 Special precautions for use

Special precautions for use in animals

Use with caution in dogs and cats with pre-existing epilepsy.

Accurate dosing is not possible in dogs weighing less than 2.1 kg and in cats weighing less than 1.9 kg. The use of the product in smaller dogs and smaller cats is therefore not recommended.

The recommended dosage regimen should be followed (see section 4.10 for information regarding overdose).

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Accidental ingestion may cause adverse reactions.

Children should not come into contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

4.6 Adverse reactions (frequency and seriousness)

Dogs

In dogs, a commonly observed adverse reaction is vomiting, which occurs in the first 48 hours after dosing and is most likely caused by a local effect on the small intestines. On the day of, or the day following administration of spinosad at a dose of 45–70 mg/kg bodyweight, the observed incidence of vomiting in the field trial was 5.6%, 4.2% and 3.6% after the first, second and third monthly treatments respectively. The incidence of vomiting observed after the first and second treatments was higher (8%) in dogs dosed at the upper end of the dose band. In the majority of cases, vomiting was transient, mild and did not require symptomatic treatment.

In dogs lethargy, anorexia and diarrhoea were uncommon and muscle tremor, ataxia and seizures were rare. In very rare cases, blindness, impaired vision and other eye disorders were observed.

Cats

In cats, a commonly observed adverse reaction is vomiting, which occurs in the first 48 hours after dosing and is most likely caused by a local effect on the small intestines. On the day of, or the day following administration of spinosad at a dose of 50–75 mg/kg bodyweight, the observed incidence of vomiting in the global field trial was between 6% and 11% in the first three months of treatment. In the majority of cases, vomiting was transient, mild and did not require symptomatic treatment.

Other commonly observed adverse reactions in cats were diarrhoea and anorexia. Lethargy, loss of condition and salivation were uncommon. Seizures, ataxia and muscle tremor were rare adverse reactions.

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 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Pregnancy:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

In pregnant dogs (bitches), the safety of spinosad has not been sufficiently established. The safety of spinosad in pregnant cats (queens) has not been evaluated.

Lactation:
In dogs, spinosad is excreted in the colostrum and milk of lactating bitches and it is therefore assumed that spinosad is excreted in the colostrum and milk of lactating queens. As the safety of this for suckling puppies and kittens has not been established, the product should only be used during pregnancy and lactation according to the benefit-risk assessment by the responsible veterinarian.

Fertility:
Laboratory studies in rats and rabbits have not produced any evidence of any effect on the reproductive capacity in males and females.

The safety of the product in male dogs and male cats used for breeding has not been determined.

4.8 Interaction with other medicinal products and other forms of interaction

Spinosad has been shown to be a substrate for P-glycoprotein (PgP). Spinosad could therefore interact with other PgP-substrates (for example, digoxin, doxorubicin) and possibly enhance adverse reactions from such molecules or compromise efficacy.

Post marketing reports, following the concomitant use of Comfortis with 'off label' high dose ivermectin indicate that dogs have experienced trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation.

4.9 Amounts to be administered and administration route

For oral use.

The veterinary medicinal product should be administered with food or immediately after feeding.

Dogs:

The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 45–70 mg/kg bodyweight for dogs:

Dog bodyweight (kg)	Number of tablets and strength (mg spinosad)
2.1–3	1 x 140 mg tablet
3.1–3.8	1 x 180 mg tablet
3.9–6	1 x 270 mg tablet
6.1–9.4	1 x 425 mg tablet
9.5–14.7	1 x 665 mg tablet
14.8–23.1	1 x 1040 mg tablet
23.2–36	1 x 1620 mg tablet
36.1–50.7	1 x 1620 mg tablet + 1 x 665 mg tablet
50.8–72	2 x 1620 mg tablets

Cats:

The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 50–75 mg/kg bodyweight for cats:

Cat bodyweight (kg)	Number of tablets and strength (mg spinosad)
1.9–2.8	1 x 140 mg tablet
2.9–3.6	1 x 180 mg tablet
3.7–5.4	1 x 270 mg tablet
5.5–8.5 †	1 x 425 mg tablet

†Cats over 8.5 kg: give the appropriate combination of tablets.

