

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Trifexis 270 mg/4.5 mg chewable tablets for dogs (3.9 – 6.0 kg)
Trifexis 425 mg/7.1 mg chewable tablets for dogs (6.1 – 9.4 kg)
Trifexis 665 mg/11.1 mg chewable tablets for dogs (9.5 – 14.7 kg)
Trifexis 1040 mg/17.4 mg chewable tablets for dogs (14.8 – 23.1 kg)
Trifexis 1620 mg/27 mg chewable tablets for dogs (23.2 – 36.0 kg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substances:

Each tablet contains:

	Spinosad	Milbemycin oxime
Trifexis 270 mg/4.5 mg	270 mg	4.5 mg
Trifexis 425 mg/7.1 mg	425 mg	7.1 mg
Trifexis 665 mg/11.1 mg	665 mg	11.1 mg
Trifexis 1040 mg/17.4 mg	1040 mg	17.4 mg
Trifexis 1620 mg/27 mg	1620 mg	27.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablets.

Mottled tan to brown, round, biconvex tablets with a debossed code on one side and dimples on the other side.

The following list shows the code and the number of dimples marked on each strength of tablet:

Trifexis 270 mg/4.5 mg tablets:	4333 and 2 dimples
Trifexis 425 mg/7.1 mg tablets:	4346 and 3 dimples
Trifexis 665 mg/11.1 mg tablets:	4347 and no dimples
Trifexis 1040 mg/17.4 mg tablets:	4349 and 4 dimples
Trifexis 1620 mg/27 mg tablets:	4336 and 5 dimples

4. CLINICAL PARTICULARS

4.1 Target species

Dogs.

4.2 Indications for use, specifying the target species

For the treatment and prevention of flea (*Ctenocephalides felis*) infestations in dogs when the concurrent prevention of heartworm disease (L3, L4 *Dirofilaria immitis*) and/or treatment of gastrointestinal nematode infections caused by hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (immature adult L5, and adult *Toxocara canis* and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*) is indicated.

The flea 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 veterinary medicinal 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 under 14 weeks of age.

Do not use in case of hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings for each target species

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also section 4.2).

All dogs within the household should be treated. Cats in the household should be treated with a veterinary medicinal product authorised for use in that species.

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

Fleas may be observed for a period of time after administration of the veterinary medicinal product due to the emergence of adult fleas from pupae already present in the environment. Regular monthly treatments with the insecticidal active substance, spinosad, break the fleas' life cycle and may be used to control the flea population in contaminated households.

Parasite resistance to any particular class of anthelmintic may develop following the frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

Maintenance of the efficacy of macrocyclic lactones is critical for *Dirofilaria immitis* control, therefore, to minimise the risk of resistance selection, it is recommended that dogs should be checked for both circulating antigens and blood microfilariae at the beginning of each season of preventative treatment.

4.5 Special precautions for use

Special precautions for use in animals

Use with caution in dogs with pre-existing epilepsy.

No studies have been performed in sick or convalescent dogs, therefore the product should only be used based on a benefit-risk assessment of the responsible veterinarian.

The safety of this product in avermectin sensitive dogs/dogs with an MDR-1 mutation has not been sufficiently demonstrated. These dogs may be at a higher risk for adverse effects when treated with it and should therefore be treated with special caution.

Accurate dosing is not possible in dogs weighing less than 3.9 kg. The use of the veterinary medicinal product in such dogs is therefore not recommended.

The recommended dosage regimen must be followed but not exceeded (see section 4.10).

Prior to first administration, dogs in heartworm endemic areas or who have visited heartworm endemic areas must be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs must be treated with an adulticide to remove adult heartworms.

It is recommended to observe the treated dog up to 24 hours post-administration of the product for possible adverse reactions (see section 4.6). In case of adverse reactions consult your veterinarian.

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

Accidental ingestion may cause adverse reactions.

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

Wash hands after use.

Children must not come into contact with the veterinary medicinal product. Accidental ingestion may cause adverse reactions.

4.6 Adverse reactions (frequency and seriousness)

A commonly observed adverse reaction is vomiting, which occurs in the first 48 hours after dosing. In the majority of cases, vomiting was transient and mild and did not require symptomatic treatment.

