EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 December 2013
EMA/18910/2014
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for NexGard (EMEA/V/C/002729/0000)

International non-proprietary name: Afoxolaner

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Introduction

The applicant MERIAL submitted on 16 October 2012 an application for marketing authorisation to the European Medicines Agency for NexGard, through the centralised procedure falling within the Article 3(2)a of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 11–13 April 2012 as NexGard contains a new active substance which was not authorised as a veterinary medicinal product in the Community on the date of entry into force of the Regulation. The rapporteur appointed was P. Hekman and co-rapporteur D. Murphy.

On 12 December 2013, the Committee for Medicinal Products for Veterinary Use (CVMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the veterinary medicinal product NexGard chewable tablets for dogs (11 mg, 28 mg, 68 mg and 136 mg).

The active substance of NexGard is afoxolaner, a new ectoparasiticide belonging to the isoxazoline group, which is systemically active against ticks and fleas. The benefits of NexGard are its efficacy in the treatment of flea and tick infestations on dogs. The product is in general well tolerated at the recommended dose, adverse reactions (gastrointestinal effects) were only observed in overdoses.

The recommended indication is:
"Treatment of flea infestation in dogs (*Ctenocephalides felis* and *C. canis*) for at least 5 weeks. Can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD).

Treatment of tick infestation in dogs *(Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus).* One treatment kills ticks for up to one month.

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. For fleas *(C. felis),* the onset of effect is within 8 hours of attachment. For ticks, the onset of effect (death) is within 48 hours of attachment."

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

On 11 February 2014, the European Commission adopted a Commission Decision for this application.

Scientific advice

The applicant did not seek scientific advice at the CVMP.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant provided a detailed description of the pharmacovigilance system which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

The active substance (afoxolaner) and the final product are mainly manufactured outside the EEA and in France, and batch released in the EU in France (Merial Chemin Du Calquet, Toulouse, France).

All relevant sites have valid manufacturing authorisations or valid GMP certificates, as appropriate. Therefore, no GMP inspections were deemed necessary within the scope of this application.

A satisfactory qualified person (QP) declaration has been issued by the QP at the site of batch release. The declaration is issued on foot of an audit of the site and is issued on behalf of all sites involved in the manufacture of the product.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites are considered to be in line with legal requirements.

Part 2 - Quality

Composition

NexGard chewable tablets for dogs are macrogol-based chewable tablets containing afoxolaner, a new ectoparasiticide active substance, in four strengths containing 11.3 mg, 28.3 mg, 68 mg or 136 mg of the active substance afoxolaner, suitable for administration to dogs with body weight ranges between 2 kg and 50 kg. The chewable tablets have a mottled red to reddish brown colour and are circular (lowest strength only) or rectangular shaped.

In addition to the active substance the chewable tables contain the following excipients: macrogol 400, potassium sorbate, triglycerides medium chain, povidone K-30, macrogol 4000, glycerol, macrogol 15 hydroxystearate, maize starch, soy protein fines, beef braised type flavour. Potassium sorbate is used as an antimicrobial preservative and beef braised type flavour is used as a flavouring agent. The excipients are widely used in veterinary medicinal products except for soy protein fines which are not routinely used in veterinary medicinal products.

Container

The primary packaging material is a blister card made of Aclar laminated PVC film with aluminium foil-paper baked. The packaging is considered standard for this type of dosage form. The primary packaging is suggested to be child-resistant. Since this is not specifically mentioned in the summary of product characteristics (SPC) this is not further considered.

The secondary packaging is a cardboard carton. Pack sizes of 1, 3 or 6 chewable tablets are available and justified by the posology.

Development pharmaceutics

The development of the product has been described, the choice of excipients is justified (except for the preservative) and their functions are explained. The inclusion of a preservative in the formulation has not been demonstrated to be necessary in accordance with European Pharmacopoeia (Ph. Eur.) section 5.1.3 and guideline CPMP/CVMP/QWP/115/95. The applicant is required to provide post authorisation appropriate data to demonstrate that the same formulation without any preservative does not pass the

Ph. Eur. testing for antimicrobial preservation. Should the data however support removal of the preservative from the formulation the appropriate variation will be submitted.

All clinical studies have been carried out with the proposed commercial formulation.