Comfortis tablets are chewable and palatable for dogs. If the dog or cat does not accept the tablets directly they may be administered with food, or directly by opening the animal's mouth and placing the tablet onto the back of the tongue.

If vomiting occurs within an hour of administration and the tablet is visible, re-dose the animal with another full dose to ensure maximum effectiveness of the product.

If a dose is missed, administer the veterinary medicinal product with the next offering of food and resume a monthly dosing schedule.

The veterinary medicinal product may safely be given at monthly intervals at the recommended dose. The residual insecticidal properties of the product persist for up to 4 weeks after a single administration. If fleas reappear in the fourth week, the treatment interval can be shortened by up to 3 days in dogs. In cats, the full 4 week gap between treatments should be maintained, even if fleas reappear before the end of the 4 weeks.

Seek veterinary advice regarding information on the optimal time to start treatment with this product.

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

There is no antidote available. In case of adverse clinical signs, the animal should be treated symptomatically.

Dogs:

The incidence of vomiting on the day of, or the day after, dosing has been observed to increase as a function of dose. Vomiting is most likely caused by a local effect on the small intestines. At doses in excess of the recommended dose vomiting becomes a very common event. At doses of approximately 2.5 times the recommended dose, spinosad caused vomiting in the vast majority of dogs.

At doses up to 100 mg/kg bodyweight per day for 10 days, the only clinical symptom of overdose was vomiting, which occurred usually within 2.5 hours of dosing. Mild elevations of ALT (alanine aminotransferase) occurred in all dogs treated with Comfortis, although values returned to their baseline by day 24. Phospholipidosis (vacuolation of lymphoid tissues) also occurred; although this was not related to clinical signs in dogs treated up to 6 months.

Cats:

After a single acute overdose corresponding to 1.6 times the maximum label dose, spinosad caused vomiting in approximately half of the cats, and depression, pacing/panting and severe diarrhoea on rare occasions.

At doses of 75 to 100 mg/kg bodyweight per day for 5 days, given at monthly intervals for a period of six months, the most commonly observed clinical sign was vomiting. Furthermore, a reduction of food intake was observed in females, however a significant reduction in their bodyweight was not observed. Phospholipidosis (vacuolation of the cells of the liver, adrenal gland and lung) also occurred. Also noted were diffuse hepatocellular hypertrophy in males and females, and this finding correlated with higher pooled mean liver weights. However there was no evidence in the clinical observations and clinical chemistry parameters that indicated any loss in organ function.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: other ectoparasiticides for systemic use.
ATCvet code: QP53BX03.

5.1 Pharmacodynamic properties

Spinosad comprises spinosyn A and spinosyn D. The insecticidal activity of spinosad is characterised by nervous excitation leading to muscle contractions and tremors, prostration, paralysis and rapid death of the flea. These effects are caused primarily by activation of nicotinic acetylcholine receptors (nAChRs). Spinosad therefore has a different mode of action to other flea control or insect control products. It does not interact with known binding sites of other nicotinic or GABAergic insecticides such as neonicotinides (imidacloprid or nitenpyram), fiproles (fipronil), milbemycins, avermectins (e.g. selamectin) or cyclodienes, but through a novel insecticidal mechanism.

The product starts killing fleas 30 minutes after administration; 100% of fleas are dead/moribund within 4 hours post-treatment in dogs, and in cats within 24 hours.

Insecticidal activity against new infestations persists for up to 4 weeks.

5.2 Pharmacokinetic particulars

Approximately 90% of spinosad is comprised of spinosyns A and D. Of that 90%, the ratio of spinosyn A to A+D is 0.85 when calculated as spinosyn A/spinosyn A+D. The consistency of this

figure in pharmacokinetic and other studies indicates comparability in the absorption, metabolism and elimination of the two major spinosyns.

