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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP Assessment Report for the extension of a community marketing authorisation for Comfortis (EMEA/V/C/002233/X/006/G)

Scope: New (lower) tablet strengths and new target species (cats)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

An application for an extension to the Community marketing authorisation for Comfortis has been submitted to the European Medicines Agency (the Agency) on 26 October 2011 by Eli Lilly and Company Limited in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

The already authorised product, Comfortis chewable tablets for dogs, was authorised for use in the Community on 11 February 2011. The tablets contain the active substance, spinosad, and are available in 5 strengths.

This grouped extension application for Comfortis tablets is to add cats as a new target species. The new indication is:

> Dogs and cats: 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).

The application also includes the addition of two new lower tablet strengths, only for cats, and the modification of two of the original tablet strengths to add cats as a target species (to the already authorised species, dogs). The pharmaceutical form (chewable tablets), route of administration (oral use), and primary packaging (blisters) all remain unchanged.

The CVMP adopted an opinion and CVMP assessment report on 8 November 2012.

On 14 January 2013 the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC, as amended.

Manufacturing authorisations and inspection status

Manufacturing authorisations and/or GMP certificates for the manufacturers of the final product were issued by EU authorities and no inspections were required.

The active substance manufacturer is the same for those products already approved and no inspections were required.

Overall conclusions on administrative particulars

The pharmacovigilance system as described by the applicant fulfils the necessary requirements and provides adequate evidence that the applicant has both the services of a qualified person responsible

for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The information provided in regard to the manufacturing sites and their GMP status is complete and no further information is necessary on the manufacturing sites, nor is any inspection necessary or requested.

Part 2 - Quality

Composition

Comfortis tablets will be presented now in a total of seven different strengths, ranging from 90 mg up to 1620 mg, to accommodate the range of bodyweights for both target species (dogs and cats). All strengths are compressed from a common tablet blend which has a percentage content of 53.33% spinosad. The two lowest strengths tablets, 90 mg and 140 mg, are introduced with this application but are simply achieved by using lower compression weights and smaller tablet sizes.

No changes to the quality of either the active substance or excipients are introduced with this application.

Container

The finished product is presented in blister packs (3 or 6 tablets) inside an outer carton. The blister foil is unchanged from that used for the already authorised tablets for dogs (clear polychlorotrifluoroethylene/polyethylene /polyvinyl chloride (PCTFE/PE/PVC) laminate) and is sealed with a PVC based heat seal coating (lacquered) aluminium foil (the product contact surface is PVC).

Development pharmaceutics

As the two new additional (lower) tablet strengths (90 mg and 140 mg, for the treatment of cats only) are derived from the same bulk powder mix as for the already authorised tablets for dogs, no additional development work was conducted or necessary.

Method of manufacture

No changes to the method of manufacture are introduced by this application, other than those relating to, for example, compression weights for the new lower strength tablets. The manufacture of the two new lower strength tablets has been satisfactorily validated.

Control of starting materials

Active substance

No changes have been introduced in this application.

Excipients

No changes to the excipients are introduced in this application.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

No changes to the excipients are introduced in this application.

Control tests during production

No changes have been introduced in this application, other than, for example, limits for some in-process controls for the new lower strength tablets which have all been defined and justified.

Control tests on the finished product

No changes have been introduced in this application, other than, for example, some of the limits in the specifications for the new strength tablets, but these have all been described to ensure the appropriate and consistent quality of the finished product.

Batch results of pilot scale batches, which comply with the specification, have been presented.

Stability

The accelerated and long term stability data presented satisfactorily demonstrate the claimed stability of 36 months (with no storage precautions) for the tablets packaged in the proposed blister packs. Since none of the tablet strengths possess a score line, no in-use stability data have been provided for half tablets.

Since the dosage regimen does not include half tablets and the tablets have no score (break) line, no in-use stability data has been provided, which is justified.

Overall conclusions on quality

The quality of the two new (lower) tablets strengths as described in the dossier is acceptable.

Part 3 – Safety

This grouped Extension/Type II application is for the addition of a new non-food producing species, cats, to the centralised marketing authorisation for Comfortis (chewable tablets for dogs) following Regulation 1234/2008, Annex II.2 (g) "variations concerning a change to or addition of a non-food producing target species". In addition to the tablet sizes previously authorised for use in dogs, 2 new smaller size tablets for cats are added (90 mg and 140 mg) through an extension procedure submitted in parallel with this application.