At doses of 30 to 60 mg spinosad and 0.5 to 1 mg milbemycin oxime per kg bodyweight, lethargy, anorexia/decreased appetite, diarrhoea, pruritus, dermatitis and reddening of the skin and pinna were commonly seen. Hypersalivation, muscle tremors, ataxia and seizures were uncommon. Post-marketing reports for spinosad indicate that in very rare cases, blindness, impaired vision and other eye disorders were observed.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reactions during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies on the effect of spinosad and milbemycin oxime in rats and rabbits have neither produced any evidence of teratogenic, foetotoxic or maternotoxic effects, nor any effect on the reproductive capacity in males and females.

In pregnant and lactating dogs (bitches), the safety of this veterinary medicinal product has not been sufficiently established. Spinosad is excreted in the colostrum and milk of lactating bitches. The excretion of milbemycin oxime in lactating dogs (bitches) has not been tested and the safety for suckling puppies has not been established. This product should therefore only be used during pregnancy and lactation according to the benefit-risk assessment of the responsible veterinarian.

As the safety of the veterinary medicinal product in male dogs used for breeding has not been determined, it should only be used according to the benefit-risk assessment of the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Spinosad and milbemycin oxime have been shown to be substrates for P-glycoprotein (P-gp) and therefore could interact with other P-gp substrates (for example, digoxin, doxorubicin) or other macrocyclic lactones. Therefore, concomitant treatment with other P-gp substrates could lead to enhanced toxicity.

Post-marketing reports following the concomitant use of spinosad with 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.

Dosage:

The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 45 to 70 mg spinosad and 0.75 to 1.18 mg milbemycin oxime/kg bodyweight.

Body-weight (kg) of dog	Strength and number of tablets to be administered:				
	Trifexis 270 mg/4.5mg	Trifexis 425 mg/7.1 mg	Trifexis 665 mg/11.1 mg	Trifexis 1040 mg/17.4 mg	Trifexis 1620 mg/27 mg
3.9–6.0	1				
6.1–9.4		1			
9.5–14.7			1		
14.8–23.1				1	
23.2–36.0					1
36.1–50.7			1		1
50.8–72.0					2

Method of administration:

The veterinary medicinal product should be administered with food or immediately after feeding. Based on the local epidemiological situation, the veterinary medicinal product may be given at monthly intervals throughout the season at the recommended dose as outlined below. This combination product (Trifexis) must, however, not be given for more than 6 consecutive months in any one year.

If the dog does not accept the tablet(s) directly in its mouth then the tablet(s) may be mixed with food. The duration of efficacy may be reduced if the dose is administered on an empty stomach.

After administration of the tablet monitor the dog closely. 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 veterinary medicinal product with the next offering of food. Then start a new monthly dosing schedule from that day.

Dogs living in non-heartworm endemic areas:

Trifexis can be used as part of the seasonal prevention of fleas (replacing treatment with a monovalent flea product) in dogs with diagnosed concurrent gastrointestinal nematode infections. A single treatment is effective for the treatment of gastrointestinal nematodes. After treatment of the nematode infection, further flea prevention should be continued with a monovalent product.

Dogs living in heartworm endemic areas:

Prior to treatment with Trifexis the advice in section 4.5 should be considered.

For the prevention of heartworm disease and the concurrent treatment and prevention of flea infestations, the veterinary medicinal product must be given at regular monthly intervals during the time of the year when mosquitoes and fleas are present. The veterinary medicinal product must be administered 1 month before the expected appearance of mosquitoes. It is recommended that heartworm prevention treatment should be continued at regular monthly intervals until at least 1 month after the last exposure to mosquitoes, but not for more than 6 consecutive months using Trifexis in any one year.

When Trifexis is used to replace another heartworm preventive product, the first dose of Trifexis must be given within a month of the last dose of the former medication.

Dogs travelling to a heartworm region should start medication within a month after arrival there. Heartworm prevention treatment should be continued monthly, with the last administration being given one month after the dog has left the region, but not for more than 6 consecutive months using Trifexis in any one year.

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

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

The oral administration of spinosad and milbemycin oxime combination tablets at mean cumulative monthly doses of up to 255 mg spinosad and 4.2 mg milbemycin oxime per kg body weight (up to 3.6 times the maximum recommended dose) for 6 consecutive dosing periods in young dogs was well tolerated. Vomiting was seen in both treated and control dogs with similar frequencies. Adverse reactions seen during the course of this study included vomiting, diarrhoea, skin lesions, salivation, tremors, decreased activity, coughing and vocalization.