In dogs, spinosyns A and D are rapidly absorbed and extensively distributed after oral administration. Bioavailability was shown to be approximately 70%. The mean T_{max} for spinosyns A and D ranged from 2–4 hours and the mean elimination half-life ranged from 127.5 to 162.6 hours and 101.3 to 131.9 hours respectively. AUC and C_{max} values were higher in fed than fasted dogs and increased approximately linearly with increasing dose-rates over the intended therapeutic dose range. Therefore, it is recommended to treat dogs with food as this maximises the opportunity for fleas to ingest lethal amounts of spinosad. The primary biliary, faecal and urinary metabolites in both the rat and the dog were identified as the demethylated spinosyns, glutathione conjugates of the parent compounds and N-demethylated spinosyns A and D. Excretion is primarily via the bile and faeces, and also to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in dogs. In lactating bitches, spinosad is excreted in the colostrum/milk.

In cats, spinosyns A and D are equally rapidly absorbed and extensively distributed after oral administration. Plasma protein binding is high (~99%). Bioavailability was shown to be approximately 100%, with maximum plasma concentrations attained approximately 4-12 hours post treatment, and with half-lives of spinosyn A and spinosyn D ranging between 5 days and 20 days in cats dosed at 50-100 mg spinosad/kg bodyweight. AUC and C_{max} values were higher in fed than fasted cats. Therefore, it is recommended to treat cats with food as this maximises the opportunity for fleas to ingest lethal amounts of spinosad. In adult cats, the AUC increased over 3 consecutive months of dosing with 75 mg spinosad/kg bodyweight, after which steady state was achieved; however, no clinical impact occurred as a result of this.

The primary faecal and urinary metabolites in both the rat and the cat were identified as the glutathione conjugates of the parent compounds and N-demethylated spinosyns A and D. Excretion is primarily via the faeces, and also to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in cats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Artificial beef flavour
Hydroxypropylcellulose
Colloidal silicon, anhydrous
Croscarmellose sodium
Magnesium stearate

6.2 Major incompatibilities

Not applicable.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

6.4 Special precautions for storage

Keep the blister in the outer carton to protect from light.

6.5 Nature and composition of immediate packaging

Clear PCTFE/PE/PVC or PVC/OPA/Alu/OPA/PVC blister sealed with aluminium foil containing 3 or 6 chewable tablets in cardboard box.

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.

7. MARKETING AUTHORISATION HOLDER

Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/10/115/018 (140 mg, 3 tablets)
EU/2/10/115/019 (140 mg, 6 tablets)
EU/2/10/115/022 (140 mg, 6 tablets)
EU/2/10/115/020 (180 mg, 3 tablets)
EU/2/10/115/021 (180 mg, 6 tablets)
EU/2/10/115/023 (180 mg, 6 tablets)
EU/2/10/115/011 (270 mg, 3 tablets)
EU/2/10/115/001 (270 mg, 6 tablets)
EU/2/10/115/024 (270 mg, 6 tablets)
EU/2/10/115/012 (425 mg, 3 tablets)
EU/2/10/115/003 (425 mg, 6 tablets)
EU/2/10/115/025 (425 mg, 6 tablets)
EU/2/10/115/013 (665 mg, 3 tablets)
EU/2/10/115/005 (665 mg, 6 tablets)
EU/2/10/115/026 (665 mg, 6 tablets)
EU/2/10/115/014 (1040 mg, 3 tablets)
EU/2/10/115/007 (1040 mg, 6 tablets)
EU/2/10/115/027 (1040 mg, 6 tablets)
EU/2/10/115/015 (1620 mg, 3 tablets)
EU/2/10/115/009 (1620 mg, 6 tablets)
EU/2/10/115/028 (1620 mg, 6 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11/02/2011.
Date of latest renewal: 07/01/2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Elanco France S.A.S.
26 rue de la Chapelle
68330 Huningue
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortis 140 mg chewable tablets for dogs and cats
Comfortis 180 mg chewable tablets for dogs and cats
Comfortis 270 mg chewable tablets for dogs and cats
Comfortis 425 mg chewable tablets for dogs and cats
Comfortis 665 mg chewable tablets for dogs
Comfortis 1040 mg chewable tablets for dogs
Comfortis 1620 mg chewable tablets for dogs

spinosad

2. STATEMENT OF ACTIVE SUBSTANCES

Spinosad 140 mg
Spinosad 180 mg
Spinosad 270 mg
Spinosad 425 mg
Spinosad 665 mg
Spinosad 1040 mg
Spinosad 1620 mg

3. PHARMACEUTICAL FORM

Chewable tablets.