Method of manufacture

The chewable tablets are not produced by a conventional tableting process, but are moulded. The manufacturing process involves different pre-mixing steps of different combinations of components introduced successively into a mixer before final mixing of the dough. The dough is divided into portions which are then formed as soft 'chews' by passing through a forming machine. The size and mass of the tablets is determined by the size of the mould cavities in the forming machine. The chews are then matured in ovens to produce the final dosage form. The manufacturing process is well described. A summary of the process validation data conducted on three commercial scale batches of each tablet strength manufactured at the proposed site of manufacture has been provided. Process validation has been performed on every critical step of the manufacturing process. Process validation results on bulk storage, weight checks and primary packaging steps have also been provided. In accordance with the process validation results it is believed that commercial scale batches of each chewable tablet strength of consistent good quality will be manufactured at the proposed manufacturing site.

Control of starting materials

Active substance

The active substance is afoxolaner, a new chemical entity. It is a white to off-white powder of the isoxazoline class. The active substance possesses one chiral centre resulting in the formation of a racemate. Full documentation on the active substance has been included in the dossier.

The synthetic process is carried out in 3 chemical steps and using starting materials for the manufacture of afoxolaner. The choice of starting materials is appropriate and adequate characterisation data have been provided. Specifications, more detailed process information, validation results and physico-chemical characterisation will be provided. The critical steps have been described and are considered acceptable for the current synthesis. The discussion on the impurity profile of the active substance is thorough. Possible impurities and their occurrence in starting materials, intermediate and the final active ingredient have been discussed.

The active substance specification has been established in-house by the applicant. The specification is acceptable in view of the route of synthesis and the various quality guidelines. The limit for a specific impurity is qualified and specified at not more than 1.0%. The limits for the other specified impurities and the lower assay limit are considered acceptable. An updated active substance specification was provided that includes all the agreed amendments to the limits, including the tightened lower limit for assay of the active substance. Since afoxolaner is in solution within the finished product, particle size distribution is not relevant.

Batch analytical data demonstrating compliance with the proposed active substance specification have been provided for a number of commercial scale batches. The batches are stored in double low density polyethylene (LDPE) bags, closed with plastic seals and placed in high density polyethylene (HDPE) drums.

Stability results have been provided for afoxolaner at long-term conditions (25 °C /60% RH (relative humidity)) for 24 months, intermediate conditions (30 °C/65% RH) for 24 months and accelerated

conditions (40 °C/75% RH) for 6 months. The proposed re-test period of 36 months when stored below 30 °C is acceptable.

Excipients

The excipients macrogol 400, potassium sorbate, triglycerides medium chain, povidone K-30, macrogol 4000, glycerol, macrogol 15 hydroxystearate and maize starch comply with their current Ph. Eur. monographs.

The excipients soy protein fines, beef braised type flavour comply with in-house specifications. The specifications and limits are appropriate for these excipients and are considered to ensure identity, purity, and effectiveness of the material as a pharmaceutical excipient.

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

None of the starting materials used for production of the active substance afoxolaner or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 Rev.3).

Control tests during production

Not applicable.

Control tests on the finished product

The product specification includes tests for appearance, identity, assay, degradation products, uniformity of dosage units, preservative content, water content, dissolution and microbiological quality. The tests and limits on the specification are acceptable and in line with current guidelines. The analytical methods have been described in sufficient detail and have been appropriately validated according to International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) requirements.

Certificates of analysis have been provided for three pilot scale batches of each tablet strength manufactured at the proposed site of manufacture. All results comply with the specifications. Post-approval certificates of analysis of three consecutive full-scale batches of each tablet strength will be provided.

Stability

Stability studies at long-term conditions at 30 °C/65% RH (18 months) and accelerated conditions at 40 °C/75% RH (6 months) are provided. A significant reduction in preservative content is seen during shelf life and the limits for this parameter are therefore widened on the shelf life specification from those at release. The product has been demonstrated to be stable and only small increases in limits for total related substances and water content are required for the shelf life specification compared to those applied at release.

Based on the maximum allowable extrapolation of stability data, a shelf life of 30 months, with no specific storage condition is supported. Additional photostability and temperature cycling studies support the stability of the finished product packaged in its primary packaging.

Overall conclusions on quality

The dossier provides a suitable description of the active substance and the chosen formulation, and demonstrates that production of the active substance and the product leads to a stable product with consistent quality. The inclusion of a preservative in the formulation has not been demonstrated to be necessary in accordance with Ph. Eur. monograph 5.1.3 and CPMP/CVMP/QWP/115/95. The applicant is required to provide post-authorisation appropriate data to demonstrate that the same formulation without any preservative does not pass the Ph. Eur. testing for antimicrobial preservation. Should the data however support removal of the preservative from the formulation the regulatory measures will be initiated to change the dossier/product.

In general, the active substance and finished product specifications are appropriate and analytical methods are well described and satisfactorily validated.

Stability studies on the finished product have been performed according to VICH guidelines and support the shelf-life of 30 months with no specific storage conditions.