At acute overdoses corresponding to 1.5 times the maximum recommended dose, vomiting occurred in 17% of the dogs, and hypersalivation occurred in 8% of the dogs. At acute overdoses corresponding to 3 times the maximum recommended dose, vomiting occurred in half of the animals, sometimes repeatedly. At three times the maximum recommended dose adverse events of potentially neurological origin e.g. decreased activity (8%), hypersalivation (17%) or stumbling (8%) were observed. Decreased activity was seen at the same frequency in both control and dogs treated with 3 times the maximum recommended dose. All adverse events were transient and did not require treatment.

After spinosad administration, the incidence of vomiting on the day of, or the day after dosing has been observed to increase as a function of the dose. Vomiting is most likely caused by a local effect on the small intestine. At doses in excess of the recommended dose, vomiting becomes a very common event.

Neurotoxicity characterised by transient mild depression, ataxia, trembling, mydriasis, and excessive salivation has been observed in dogs given higher dose multiples of milbemycin oxime alone (5 to 10 mg/kg).

There is no antidote available. In the case of adverse clinical signs, treat symptomatically.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antiparasitic products, insecticides and repellents – endectocides.
ATCvet code: QP54AB51 (milbemycin combinations).

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). 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. Spinosad therefore has a different mode of action to other flea control or insect control products. Spinosad starts killing fleas 30 minutes after administration; 100% of fleas are dead/moribund within 4 hours post-treatment.

Milbemycin oxime is an antiparasitic endectocide belonging to the macrocyclic lactones. Milbemycin oxime is isolated from the fermentation of *Streptomyces hygroscopicus* var. aureolacrimosus. It is active against mites, larval and adult stages of nematodes as well as larvae of *Dirofilaria immitis*. The activity of milbemycin oxime 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 and glycine receptors). This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.

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.

After oral administration of 45 mg spinosad and 0.75 mg milbemycin oxime/kg bodyweight to fed dogs, spinosyns A and D are rapidly absorbed and extensively distributed. Plasma protein binding is high (>98%). Bioavailability was shown to be high. The mean T_{max} for spinosyns A and D was 4 hours and the mean elimination half-lives ranged between 131 and 135 hours. AUC values increased approximately linearly while C_{max} increased slightly less than linearly with increasing dose-rates over the intended therapeutic dose range. In addition, in studies containing only spinosad, AUC and C_{max} values were higher in fed than fasted dogs and therefore it is recommended to treat dogs with food as this maximises the opportunity for fleas to ingest lethal amounts of spinosad.

In studies performed with spinosad only, the primary biliary, faecal and urinary metabolites in both rat and 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 to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in dogs.

Milbemycin oxime is a systemic macrocyclic lactone containing two major factors, A₃ and A₄ (ratio of A₃:A₄ is 20:80). Unlike spinosad, the consistent ratio of the individual factors is not maintained in pharmacokinetic studies. Milbemycin A₄ 5-oxime tends to eliminate slower resulting in approximately 10-fold higher exposure than Milbemycin A₃ 5-oxime. Milbemycin oxime plasma concentrations and some pharmacokinetic parameters are increased in the presence of spinosad. Milbemycin A₃ and A₄ 5-oximes are rapidly absorbed and extensively distributed in dogs after oral administration. Plasma protein binding is high (>96%). Bioavailability was shown to be high. The mean T_{max} for milbemycin A₃ and A₄ 5-oximes was typically 4 hours and the mean elimination half-lives were 33.9 and 77.2 hours. AUC values increased approximately linearly while C_{max} increased slightly less than linearly with increasing dose-rates over the intended therapeutic dose range.

The primary faecal and urinary metabolites in dog were identified as glucuronide conjugates of milbemycin A₃ or A₄ 5-oximes, dealkylated milbemycin A₃ or A₄ 5-oximes, and hydroxylated milbemycin A₄ 5-oxime. In rats dosed with milbemycin A₄ 5-oxime, the main metabolites identified in urine and faeces were mono-, di-, and trihydroxy milbemycin A₄ 5-oximes. In dogs, hydroxymilbemycin A₄ 5-oxime was detected only in plasma, but not in urine or faeces, suggesting predominant excretion of conjugated metabolites in the dog. Excretion is primarily via faeces, and also to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in dogs.

Monthly repeated oral administration of spinosad and milbemycin oxime over six months revealed evidence of spinosad and milbemycin oxime accumulation in juvenile dogs. Accumulation cannot be discounted in adult dogs. In juvenile dogs, repeated oral administration of spinosad and milbemycin oxime over six months resulted in the trough plasma concentrations of spinosad and milbemycin increasing throughout the study. Trough concentrations of spinosad doubled monthly up to month 5. The increase in plasma concentrations was strongly correlated with an increase in terminal elimination half-lives.