4. PACKAGE SIZE

3 tablets
6 tablets

5. TARGET SPECIES

Dogs
Dogs and cats

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Administer with food.
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

11. SPECIAL STORAGE CONDITIONS

Keep the blister in the outer carton.

12. SPECIFIC 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. To be supplied only on veterinary prescription.

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

Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/10/115/018 (140 mg, 3 tablets)
EU/2/10/115/019 (140 mg, 6 tablets)
EU/2/10/115/022 (140 mg, 6 tablets)

EU/2/10/115/020 (180 mg, 3 tablets)
EU/2/10/115/021 (180 mg, 6 tablets)
EU/2/10/115/023 (180 mg, 6 tablets)
EU/2/10/115/011 (270 mg, 3 tablets)
EU/2/10/115/001 (270 mg, 6 tablets)
EU/2/10/115/024 (270 mg, 6 tablets)
EU/2/10/115/012 (425 mg, 3 tablets)
EU/2/10/115/003 (425 mg, 6 tablets)
EU/2/10/115/025 (425 mg, 6 tablets)
EU/2/10/115/013 (665 mg, 3 tablets)
EU/2/10/115/005 (665 mg, 6 tablets)
EU/2/10/115/026 (665 mg, 6 tablets)
EU/2/10/115/014 (1040 mg, 3 tablets)
EU/2/10/115/007 (1040 mg, 6 tablets)
EU/2/10/115/027 (1040 mg, 6 tablets)
EU/2/10/115/015 (1620 mg, 3 tablets)
EU/2/10/115/009 (1620 mg, 6 tablets)
EU/2/10/115/028 (1620 mg, 6 tablets)

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blisters

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortis 140 mg chewable tablets for dogs and cats
Comfortis 180 mg chewable tablets for dogs and cats
Comfortis 270 mg chewable tablets for dogs and cats
Comfortis 425 mg chewable tablets for dogs and cats
Comfortis 665 mg chewable tablets for dogs
Comfortis 1040 mg chewable tablets for dogs
Comfortis 1620 mg chewable tablets for dogs

spinosad

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Elanco

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET
Comfortis 140 mg chewable tablets for dogs and cats
Comfortis 180 mg chewable tablets for dogs and cats
Comfortis 270 mg chewable tablets for dogs and cats
Comfortis 425 mg chewable tablets for dogs and cats
Comfortis 665 mg chewable tablets for dogs
Comfortis 1040 mg chewable tablets for dogs
Comfortis 1620 mg chewable tablets for dogs

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

Marketing authorisation holder:

Elanco GmbH
Heinz-Lohmann-Str. 4
27472 Cuxhaven
Germany

Manufacturer responsible for batch release:

Elanco France S.A.S.
26 rue de la Chapelle
68330 Huningue
France

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Comfortis 140 mg chewable tablets for dogs and cats
Comfortis 180 mg chewable tablets for dogs and cats
Comfortis 270 mg chewable tablets for dogs and cats
Comfortis 425 mg chewable tablets for dogs and cats
Comfortis 665 mg chewable tablets for dogs
Comfortis 1040 mg chewable tablets for dogs
Comfortis 1620 mg chewable tablets for dogs

Spinosad

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

Each tablet contains:

Active substance:

Comfortis 140 mg	140 mg spinosad
Comfortis 180 mg	180 mg spinosad
Comfortis 270 mg	270 mg spinosad
Comfortis 425 mg	425 mg spinosad
Comfortis 665 mg	665 mg spinosad
Comfortis 1040 mg	1040 mg spinosad
Comfortis 1620 mg	1620 mg spinosad

Chewable tablets.