Recommendations for future quality development

In the context of the obligation of a marketing authorisation holder to take account of technical and scientific progress the CVMP recommends the following points for investigation:

1. The applicant should provide for two starting materials, specifications, more detailed process information, validation results and physico-chemical characterisation, once completed by 1Q 2014.
2. The applicant should submit post-approval certificates of analysis of three consecutive full-scale batches of each tablet strength.

Part 3 – Safety

Pharmacodynamics

The active substance of NexGard, afoxolaner, is an acaricide and insecticide belonging to the isoxazoline group. Isoxazolines act at the central nervous system or the neuromuscular junction of the insect, rather than directly on muscles fibres. Isoxazolines are potent inhibitors of the neurotransmitter gamma-aminobutyric acid (GABA) receptor function and work by blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarines.

Data provided show that a number of pharmacological differences exist between GABA gated chloride channels of insects and vertebrates and selectivity for insect over mammalian GABA receptors has been demonstrated for other isoxazolines. Also, *in vivo* studies provided by the applicant (repeat-dose toxicology in laboratory animals, target animal safety, field studies) did not show evidence of neurological or behavioural effects suggestive of GABA-mediated perturbations in mammals. The CVMP therefore concluded that binding to dog, rat or human GABA receptors is expected to be low for afoxolaner.

In vitro studies reported that afoxolaner can bind to dopamine and norepinephrine cellular transport receptor systems and the CB1 receptor. Inhibition of these catecholaminergic systems and certain types of competitive binding at CB1 receptors may mediate pharmacodynamic effects of diuresis, decreased food consumption, and decreased body weight in animals. The oral toxicity profile of

afoxolaner consists of a diuretic effect (rats only), effects secondary to a reduction in food consumption (rats and rabbits only) and occasional vomiting and/or diarrhoea (dogs, 120 and 200 mg/kg bodyweight (bw)) following high oral doses. No treatment-related effects on vomiting or diarrhoea were noted following oral doses of up to 31.5 mg/kg bw in the pivotal target animal safety study, nor in the EU field trial.

The ability of afoxolaner to kill fleas and ticks is confirmed in a series of efficacy studies (see Part 4). Based on the findings of these studies, it is accepted that:

- Afoxolaner is a potent acaricide and insecticide,
- Afoxolaner has a prominent feeding activity against ticks and fleas (that is, the primary route of exposure is via feeding),
- Afoxolaner demonstrated similar potency for both flea species tested, *Ctenocephalides felis (C. felis)* and *Ctenocephalides canis (C. canis).*

Pharmacokinetics

The applicant provided pharmacokinetic studies following oral administration in dogs.

Afoxolaner is rapidly absorbed from the gastrointestinal tract. In dogs administered doses varying from 1 to 4 mg/kg bw, T_{max} ranged from 2 to 12 hours; the mean C_{max} ranged from 538 (1 mg/kg bw) to 2,147 ng/ml (4 mg/kg bw); the mean half-life ranged from 7.7 to 17.8 days; and, the mean AUC_{inf} ranged from 7225 (1.0 mg/kg bw) to 30,107 day·ng/ml (4.0 mg/kg bw). After oral administration of 2.5 mg afoxolaner/kg bw bioavailability was calculated to be approximately 74%.

For the pivotal pharmacokinetic parameters, there was no significant difference between the fed and fasted state.

While a dose-dependent increase was seen for AUC_{inf} and C_{max} at doses up to 40 mg/kg bw, maximum plasma concentrations increased less than proportionally at higher doses (100 mg/kg bw and more). The dose proportionality is limited for afoxolaner due to solubility limited absorption.

In ivermectin sensitive Collies, C_{max} was markedly higher at a dose of 25 mg/kg bw compared to studies using Beagles receiving 20 mg/kg bw, 14,000 ± 4,000 ng/ml and 7,690 ± 1,920 ng/ml respectively. Also, afoxolaner appeared to have a longer half-life in Collies (mean of 33 days at a dose of 25 mg/kg bw) than in Beagles. However, there were no serious adverse events observed following the dose of 25 mg/kg bw (i.e. 10x the therapeutic dose) administered to Collie dogs. Using the longest half-life of 47.7 days, and the maximum exposure dose (following recommended use) of 6.3 mg/kg bw, the highest steady state afoxolaner plasma concentrations predicted in Collie dogs would not exceed the maximum exposure (100 mg/kg bw and higher) achieved in toxicology studies in the target animal.

Tissue distribution of afoxolaner is moderate: 2.9 ± 0.4 l/kg and 2.6 ± 0.6 l/kg after intravenous administration of 0.25 or 1.0 mg/kg bw, respectively.