In adult dogs, after repeated oral administration of spinosad and milbemycin oxime for six consecutive months, increases in elimination half-lives were observed up to month 3. In a separate study with three consecutive monthly administrations, no increases in C_{max}, AUC, or elimination half-lives were noted when comparing values from the third and first months. Sufficient data on the C_{max} or AUC following repeated oral administration are not available beyond three months of treatment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Hydroxypropyl cellulose
Silica, colloidal anhydrous
Croscarmellose sodium
Magnesium stearate
Artificial beef flavour

6.2 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

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

6.5 Nature and composition of immediate packaging

Blister packs (of 1, 3 or 6 chewable tablets) in a carton. The blister packs are formed from aluminium laminates, heat sealed with a PVC based coating (the product contact surface is PVC).

Carton containing 1 blister pack.

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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Ltd
Elanco Animal Health
Priestley Road
Basingstoke
Hampshire
RG24 9NL
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/155/001 (1 tablet, 270 mg/4.5 mg)
EU/2/13/155/002 (1 x 3 tablets, 270 mg/4.5 mg)
EU/2/13/155/003 (1 x 6 tablets, 270 mg/4.5 mg)
EU/2/13/155/004 (1 tablet, 425 mg/7.1 mg)
EU/2/13/155/005 (1 x 3 tablets, 425 mg/7.1 mg)
EU/2/13/155/006 (1 x 6 tablets, 425 mg/7.1 mg)
EU/2/13/155/007 (1 tablet, 665 mg/11.1 mg)
EU/2/13/155/008 (1 x 3 tablets, 665 mg/11.1 mg)
EU/2/13/155/009 (1 x 6 tablets, 665 mg/11.1 mg)
EU/2/13/155/010 (1 tablet, 1040 mg/17.4 mg)
EU/2/13/155/011 (1 x 3 tablets, 1040 mg/17.4 mg)
EU/2/13/155/012 (1 x 6 tablets, 1040 mg/17.4 mg)
EU/2/13/155/013 (1 tablet, 1620 mg/27.0 mg)
EU/2/13/155/014 (1 x 3 tablets, 1620 mg/27.0 mg)
EU/2/13/155/015 (1 x 6 tablets, 1620 mg/27.0 mg)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19/09/2013

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/>).

11. PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE**
- C. STATEMENT OF THE MRLs**
- D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Eli Lilly and Company Ltd
Speke Operations
Fleming Road
Liverpool
L24 9LN
UNITED KINGDOM

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY OR USE

To be supplied only on veterinary prescription.

C. STATEMENT OF THE MRLs

Not applicable.

D. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

The MAH shall complete, within the stated timeframe, the measure below:

Description	Due date
A non-interventional study to evaluate the occurrence of neurological and ophthalmic adverse events (to be coded using the relevant Veddra terminology) in dogs treated with Trifexis. The protocol should be submitted to the Committee for review and agreement promptly, and no later than 3 months after the Commission Decision granting the marketing authorisation, in order to allow for the study to be conducted in the stipulated period.	31 July 2015

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Outer carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Trifexis 270 mg/4.5 mg chewable tablets for dogs (3.9 – 6.0 kg)
Trifexis 425 mg/7.1 mg chewable tablets for dogs (6.1 – 9.4 kg)
Trifexis 665 mg/11.1 mg chewable tablets for dogs (9.5 – 14.7 kg)
Trifexis 1040 mg/17.4 mg chewable tablets for dogs (14.8 – 23.1 kg)
Trifexis 1620 mg/27 mg chewable tablets for dogs (23.2 – 36.0 kg)

spinosad/milbemycin oxime

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

spinosad 270 mg/milbemycin oxime 4.5 mg
spinosad 425 mg/milbemycin oxime 7.1 mg
spinosad 665 mg/milbemycin oxime 11.1 mg
spinosad 1040 mg/milbemycin oxime 17.4 mg
spinosad 1620 mg/milbemycin oxime 27 mg

3. PHARMACEUTICAL FORM

Chewable tablets

4. PACKAGE SIZE

1 chewable tablet
3 chewable tablets
6 chewable tablets

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Treatment and prevention of flea infestation when concurrent prevention of heartworm disease and/or concurrent treatment of nematode infections is indicated.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Administer with food.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD**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**

Disposal: read package leaflet.