Extensive reference is made to the documentation provided as part of the marketing authorisation application for Comfortis (flavoured chewable tablets for dogs). These data are summarised and discussed in the published European Public Assessment Report (EPAR) (EMA/CVMP/63440/2010).

Safety documentation

Pharmacodynamics

(Unchanged by this application.)

Pharmacokinetics

See Part 4.

Toxicological studies

The toxicity of spinosad is well defined (see the original EPAR, EMA/CVMP/63440/2010). The additional studies submitted in this application on its tolerance in cats do not alter the conclusions previously drawn on the potential hazards of spinosyns.

Spinosad is of low acute toxicity. In repeat-dose studies, phospholipidosis was the principle finding in all the species examined, including both of the target species, dogs (previously authorised) and cats (introduced in this grouped application). It was concluded that this finding was not relevant to man, or to the target species at the therapeutic dose.

Spinosad was demonstrated to have no teratogenic potential; in rats, the NOAEL for maternal and developmental toxicity respectively were 50 mg/kg/day and 200 mg/kg/day and in rabbits, the NOAEL for maternal and developmental toxicity was 50 mg/kg/day. In the two generation study, there were no effects on development or fertility parameters. The NOAEL for parental toxicity and developmental (foetal) toxicity was 10 mg/kg/day.

Spinosad has no genotoxic potential since all *in vitro* and *in vivo* studies were clearly negative.

Long-term controlled studies of up to 18 months were conducted in rats and mice. No increases in tumour incidence were observed at the end of the study and therefore it can be concluded spinosad does not have carcinogenic potential.

Studies of other effects

(Unchanged by this application.)

User safety

The selective toxicity of spinosad in insects over mammals is the result of the lack of homology between insects and mammalian nicotinic or GABA receptors. The acute mammalian toxicity is low following oral, intra-peritoneal or inhalation exposure.

A comprehensive user safety assessment of the active substance and the formulated product was submitted and evaluated as part of the original marketing application (see the original EPAR, EMA/CVMP/63440/2010).

As the subject of this application was use of the product in a new target species, cats, and the addition of two lower strength tablets for cats (highest strength for cats is 425 mg compared to strengths of up to 1620 mg for dogs), any risks to users administering the spinosad tablets for cats are significantly

less than those faced by users administering the (higher strength) tablets to dogs. The user safety warnings are therefore justifiably unchanged.

The user safety data is in accordance with the current Guideline on User Safety (EMEA/CVMP/543/03-Rev.1) and the user safety warnings are satisfactory.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

Comfortis chewable tablets for cats are not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

The toxicity of spinosad is well defined. The additional studies submitted on its tolerance in cats do not alter the conclusions previously drawn on the potential hazard of spinosyns.

The product can be handled safely when the proposed precautions are observed. The warnings are adequate to ensure user safety.

The use of Comfortis chewable tablets in cats is not expected to pose a risk to the environment when used in accordance with the product literature.

Part 4 – Efficacy

This grouped application for Comfortis tablets is to add cats as a new target species. The new indication is:

> Dogs and cats: 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).

Pharmacodynamics

(Unchanged by this application.)

Pharmacokinetics

The pharmacokinetic properties of the two major constituents of spinosad, spinosyn A and D, have been evaluated in a number of non-GLP and GLP compliant laboratory studies in cats following either the single or repeated administration of spinosad at different dose levels, including the therapeutic dose range of 50 to 75 mg/kg bw, and comparing fed and fasted cats. Different oral formulations were

used (in most cases, powder in capsules). The final tablet formulation intended for marketing was used in one study in a comparison with powder in capsules. In this study it was demonstrated that the pharmacokinetic parameters are comparable in animals following treatment with these two formulations. The use of powder in capsules instead of the final formulation is therefore accepted. Spinosad was also administered intravenously to allow for the calculation of bioavailability.

In fed animals, spinosad (spinosyns A and D) is completely absorbed after oral administration and extensively distributed with a mean volume of distribution of 82 l/kg. The mean clearance is 203 ml/hr/kg. Maximum plasma concentrations following a single dose of 75 mg/kg are 4496 +/- 1309 ng/ml and are reached within 4-12 hours in the majority of animals. The half life is long, up to 20 days (5 to 20 days). Bioavailability can be considered dose-linear at 50, 75 and 100 mg/kg bw. A notable inter-individual variability of pharmacokinetic parameters was observed when comparing data within and between studies, which is, however, not considered to be clinically relevant and the times of blood sampling may have missed the true T_{max}/C_{max}.