Clearance was low with 8.47 ± 1.18 ml/h/kg after an intravenous administration of 0.25 mg/kg bw afoxolaner in dogs; i.e. less than 1% of the hepatic blood flow. Systemic clearance of 5.0 ± 1.2 ml/h/kg was calculated after intravenous administration of 1.0 mg afoxolaner/kg bw.

Thirty days after administration of 1.5, 2.5 or 3.5 mg afoxolaner/kg bw, plasma concentrations were below 400 ng/ml in all groups. As lean dogs are known to have a more rapid depletion rate, a separate study compared the pharmacokinetics of Beagles with Greyhounds (very low body fat percentage).

However, the results showed that only a slightly higher dose (2.76 mg/kg bw) in lean dogs would be required to achieve a similar plasma level at 30 days to that expected for Beagles administered a dose of 2.5 mg/kg bw.

A protein binding study demonstrated that over 99% of afoxolaner is bound to plasma proteins in cats, dogs and rats. This high level of protein binding of afoxolaner was consistent across different concentrations (200–10,000 ng/ml). Concentrations of 10,000 ng/ml did not saturate protein binding sites and had the same protein binding percentage observed at 200 ng/ml. Afoxolaner does not have a high potential for saturable protein binding. This is consistent with the results from the US and EU field trials in which a number of concomitant medications were administered (e.g. NSAIDs (non-steroidal anti-inflammatory drugs), antibiotics, anxiolytics, antihistamines and anaesthetics) to treated animals and no evidence of interactions was noted. Therefore it was considered that afoxolaner does not form a real risk for displacement of drugs with high protein binding capacities.

Puppies of 8 or 9 weeks receiving an oral exposure dose of up to 32 mg/kg bw 3 times at monthly intervals did not demonstrate a significant difference between plasma concentrations measured at Days 27, 55 and 83 (that is, no evidence of accumulation).

Adult dogs receiving three doses of 2.5 mg/kg bw at monthly intervals by oral gavage showed no signs of dose accumulation.

The relationship between afoxolaner concentration in plasma and efficacy was explored following oral administration of afoxolaner in two dose characterisation studies. In both studies, the efficacy of three doses of afoxolaner (1.5, 2.5 and 3.5 mg/kg bw) against fleas (*C. felis*) and ticks (*Dermacentor variabilis* (*D. variabilis)* or *Rhipicephalus sanguineus (R. sanguineus)*) were investigated. A direct relationship between plasma concentration and per cent of effectiveness relative to control dogs was modelled using a Sigmoidal Emax model. The following afoxolaner EC_{90} (effective concentrations) were determined:

- *C. felis* 23 ng/ml
- *R. sanguineus* 91 ng/ml
- *D. variabilis* 110 ng/ml

The findings from these studies suggest that all dogs administered a single 2.5 mg afoxolaner/kg bw oral chewable formulation will have afoxolaner plasma concentrations above the EC_{90} for fleas (*C. felis*, >25 ng/ml), and most dogs will have afoxolaner plasma concentrations above the EC_{90} for ticks (*R. sanguineus* and *D. variabilis*, >110 ng/ml) on Day 28 after administration.

Afoxolaner in dogs is metabolised into various metabolites, the major ones being a hydroxylate and a glucuronide. The metabolites and parent compound are eliminated mainly via biliary excretion (biliary clearance is about 30%) and to a lesser extent via urine (renal clearance less than 0.01% of the total clearance).

Toxicological studies

Single dose toxicity

A well performed acute oral good laboratory practice (GLP) toxicity study was conducted in rats. No severe effects were observed at doses of up to 1,000 mg afoxolaner/kg bw (oral LD_{50} > 1,000 mg/kg bw). Significant effects on bodyweight and/or food consumption were observed at dose levels of 100, 300 and 1,000 mg/kg bw, resulting in a no-observed effect level (NOEL) of 30 mg/kg bw. However, as the effects on body weight were minimal (max. 6.5% reduction at a dose of 300 mg/kg bw) and

rapidly reversible at 100 and 300 mg/kg bw, a no-observed adverse effect level (NOAEL) of 300 mg/kg bw is acceptable based on this study.

A single dose acute dermal toxicity study (limit test: dose 2,000 mg/kg bw) using the active substance was performed in rats. The dermal LD_{50} is > 2,000 mg/kg bw. Adverse effects (abnormal gait and stance, decreased body tone, piloerection) were observed at this dose in this study, though these effects were not severe or irreversible.

In conclusion, afoxolaner is of low acute oral and dermal toxicity. The acute toxicity studies were conducted in line with relevant The Organisation for Economic Co-operation and Development (OECD) guidelines and in accordance with GLP.