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

Eli Lilly and Company Ltd
Elanco Animal Health
Priestley Road
Basingstoke
Hampshire
RG24 9NL
UNITED KINGDOM

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/155/001 (1 tablet, 270 mg/4.5 mg)
EU/2/13/155/002 (1 x 3 tablets, 270 mg/4.5 mg)
EU/2/13/155/003 (1 x 6 tablets, 270 mg/4.5 mg)
EU/2/13/155/004 (1 tablet, 425 mg/7.1 mg)
EU/2/13/155/005 (1 x 3 tablets, 425 mg/7.1 mg)
EU/2/13/155/006 (1 x 6 tablets, 425 mg/7.1 mg)

EU/2/13/155/007 (1 tablet, 665 mg/11.1 mg)
EU/2/13/155/008 (1 x 3 tablets, 665 mg/11.1 mg)
EU/2/13/155/009 (1 x 6 tablets, 665 mg/11.1 mg)
EU/2/13/155/010 (1 tablet, 1040 mg/17.4 mg)
EU/2/13/155/011 (1 x 3 tablets, 1040 mg/17.4 mg)
EU/2/13/155/012 (1 x 6 tablets, 1040 mg/17.4 mg)
EU/2/13/155/013 (1 tablet, 1620 mg/27.0 mg)
EU/2/13/155/014 (1 x 3 tablets, 1620 mg/27.0 mg)
EU/2/13/155/015 (1 x 6 tablets, 1620 mg/27.0 mg)

17. MANUFACTURER'S BATCH NUMBER
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Lot {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS**BLISTER****1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

Trifexis 270 mg/4.5 mg for dogs (3.9 – 6.0 kg)

Trifexis 425 mg/7.1 mg for dogs (6.1 – 9.4 kg)

Trifexis 665 mg/11.1 mg for dogs (9.5 – 14.7 kg)

Trifexis 1040 mg/17.4 mg for dogs (14.8 – 23.1 kg)

Trifexis 1620 mg/27 mg for dogs (23.2 – 36.0 kg)

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly and Company Ltd

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 FOR:
Trifexis 270 mg/4.5 mg chewable tablets for dogs
Trifexis 425 mg/7.1 mg chewable tablets for dogs
Trifexis 665 mg/11.1 mg chewable tablets for dogs
Trifexis 1040 mg/17.4 mg chewable tablets for dogs
Trifexis 1620 mg/27 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:

Eli Lilly and Company Ltd
Elanco Animal Health
Priestley Road
Basingstoke
Hampshire
RG24 9NL
UNITED KINGDOM

Manufacturer responsible for batch release:

Eli Lilly and Company Ltd
Speke Operations
Fleming Road
Liverpool
L24 9LN
UNITED KINGDOM

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Trifexis 270 mg/4.5 mg chewable tablets for dogs (3.9 – 6.0 kg)
Trifexis 425 mg/7.1 mg chewable tablets for dogs (6.1 – 9.4 kg)
Trifexis 665 mg/11.1 mg chewable tablets for dogs (9.5 – 14.7 kg)
Trifexis 1040 mg/17.4 mg chewable tablets for dogs (14.8 – 23.1 kg)
Trifexis 1620 mg/27 mg chewable tablets for dogs (23.2 – 36.0 kg)

spinosad / milbemycin oxime

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

Active substances:

Each tablet contains:

Trifexis 270 mg/4.5 mg	spinosad 270 mg/milbemycin oxime 4.5 mg
Trifexis 425 mg/7.1 mg	spinosad 425 mg/milbemycin oxime 7.1 mg
Trifexis 665 mg/11.1 mg	spinosad 665 mg/milbemycin oxime 11.1 mg
Trifexis 1040 mg/17.4 mg	spinosad 1040 mg/milbemycin oxime 17.4 mg
Trifexis 1620 mg/27 mg	spinosad 1620 mg/milbemycin oxime 27.0 mg

The tablets are a mottled tan to brown colour, and are round and chewable. The following list shows the code and the number of dimples marked on each strength of tablet:

Trifexis 270 mg/4.5 mg tablets:	4333 and 2 dimples
Trifexis 425 mg/7.1 mg tablets:	4346 and 3 dimples
Trifexis 665 mg/11.1 mg tablets:	4347 and no dimples

Trifexis 1040 mg/17.4 mg tablets: 4349 and 4 dimples
Trifexis 1620 mg/27 mg tablets: 4336 and 5 dimples

4. INDICATION(S)

For the treatment and prevention of flea (*Ctenocephalides felis*) infestations in dogs when the concurrent prevention of heartworm disease (L3, L4 *Dirofilaria immitis*) and/or treatment of gastrointestinal nematode infections caused by hookworm (L4, immature adult (L5) and adult *Ancylostoma caninum*), roundworms (immature adult L5, and adult *Toxocara canis* and adult *Toxascaris leonina*) and whipworm (adult *Trichuris vulpis*) is indicated.