Like in the rat and dog, the C_{max} and AUC of spinosyns A and D in cats proved to be consistently in ratio, comparable to that determined in the test formulation. Approximately 90% of spinosad is comprised of spinosyns A and D. Of that 90%, the ratio of spinosyn A to spinosyn D is 85:15.

No differences in pharmacokinetics in relation to gender were observed.

In contrast to dogs, in a 6 month study in adult cats, spinosad appears to accumulate after monthly oral doses of 75 mg/kg bw, and steady state is reached within three to four months. In juvenile cats that were treated monthly with higher (than recommended therapeutic) doses of 75-100 mg/kg bw, their plasma levels did not reach a plateau within the six month study period.

It has been shown that the bioavailability of spinosad is increased in fed cats compared to fasted cats. Advice on giving spinosad to fed cats is therefore included in the SPC accordingly.

Spinosad is highly bound to cat plasma proteins, as was demonstrated *in vitro* by using the standard rapid equilibrium dialysis method, and this information is reflected in section 5.2 of the SPC.

The metabolism and elimination of spinosad in cats was studied using a radiolabelled compound. These studies revealed extensive metabolic degradation of the spinosad by dealkylation and glucuronidation. Spinosad was mainly eliminated in the faeces and to a minor extent in the urine. The parent compound (spinosyns) and metabolites were detected in the plasma, faeces and urine of cats, and were similar to the metabolites known from rats and dogs.

Development of resistance

The spinosyns are a novel class of insecticides with a unique mode of action primarily targeting nicotinic acetylcholinergic receptors (nAChRs). Although neonicotinoid insecticides (for example, imidacloprid) also affect nAChR receptors, they interact with completely different subunits, thus cross-resistance between spinosyns and neonicotinoid insecticides is not very likely.

Fleas on cats in Europe had not been exposed to spinosyns prior to the introduction of the first spinosad authorised veterinary medicinal product in the EU (in 2011 for dogs). Therefore, the development of resistance would not be expected at this time. A search in open databases for "spinosad" combined with "resistance" resulted in no publication attributable to the cat flea.

Target Animal Tolerance

Data on the effect of single doses of spinosad, including acute overdose, are available from various studies, covering a wide range of dosages, from below the minimum label dose of 50 mg/kg spinosad up to 240 mg/kg bw (3.2 times the upper label dose of 75 mg/kg bw). No serious adverse events were observed, however, a number of adverse reactions could be identified.

Emesis is the predominant acute adverse effect of spinosad in cats, occurring in most cases within the first 5 hours post dose. Although the frequency of emesis is somewhat variable when comparing studies using the same or similar doses, the effect does appear to be dose related. Data support the assumption that emesis is more likely to be an effect of an acute oral dose, rather than an effect of high plasma levels. As in the dog, a local intestinal effect appears to be the most likely reason for the emesis. Further adverse events observed at the label dose of 50-75 mg/kg bw are loose or soft faeces, anorexia and salivation, lethargy, loss of condition and seizures, and all these are appropriately reflected in the SPC (and other product information).

At an acute overdose of 120 mg/kg, that is, at 1.6 times the maximum label dose, about 50% of cats vomit. Pacing/panting, depression and severe diarrhoea were observed in single cats.

Data on the effects of long-term use and long-term overdose of spinosad were generated from one pilot and one pivotal target animal safety study in healthy young cats. This was done by the administration of a single dose of 70 mg/kg bw in the pilot study, and by the administration of a dose of 75-100 mg/kg bw in the pivotal target animal safety study on one day for the 1x group, or on 3 or 5 consecutive days for the 3x and 5x groups, respectively, at the beginning of each treatment round. These treatment rounds were conducted every 28 days for up to six months. No severe adverse events occurred. In addition to the above mentioned events, cell vacuolation, interpreted as phospholipidosis, was noticed as a dose-related effect. In the pivotal TAS study, cell vacuolation of hepatocytes was seen in cats in the 3x and 5x groups, in some animals accompanied by elevations in liver enzymes, hepatocellular hypertrophy and/or an increase in absolute and relative liver weights. These findings were subtle and lacked clinical correlation. Cell vacuolation in the lungs was also observed, including one animal in the 1x group, but this did not correlate with other findings, thus, there is no evidence for related adverse functional changes.