Tan to brown, or speckled with embedded darker particles, round, flat, bevelled edge tablets, plain on one side and debossed with a letter on the other side:

140 mg: C
180 mg: L
270 mg: J
425 mg: C
665 mg: J
1040 mg: L
1620 mg: J

4. INDICATION(S)

Treatment and prevention of flea infestations (*Ctenocephalides felis*).

The preventive effect against re-infestations is a result of the activity against adult fleas and the reduction in their production of eggs. This activity persists for up to 4 weeks after a single administration of the product.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

5. CONTRAINDICATIONS

Do not use in dogs or cats under 14 weeks of age.
Do not use in case of known hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

In dogs, a commonly observed adverse reaction is vomiting, which most commonly occurs in the first 48 hours after dosing. This vomiting is most likely caused by a local effect on the small intestines. On the day of, or the day following administration of spinosad at a dose of 45–70 mg/kg bodyweight, the observed incidence of vomiting in the field trial was 5.6%, 4.2% and 3.6% after the first, second and third monthly treatments respectively. The incidence of vomiting observed after the first and second treatments was higher (8%) in dogs dosed at the upper end of the dose band. In the majority of cases, vomiting was transient, mild and did not require symptomatic treatment.

In dogs lethargy, anorexia and diarrhoea were uncommon and muscle tremor, ataxia and seizures were rare. In very rare cases, blindness, impaired vision and other eye disorders were observed.

In cats, a commonly observed adverse reaction is vomiting, which occurs in the first 48 hours after dosing and is most likely caused by a local effect on the small intestines. On the day of, or the day following administration of spinosad at a dose of 50–75 mg/kg bodyweight, the observed incidence of vomiting in the global field trial was between 6% and 11% in the first three months of treatment. In the majority of cases, vomiting was transient, mild and did not require symptomatic treatment.

Other commonly observed adverse reactions in cats were diarrhoea and anorexia. Lethargy, loss of condition and salivation were uncommon. Seizures, ataxia and muscle tremor were rare adverse reactions.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reactions
- 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 animal 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.

7. TARGET SPECIES

Dogs and cats.

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

For oral use.

Dogs:
The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 45–70 mg/kg bodyweight in dogs:

Dog bodyweight (kg)	Number of tablets and strength (mg spinosad)
2.1–3	1 x 140 mg tablet
3.1–3.8	1 x 180 mg tablet
3.9–6	1 x 270 mg tablet
6.1–9.4	1 x 425 mg tablet
9.5–14.7	1 x 665 mg tablet
14.8–23.1	1 x 1040 mg tablet
23.2–36	1 x 1620 mg tablet
36.1–50.7	1 x 1620 mg tablet + 1 x 665 mg tablet
50.8–72	2 x 1620 mg tablets

Cats:
The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 50–75 mg/kg bodyweight in cats:

Cat bodyweight (kg)	Number of tablets and strength (mg spinosad)
1.9–2.8	1 x 140 mg tablet
2.9–3.6	1 x 180 mg tablet
3.7–5.4	1 x 270 mg tablet
5.5–8.5†	1 x 425 mg tablet

†Cats over 8.5 kg: give the appropriate combination of tablets.

The residual insecticidal properties of the product persist for up to 4 weeks after a single administration. If fleas reappear in the fourth week, the treatment interval can be shortened by up to 3 days in dogs. In cats, the full 4 week gap between treatments should be maintained, even if fleas reappear (due to an occasional slightly reduced persistent efficacy) before the end of the 4 weeks.

Seek veterinary advice regarding information on the optimal time to start treatment with this product.

9. ADVICE ON CORRECT ADMINISTRATION

The veterinary medicinal product should be administered with food or immediately after feeding. The duration of efficacy may be reduced if the dose is administered on an empty stomach.

To ensure maximum effectiveness, if vomiting occurs within an hour of administration and the tablet is visible, re-dose with another full dose. If a dose is missed, administer the product with the next offering of food and resume a monthly dosing schedule.

The veterinary medicinal product may safely be given at monthly intervals at the recommended dose.

Comfortis tablets are chewable and palatable for dogs. If the dog or cat does not accept the tablets directly they may be administered with food, or directly by opening the animal's mouth and placing the tablet onto the back of the tongue.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

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. Keep the blister in the outer carton to protect from light.