The flea 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 this 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 under 14 weeks of age.

Do not use in case of hypersensitivity to the active substance or to any of the excipients.

6. ADVERSE REACTIONS

A commonly observed adverse reaction is vomiting, which occurs in the first 48 hours after dosing. In the majority of cases, vomiting was transient and mild and did not require symptomatic treatment.

At doses of 30 to 60 mg spinosad and 0.5 to 1 mg milbemycin oxime per kg bodyweight, lethargy, anorexia/decreased appetite, diarrhoea, pruritus, dermatitis and reddening of the skin and pinna were commonly seen. Hypersalivation, muscle tremors, ataxia and seizures were uncommon. Post-marketing reports for spinosad indicate that in very rare cases, blindness, impaired vision and other eye disorders were observed.

The frequency of adverse reactions is defined using the following convention:

- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please, inform your veterinary surgeon.

7. TARGET SPECIES

Dogs.

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

For oral use.

Dosage:

The veterinary medicinal product should be administered in accordance with the following table to ensure a dose of 45 to 70 mg spinosad and 0.75 to 1.18 mg milbemycin oxime/kg bodyweight.

Bodyweight (kg) of dog	Strength and number of tablets to be administered:				
	Trifexis 270 mg/4.5mg	Trifexis 425 mg/7.1 mg	Trifexis 665 mg/11.1 mg	Trifexis 1040 mg/17.4 mg	Trifexis 1620 mg/27 mg
3.9–6.0	1				
6.1–9.4		1			
9.5–14.7			1		
14.8–23.1				1	
23.2–36.0					1
36.1–50.7			1		1
50.8–72.0					2

Method of administration:

Trifexis tablets should be administered to the dog with its food, or immediately after feeding.

Based on the local epidemiological situation and the decision of the prescribing veterinarian, the veterinary medicinal product may be given at monthly intervals throughout the season at the recommended dose as outlined below. This combination product (Trifexis) must, however, not be given for more than 6 consecutive months in any one year.

If the dog does not accept the tablet(s) directly in its mouth, then the tablet(s) may be administered with the dog's food. The duration of efficacy may be reduced if the dose is administered on an empty stomach.

Dogs living in non-heartworm endemic areas:

Trifexis can be used as part of the seasonal prevention of fleas (replacing treatment with a monovalent flea product) in dogs with diagnosed concurrent gastrointestinal nematode infections. A single treatment is effective for the treatment of gastrointestinal nematodes. After treatment of the nematode infection, further flea prevention should be continued with a monovalent product.

Dogs living in heartworm endemic areas:

Prior to treatment with Trifexis the advice in section 12 should be considered.

For the prevention of heartworm disease and the concurrent treatment and prevention of flea infestations, the veterinary medicinal product must be given at regular monthly intervals during the time of the year when mosquitoes and fleas are present. The veterinary medicinal product must be administered 1 month before the expected appearance of mosquitoes. It is recommended that heartworm prevention treatment should be continued at regular monthly intervals until at least 1 month after the last exposure to mosquitoes, but not for more than 6 consecutive months using Trifexis in any one year.

When Trifexis is used to replace another heartworm preventive product, the first dose of Trifexis must be given within a month of the last dose of the former medication.

Dogs travelling to a heartworm region should start medication within a month after arrival there. Heartworm prevention treatment should be continued monthly, with the last administration being given one month after the dog has left the region, but not for more than 6 consecutive months using Trifexis in any one year.

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

9. ADVICE ON CORRECT ADMINISTRATION

The veterinary medicinal product should be administered with food or immediately after feeding. If the dog does not accept the tablet(s) directly in its mouth then the tablet(s) may be mixed with food. The duration of efficacy may be reduced if the dose is administered on an empty stomach.

After administration of the tablet monitor the dog closely. 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. Then start a new monthly dosing schedule from that day.

10. WITHDRAWAL PERIOD

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 blister after EXP.

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

12. SPECIAL WARNING(S)

Special precautions for each target species:

Trifexis tablets should only be used when the veterinarian has confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see section 4).

All dogs within the household should be treated. Cats in the household should be treated with a product authorised for use in that species.