The effects of an acute overdose of 120 mg/kg are adequately reflected in the SPC (and other product information).

The results of the pivotal target animal safety study are adequate for the safety assessment of long term treatment of cats with a monthly treatment with the product using a dose range of 50-75 mg/kg. In the pharmacokinetic study using 75 mg/kg bw spinosad for six months, steady state was reached within three to four months which supports the 75 mg/kg bw maximum recommended dose.

The applicant proposed a restriction of the use of Comfortis to cats over 14 weeks old. This was accepted by the Committee, since the pivotal target animal safety study started at this age of cats and the minimum age cats in the field studies was also 14 weeks.

The minimum bodyweight according to the proposed SPC (1.2 kg) is calculated from the maximum label dose and the available tablet sizes.

Studies with pregnant or lactating cats have not been performed. No data on the excretion of spinosad in the milk of lactating cats is presented, but it is reasonable to assume that excretion of spinosad in the milk in lactating cats is comparable to the situation in the bitch, based on the lipophilic properties of the substance and the similarity in milk production in the different mammalian species. This is reflected in the SPC and other product literature.

Dose determination / justification

Three dose determination studies were conducted to identify the minimum dose needed for a treatment and prevention claim for 4 weeks against flea infestations in cats. Two of these studies were performed in accordance with both VICH-GCP and the CVMP ectoparasiticide guidelines. Cats were infested with 100 *C. felis* at weekly intervals and flea counts were carried out either at 24 hours post treatment and/or 48 hours after each re-infestation up to five weeks. Spinosad was administered to cats at single oral point doses ranging from 30 to 80 mg/kg bw as liquid suspension or gelatine capsules, both administered with food. Administration of spinosad at an oral point dose of 50 mg/kg bw resulted in >95% reduction of the flea burden based on arithmetic mean. Higher doses of spinosad did not improve the efficacy. The residual insecticidal activity lasted for 4 weeks. Hence, the minimum effective dose of spinosad is 50 mg/kg bw.

Dose confirmation

A GCP compliant "speed of killing fleas" study in cats was provided to calculate the efficacy at 30 min, 2 hours (h), 4 h, 8 h and 24 h post treatment. In this study the final flavoured oral tablet formulation of spinosad was used at a single dose of 50-100 mg/kg bw. The insecticidal efficacy amounted to 15.9%, 85.8%, 85.2%, 91.3% and 100% based on arithmetic means at 0.5h, 2h, 4h, 8 h and 24 h post dosing, respectively. The sentence in section 5.1 of the SPC "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." is, therefore, acceptable and justified.

Three GCP-compliant dose confirmation studies (two EU and one US) were conducted using the final tablet formulation. The assignment of cats to the study groups was based on pre-treatment flea count ranking. Spinosad tablets were administered orally at a dose of 50–75 mg/kg bw to overnight fasted cats, which were then fed prior to dosing with 25% of their daily food ration. Treated and control cats were infested weekly with 100 fleas each, and flea counts were carried out either at 24 h post treatment and/or 48 h after each re-infestation up to five weeks. Based on the threshold level of 95% as recommended in the relevant EU guideline, spinosad proved to be effective in the reduction of flea infestation for up to 4 weeks in the EU studies, whereas in the US study the persistent insecticidal efficacy lasted only for 2 weeks above 95%; this was considered likely due to early vomiting observed in 2 treated cats, which had not been redosed.

This matter is considered in section 4.9 of the SPC by advising the user that the full 4 week gap between subsequent treatments should be maintained, even if fleas reappear in some cats before the end of the 4 weeks.

One additional GCP compliant Simulated Home Environment laboratory study was submitted in order to substantiate the claim "prevention of flea infestation". A severe flea pressure was steadily maintained, resembling natural home environmental conditions. Twelve cats per group were orally dosed with 50-75 mg/kg bw (final tablet formulation) on days (D)0, D+30 and D+60. Flea counts found during the study period in the controls ranged from 58.8 to 118.1 fleas on average until the end of the study. Prevention of 100% was observed during the entire study period in the spinosad treated animals, confirming a "treatment and prevention of flea infestation (*Ctenocephalides felis*)" claim in cats.