12. SPECIAL WARNING(S)

Special warnings for each target species:
All dogs and cats within the household should be treated.

Fleas from pets often infest the animal's basket, bedding and regular resting areas such as carpets and soft furnishings, which should be treated in case of massive infestation and at the beginning of the treatment with a suitable insecticide and vacuumed regularly.

Fleas may persist for a period of time after administration of the product due to the emergence of adult fleas from pupae already in the environment. Regular monthly treatments with Comfortis break the fleas' life cycle and may be needed to control the flea population in contaminated households.

Special precautions for use in animals:
Use with caution in dogs and cats with pre-existing epilepsy.

Accurate dosing is not possible in small dogs weighing less than 2.1 kg and in cats weighing less than 1.9 kg. The use of the product in smaller dogs and smaller cats is therefore not recommended.

The recommended dosage regimen should be followed.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Accidental ingestion may cause adverse reactions.

Children should not come into contact with the veterinary medicinal product.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Pregnancy and lactation:
Laboratory studies in rats and rabbits have not produced any evidence of teratogenic, foetotoxic or maternotoxic effects.

In pregnant dogs (bitches), the safety of spinosad has not been sufficiently established. The safety of spinosad in pregnant cats (queens) has not been evaluated.

In dogs, spinosad is excreted in the colostrum and milk of lactating bitches and it is therefore assumed that spinosad is excreted in the colostrum and milk of lactating queens. As the safety of this for suckling puppies and kittens has not been established, the product should only be used during pregnancy and lactation according to the benefit/risk assessment by the responsible veterinarian.

Fertility:
Laboratory studies in rats and rabbits have not produced any evidence of any effect on the reproductive capacity in males and females.
The safety of this product in male dogs and cats used for breeding has not been determined.

Interaction with other medicinal products and other forms of interaction:
Spinosad has been shown to be a substrate for P-glycoprotein (PgP). Spinosad could therefore interact with other PgP-substrates (for example, digoxin, doxorubicin) and possibly enhance adverse reactions from such molecules or compromise efficacy.

Post marketing reports, following the concomitant use of Comfortis with 'off label' high dose ivermectin indicate that dogs have experienced trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation.

Overdose:
There is no antidote available. In case of adverse clinical signs, the animal should be treated symptomatically.

In dogs, the incidence of vomiting on the day of, or the day after, dosing has been observed to increase as a function of dose. This vomiting is most likely caused by a local effect on the small intestines. At doses in excess of the recommended dose vomiting becomes a very common event. At doses of approximately 2.5 times the recommended dose, spinosad caused vomiting in the vast majority of dogs.

In dogs, at doses up to 100 mg/kg bodyweight per day for 10 days, the only clinical symptom of overdose was vomiting, which occurred usually within 2.5 hours of dosing. Mild elevations of an enzyme called ALT (alanine aminotransferase) occurred in all dogs treated with Comfortis, although values returned to their baseline by day 24. Phospholipidosis (vacuolation of lymphoid tissue) also occurred; although this was not related to clinical signs in dogs treated up to 6 months.

In cats, after a single acute overdose of 1.6 times the maximum label dose, spinosad caused vomiting in approximately half of the cats, and depression, pacing/panting and severe diarrhoea on rare occasions.

In cats, at doses of 75 to 100 mg/kg bodyweight per day for 5 days, given monthly for a period of six months, the most commonly observed clinical sign was vomiting. Furthermore, a reduction of food intake was observed in females, however a significant reduction in their bodyweight was not observed. Phospholipidosis (vacuolation of the cells of the liver, adrenal gland and lung) also occurred. Also noted was diffuse hepatocellular hypertrophy in both males and females, and this finding correlated with higher pooled mean liver weights. However there was no evidence in the clinical observations and clinical chemistry parameters that indicated any loss in organ function.

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.
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

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

15. OTHER INFORMATION

Cardboard box containing blister, each containing 3 or 6 chewable tablets.

Not all pack sizes may be marketed.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.