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

Fleas may be observed for a period of time after administration of the product due to the emergence of adult fleas from pupae already present in the environment. Regular monthly treatments with the insecticidal active substance in this product (spinosad) break the fleas' life cycle and may be used to control the flea population in contaminated households.

Parasite resistance to any particular class of anthelmintic may develop following the frequent, repeated use of an anthelmintic of that class. Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

Maintenance of the efficacy of macrocyclic lactones is critical for *Dirofilaria immitis* control, therefore, to minimise the risk of resistance selection, it is recommended that dogs should be checked for both circulating antigens and blood microfilariae at the beginning of each season of preventative treatment.

Special precautions for use in animals:

Use with caution in dogs with pre-existing epilepsy.

No studies have been performed in sick or convalescent dogs, therefore the product should only be used based on a benefit-risk assessment of the responsible veterinarian.

The safety of this product in avermectin sensitive dogs/dogs with an MDR-1 mutation has not been sufficiently demonstrated. These dogs may be at a higher risk for adverse effects when treated with it and should therefore be treated with special caution.

Accurate dosing is not possible in dogs weighing less than 3.9 kg. The use of the product in such dogs is therefore not recommended.

The recommended dosage regimen must be followed but not exceeded.

Prior to first use of this product, dogs in heartworm endemic areas or who have visited heartworm endemic areas must be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs must be treated with an adulticide to remove adult heartworms.

It is recommended to observe the treated dog up to 24 hours post-administration of the product for possible adverse reactions (see section 6). In case of adverse reactions consult your veterinarian.

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

Wash hands after use.

Accidental ingestion may cause adverse reactions.

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

Children must not come into contact with the veterinary medicinal product. Accidental ingestion may cause adverse reactions.

Pregnancy and lactation:

Laboratory studies (in rats and rabbits) on the effect of spinosad and milbemycin oxime have neither produced any evidence of teratogenic, foetotoxic or maternotoxic effects, nor any effect on the reproductive capacity in males and females.

In pregnant and lactating dogs (bitches), the safety of this veterinary medicinal product has not been sufficiently established. Spinosad is excreted in the colostrum and milk of lactating bitches. The excretion of milbemycin oxime in lactating dogs (bitches) has not been tested and the safety for suckling puppies has not been established. This product should therefore only be used during pregnancy and lactation according to the benefit-risk assessment by the responsible veterinarian.

Fertility:

As the safety of this veterinary medicinal product in male dogs used for breeding has not been determined, it should only be used according to the benefit-risk assessment by the responsible veterinarian

Interaction with other medicinal products and other forms of interaction:

Spinosad and milbemycin oxime have been shown to be substrates for P-glycoprotein (P-gp) and therefore could interact with other P-gp substrates (for example, digoxin, doxorubicin) or other macrocyclic lactones. Therefore, concomitant treatment with other P-gp substrates could lead to enhanced toxicity.

Post-marketing reports: following the concomitant use of spinosad with ivermectin indicate that dogs have experienced trembling/twitching, salivation/drooling, seizures, ataxia, mydriasis, blindness and disorientation.

Overdose (symptoms, emergency procedures, antidotes):

The oral administration of spinosad and milbemycin oxime combination tablets at mean cumulative monthly doses up to 255mg spinosad and 4.2 mg milbemycin oxime per kg body weight (up to 3.6 times the recommended treatment dose) for 6 consecutive dosing periods in young dogs was well tolerated. Vomiting was seen in both treated and control dogs with similar frequencies. Adverse reactions seen during the course of this study included vomiting, diarrhoea, skin lesions, salivation, tremors, decreased activity, coughing and vocalization.

At acute overdoses corresponding to 1.5 times the maximum recommended dose, vomiting occurred in 17% of the dogs, and hypersalivation occurred in 8% of the dogs. At acute overdoses corresponding to 3 times the maximum recommended dose, vomiting occurred in half of the animals, sometimes repeatedly. At three times the maximum recommended dose adverse events of potentially neurological origin e.g. decreased activity (8%), hypersalivation (17%) or stumbling (8%) were observed. Decreased activity was seen at the same frequency in both control and dogs treated with 3 times the maximum recommended dose. All adverse events were transient and did not require treatment.

After spinosad administration, the incidence of vomiting on the day of, or the day after dosing has been observed to increase as a function of the dose. Vomiting is most likely caused by a local effect on the small intestine. At doses in excess of the recommended dose, vomiting becomes a very common event.