Field trials

Two GCP compliant multi-site clinical field studies were conducted, one in Europe and one in the US. Both studies followed more or less the same protocol. Spinosad flavoured tablets were administered to cats at a dose of 50-100 mg/kg bw at monthly intervals, for a duration of 2 months in EU, and for 3 months in the US. A reference product (spot-on formulation) containing selamectin was used for the positive control and was administered according to the product's label instructions. In the European study, cats were enrolled at geographically diverse areas in Germany (10 sites) and Italy (12 sites). In the US study, cats were enrolled at 8 geographically diverse regions across the US. The average flea count prior to treatment was significantly lower in the EU study (18.6 fleas in the spinosad and 16.5 fleas in the selamectin group (arithmetic means)), compared to the US study (85.1 and 108.9 fleas in the spinosad and selamectin group, respectively). For the EU study, recalculation of a subset of cats that received the refined treatment dose of 50-75 mg spinosad/kg bw was performed. Flea count reductions were >95% (based on adjusted geometric means) compared to baseline at all assessment days, and 77% to 91% of cats treated with spinosad had zero fleas on assessment days 14, 30 and 60, compared to 78.9%-87.3% in the selamectin group. The treatment success rates (any individual cat with $\geq$90% flea count reduction was classified as successfully treated) in the spinosad group proved to be non-inferior (with a non-inferiority margin of -15 percent points) to those ones in the selamectin group throughout the course of the study. These efficacy results were largely confirmed following a respective recalculation of the US field study data.

In the EU study there were several cats in the spinosad group (but none in the selamectin group) showing heavy flea infestations on day 0 prior to treatment, and being flea-free on day 14, but showing again considerable flea burdens on day 30. However, this was attributed to the domestic reservoir of developing fleas rather than new fleas coming from the outside. Appropriate advice to clean and vacuum the pets' bedding, carpet, soft furnishings, etc, and to treat the home environment with an appropriate insecticide in the case of heavy flea infestations is already included in the product literature.

The data obtained in both the EU and US studies show that spinosad can be effectively used as a part of the treatment strategy for flea allergic dermatitis.

Data in both the clinical field studies show that, overall, the cats accepted the spinosad flavoured tablets freely or in food about 40% of the time, and for 60% of the time the tablets had to be administered by opening the cat's mouth and placing the tablet onto the back of the tongue. These data do not support palatability of the product in cats, and this is correctly reflected in section 4.9 of the SPC (and in the package leaflet).

As expected, emesis was the most frequently observed adverse event in cats treated with spinosad in both clinical field studies, but the overall emesis rate in the US study was significantly higher than in the EU study. Based on the recalculation of a subset of cats that received the recommended treatment dose of 50-75 mg spinosad/kg bw, the percentage of cats vomiting during the first, second and third dosing interval in the US study was 10.7%, 12.7% and 11.3%, respectively, compared to 6.1% and 2.6% in the first and second treatment interval in the EU study. Vomiting occurred most commonly within two days after dosing, and in the US study the average monthly rate remained about the same with repeated monthly doses (10.7%, 12.7% and 11.3% of spinosad cats vomited on the day of, or day after, the first, second and third dosing, respectively), while in the EU study the emesis rate decreased to 5.3% and 1.7% following the first and second dose, respectively.

The reason for the differences in emesis rates between the US and EU study could not be convincingly explained. In both studies an unknown proportion of indoor and outdoor cats had been enrolled, and

systematic measures to ensure a close monitoring of the treated cats, in particular on the day of, or day after were missing.

Overall, vomiting was stated as mild and transient and did not require symptomatic treatment, and the efficacy appeared to be unaffected.

Field study data were analysed regarding a dose-emesis relationship within the dose span of 50-100 mg/kg by using a logistic regression approach. Analyses did not show a distinct relationship between dose and emesis over this dose range. In this context it is noticed that according to the protocol, cats that vomited within one hour after dosing had to be re-dosed in both EU and US studies. Respective advice is included in the SPC and other product literature.

Other commonly observed adverse reactions in cats were diarrhoea and anorexia. Lethargy, loss of condition and salivation were uncommon.

Information on emesis and other adverse reactions is adequately reflected in section 4.6 (Adverse effects) of the SPC (and other product literature).

Other studies

None.