Neurotoxicity characterised by transient mild depression, ataxia, trembling, mydriasis, and excessive salivation has been observed in dogs given higher dose multiples of milbemycin oxime alone (5 to 10 mg/kg).

There is no antidote available. In case of adverse clinical signs, treat symptomatically.

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 product is available on the website of the European Medicines Agency (<http://www.ema.europa.eu/>).

15. OTHER INFORMATION

Further information for the prescribing veterinarian:

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). 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. Spinosad therefore has a different mode of action to other flea control or insect control products. Spinosad starts killing fleas 30 minutes after administration; 100% of fleas are dead/moribund within 4 hours post-treatment.

Milbemycin oxime is an antiparasitic endectocide belonging to the macrocyclic lactones. Milbemycin oxime is isolated from the fermentation of *Streptomyces hygroscopicus* var. *aureolacrimosus*. It is

active against mites, larval and adult stages of nematodes as well as larvae of *Dirofilaria immitis*. The activity of milbemycin oxime 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 and glycine receptors). This leads to hyperpolarisation of the neuromuscular membrane and flaccid paralysis and death of the parasite.

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.

After oral administration of 45 mg spinosad and 0.75 mg milbemycin oxime/kg bodyweight to fed dogs, spinosyns A and D are rapidly absorbed and extensively distributed. Plasma protein binding is high (>98%). Bioavailability was shown to be high. The mean T_{max} for spinosyns A and D was 4 hours and the mean elimination half-lives ranged between 131 and 135 hours. AUC values increased approximately linearly while C_{max} increased slightly less than linearly with increasing dose-rates over the intended therapeutic dose range. In addition, in studies containing only spinosad, AUC and C_{max} values were higher in fed than fasted dogs and therefore it is recommended to treat dogs with food as this maximises the opportunity for fleas to ingest lethal amounts of spinosad.

In studies performed with spinosad only, the primary biliary, faecal and urinary metabolites in both rat and 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 to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in dogs.

Milbemycin oxime is a systemic macrocyclic lactone containing two major factors, A3 and A4 (ratio of A3:A4 is 20:80). Unlike spinosad, the consistent ratio of the individual factors is not maintained in pharmacokinetic studies. Milbemycin A4 5-oxime tends to eliminate slower resulting in approximately 10-fold higher exposure than Milbemycin A3 5-oxime. Milbemycin oxime plasma concentrations and some pharmacokinetic parameters are increased in the presence of spinosad. Milbemycin A3 and A4 5-oximes are rapidly absorbed and extensively distributed in dogs after oral administration. Plasma protein binding is high (>96%). Bioavailability was shown to be high. The mean T_{max} for milbemycin A3 and A4 5-oximes was typically 4 hours and the mean elimination half-lives were 33.9 and 77.2 hours. AUC values increased approximately linearly while C_{max} increased slightly less than linearly with increasing dose-rates over the intended therapeutic dose range.

The primary faecal and urinary metabolites in dog were identified as glucuronide conjugates of milbemycin A3 or A4 5-oximes, dealkylated milbemycin A3 or A4 5-oximes, and hydroxylated milbemycin A4 5-oxime. In rats dosed with milbemycin A4 5-oxime, the main metabolites identified in urine and faeces were mono-, di-, and trihydroxy milbemycin A4 5-oximes. In dogs, hydroxymilbemycin A4 5-oxime was detected only in plasma, but not in urine or faeces, suggesting predominant excretion of conjugated metabolites in the dog. Excretion is primarily via faeces, and also to a lesser extent in the urine. Faecal excretion accounted for the vast majority of metabolites in dogs.

Monthly repeated oral administration of spinosad and milbemycin oxime over six months revealed evidence of spinosad and milbemycin oxime accumulation in juvenile dogs. Accumulation cannot be discounted in adult dogs.

In juvenile dogs, repeated oral administration of spinosad and milbemycin oxime over six months resulted in the trough plasma concentrations of spinosad and milbemycin increasing throughout the study. Trough concentrations of spinosad doubled monthly up to month 5. The increase in plasma concentrations was strongly correlated with an increase in terminal elimination half-lives.

In adult dogs, after repeated oral administration of spinosad and milbemycin oxime for six consecutive months, increases in elimination half-lives were observed up to month 3. In a separate study with three consecutive monthly administrations, no increases in C_{max} , AUC, or elimination half-lives were noted

when comparing values from the third and first months. Sufficient data on the C_{\max} or AUC following repeated oral administration are not available beyond three months of treatment.

Cartons containing a blister pack with 1, 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.