Overall conclusion on efficacy

The minimum recommended dose of 50 mg/kg bw for the treatment and prevention of flea infestations was derived from three dose determination studies. The efficacy of spinosad at a single dose of 50-75 mg/kg bw was proven in three laboratory dose confirmation studies. All studies were performed according to GCP and conducted according to the provisions of the EMA/CVMP ectoparasiticide guideline. The persistent pulicidal efficacy is up to 4 weeks after single treatment.

The efficacy of spinosad at monthly oral doses of 50-75 mg/kg bw was confirmed in two GCP-compliant, multi-site, controlled, randomized clinical field studies, one in Europe and one in the US. Both studies were run according to more or less the same study protocol. In both field studies, emesis was the most commonly observed adverse effect and occurred on the day of, or day after, dosing. Emesis, however, was transient, mild and did not require any symptomatic treatment. Further commonly observed adverse reactions in cats were diarrhoea and anorexia. Lethargy, loss of condition and salivation were found to be uncommon. Appropriate information to ensure efficacious and safe use of the product is included in the SPC and other product literature.

In view of the extension of the indications to the new target species (cats) the Committee considered it important to restart the PSUR cycle in order to ensure more frequent pharmacovigilance monitoring initially, that is, submission of 6-monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals.

Part 5 – Benefit risk assessment

Introduction

Comfortis chewable tablets contain spinosad and are already authorised in the EU for the treatment and prevention of flea infestations (*Ctenocephalides felis*) in dogs using a single dose of 45-70 mg/kg bw, which can be repeated every month. This grouped extension/variation application is to add cats as new target species, and to add two new lower tablet strengths (90 mg and 140 mg) for cats, and to add cats as a target species for two of the original tablet strengths (270 and 425 mg). The pharmaceutical form and route of administration, as well as the primary packaging, is unchanged. The treatment dose for cats is a single dose of 50-75 mg spinosad/kg bw, which (like for the dog) can be repeated monthly.

Benefit assessment

Direct therapeutic benefit

The efficacy of spinosad in the treatment of flea infestations in cats has been demonstrated in a set of well controlled laboratory studies. The residual insecticidal efficacy lasts for up to 4 weeks, hence, justifying a prevention claim.

As in dogs, spinosad shows a rapid flea killing effect in cats and starts killing fleas 30 minutes after administration, which provides fast relief for cats harbouring fleas. Moreover, the rapid kill of fleas after a blood meal prevents the fleas subsequently laying eggs, and this leads to long term effects in the cat's surroundings by eliminating the source of the underlying flea problems (eggs).

In two multi-centre field studies, spinosad at the recommended dosage regimen proved to be non-inferior to the reference product (selamectin) in the treatment and prevention of flea infestations in cats.

Additional control measures, including the use of suitable insecticides in the home environment and vacuum cleaning, are deemed necessary at the start of treatment and also in cases of heavy infestations. The treatment of other pet animals living in the same household is also necessary. Appropriate information is included in the product literature.

There is clear evidence from the data that the frequency and severity of flea allergy dermatitis is significantly decreased in cats treated with Comfortis. This is an indirect beneficial effect and, therefore, the claimed use as part of a treatment strategy for the control of flea allergy dermatitis is justified.

Additional benefits

The mode of action of spinosad is different from that of other chemical classes of veterinary medicines used for flea control, such as neonicotinoides, fiproles, milbemycins, and avermectin (selamectin). At the present time no cross-resistance is expected. The low flea egg drop after treatment with spinosad prevents to a certain extent the spread of resistance genes into the next population of fleas. Hence, Comfortis increases the range of available treatment possibilities.

Fleas do have a considerable negative impact on animal welfare because of their irritating bites causing distress in cats. Hypersensitive animals may also develop signs of flea allergy dermatitis. Fleas

transmit a number of pathogens such as *Dipylidium caninum* and *Bartonella henselae*. Fleas also attack humans, causing bites with subsequent irritation. Therefore, the treatment and prevention of flea infestations is considered beneficial to both animal and human health.

The indirect benefits of treatment with spinosad are particularly relevant to children living in close contact with treated cats as, unlike with many other flea products, there is no opportunity to transfer spinosad to human skin. This is an orally administered, systemically acting product, which in contrast to spot on products or insecticidal sprays, contains an active substance which will not be washed off during rain, or licked off, and does not undergo UV degradation. There is also negligible opportunity for a direct transfer of spinosad to household items.

Moreover, also humans will benefit from treatment of their cats, as the cats' fleas can also attack humans.

Risk assessment

The dossier takes into account current guidelines on pharmaceutical quality and the provisions of the pharmacopoeias. The formulation development and the manufacture of Comfortis (tablets for cats) are well described. The manufacturing process has been established and leads to a product of consistent quality. Specifications set are relevant to control the quality of the product. The proposed shelf-life of 36 months has been substantiated by the findings of the stability study.

- *for the target animal*

Preclinical and clinical data reveal that the most prominent adverse reaction to spinosad in the cat is emesis. Emesis usually occurred within the first five hours post dosing, and is most likely to be caused by a local effect on the small intestines.

The overall rate of emesis recorded in global field studies following monthly treatment at a dose of 50-75 mg/kg bw was between 6 and 11% in the first three months of treatment. It was stated that vomiting was usually mild and transient and did not require symptomatic treatment. The incidence of emesis is appropriately reflected in the SPC and other product literature.

Other observed common adverse reactions included diarrhoea and anorexia; lethargy, loss of condition and salivation were uncommon, and seizures were recorded rarely. The adverse reactions are adequately reflected in the SPC and other product information.

Although cell vacuolation/phospholipidosis was found in a dose dependant manner in cats, in the margin of safety study, the Committee considered that the risk of phospholipidosis at the recommended treatment dose was negligible because of a lack of clinical relevance.

No severe adverse events occurred in cats after excessive overdosing. However, vomiting was observed in about 50% of cats after a single oral dose of 120 mg/kg bw, which corresponds to 1.6 times the maximum label dose. In addition to the emesis, pacing/panting, depression or severe diarrhoea was observed in single cats. The effects of overdoses are appropriately reflected in the SPC and other product literature.

The applicant proposes a restriction of the use of Comfortis to cats over 14 weeks old. This is acceptable as the pivotal target animal safety study started at this age, and the minimum age in the field studies was also 14 weeks.

The minimum bodyweight stated in the SPC (1.2 kg) is calculated from the maximum label dose and the available tablet sizes.

Studies with pregnant or lactating cats have not been performed. No data on the excretion of spinosad in the milk of lactating cats is present, but it is reasonable to assume that this is comparable to the situation in the bitch based on the lipophilic properties of the substance, and the similarity in milk production between these two mammalian species. This is correctly reflected in the SPC.

- *for the user*

There is no health concern for adults, including pregnant and nursing women, administering this product (to cats) when used in accordance with the SPC. Child-resistant packaging and the user safety warning phrases on the already authorised dog (higher strength) tablets are considered satisfactorily to minimise the risks for children. As the tablets for cats are all lower strengths than the maximum strength dog tablets it was agreed that no changes to the existing user safety warnings were needed.

- *for the environment*

Comfortis chewable tablets are not expected to pose a risk for the environment when used according to the SPC and product information.

Risk management or mitigation measures

Regarding the target animal, the provisions to ensure a safe and efficacious use, as proposed by the applicant are sufficient.

In view of the extension of the indications to the new target species (cats) it is considered necessary to restart the PSUR cycle in order to ensure initially more frequent pharmacovigilance monitoring, that is, submission of 6-monthly reports (covering all authorised presentations of the product) for the next two years, followed by yearly reports for the subsequent two years and thereafter at 3 yearly intervals.

As for the user safety and the environment, appropriate phrases and precautionary warnings have been included in the product information. (These are the same as for the previously authorised dog product. The Committee agreed no changes were necessary.)

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall. The product has been shown to be efficacious for the treatment and prevention of flea infestations in cats at a single oral dose of 50-75 mg/kg bw with efficacy rates of >95% for up to 4 weeks. Treatment may be repeated at monthly intervals. Measures to ensure an efficacious and safe use of the product in cats are adequately included in the SPC and other product literature. The dossier takes into account current guidelines on pharmaceutical quality and the provisions of the pharmacopoeias. The formulation development and the manufacture of Comfortis (tablets for cats) are well described. The manufacturing process has been established and leads to a product of constant quality. Specifications set are relevant to control the quality of the product and the proposed shelf-life of 36 months has been substantiated by the findings of the stability study.

Comfortis tablets present a low risk for users and the environment and appropriate warnings have been included in the SPC and other product information.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for Comfortis tablets for cats is approvable. In view of the extension of the indications to the new target species (cats) it is considered necessary to restart the PSUR cycle.