Repeat-dose toxicity

In rats, a well performed 14 day oral toxicity (gavage) was conducted using doses up to 1,000 mg afoxolaner/kg bw/day. At 30 mg/kg bw substance-related lower food intake (resulting in decreases in bw) and inanition occur (i.e. transient haemoconcentration, decreased absolute reticulocytes, neutrophil and monocytes-counts, decreased absolute weight of heart and kidney). An oral NOAEL of 10 mg/kg bw/day was derived from this study.

In mice, receiving either 10, 30, 100 or 550 mg/kg bw orally over 7 or 12 day, no mortality occurred and there were no clinical signs of toxicity and no effects on body weight, food consumption or pathological findings were found. The oral NOEL in mice was considered 550 mg/kg bw/day. In rabbits, administration of 300 or 1,000 mg afoxolaner/kg bw/day for four days resulted in reduced food consumption and loss of body weight gain. In cats, administration of up to 100 mg/kg bw twice, with a week interval, did not lead to mortality or any other effects on body weight, food consumption, haematology, serum chemistry and urinalysis parameters compared to the control group.

A 56-day repeated dose acute dermal toxicity study was performed in rats in accordance with OECD guideline 410. The dose level of 3 mg/kg bw was increased to 60 mg/kg bw on study Days 28–55. Significant adverse effects were observed in the 30 mg/kg bw group. A NOAEL of 10 mg/kg bw can also be established for the dermal toxicity study.

From another dermal toxicity study in cats it appears that afoxolaner may cause adverse liver effects (centrilobular vacuolation, biliary hyperplasia and/or hepatocellular necrosis, only in females) in all dose groups including the lowest dose of 10 mg/kg bw. In this study the test substance was administered once a month during 6 months. However, it is recognized that cats are a unique species considering the metabolic system when compared to e.g. rats, dogs and human. For instance, cats have a deficient glucuronidation. Moreover, in another toxicity study in cats using a 2 once-weekly oral dose up to 100 mg/kg bw, no dose-related adverse effects on liver were observed. Hepatocellular vacuolation was also not observed in the other, more relevant, species tested. Therefore, the liver effects observed in the dermal study in cats are considered not relevant for user and/or target animal safety.

For further toxicology studies in dogs, see below ("tolerance in the target species of animal").

In summary, both the oral and dermal NOAEL can be established at 10 mg afoxolaner/kg bw/day for repeated exposure. This is conceivable as the bioavailability for oral and dermal exposure is similar. The repeat-dose toxicity studies were conducted in line with relevant OECD guidelines and in accordance with GLP.

Tolerance in the target species

One pivotal GLP study and several supportive non-GLP studies were provided.

In the pivotal GLP compliant target animal safety (TAS) study, puppies (aged 8 or 9 weeks, 8 puppies per treatment group) received doses of 6.3, 18.9 and 31.5 mg afoxolaner/kg bw (i.e. approximately 1x, 3x and 5x the maximum recommended therapeutic dose (RTD) once monthly for 3 months, followed by a further 3 administrations at two week intervals. The study was conducted in accordance with VICH GL 43.

No mortalities occurred, and no test article related changes were seen in clinical parameters, daily food consumption, body weight, haematology and urinalysis parameters or plasma chemistry values. Therefore, it was concluded that afoxolaner is well tolerated in puppies at an age of 8 weeks.

In addition to the pivotal TAS study, several other non-GLP compliant supportive studies were provided.

In an exploratory pharmacokinetic/safety study, Collies sensitive to ivermectin (MDR1-Collies) were treated orally with 25 mg afoxolaner/kg bw. Afoxolaner was generally well tolerated confirming that P-glycoprotein does not play a role in afoxolaner transport. One treated animal had diarrhoea and one animal vomited 6 hours after administration.

In a repeat-dose toxicity study, Beagle dogs were orally administered doses of afoxolaner up to 25 mg/kg bw once every other week for 70 days. The NOEL was established to be 15 mg/kg bw and the NOAEL was 25 mg/kg bw per two week interval in these dogs (based on a significantly lower mean urine specific gravity values for two males in the 25 mg/kg bw group).

A repeat-dose toxicity study in dogs administered 2.5, 25 or 100 mg/kg afoxolaner orally on Day 0 and Day 7 did not result in any test article related effects on clinical signs, body weight, food consumption, clinical pathology parameters and necropsy. None of the dogs died.

Another repeat-dose toxicity study, evaluated the effects of high doses of afoxolaner (40, 120 and 200 mg afoxolaner/kg) in dogs, administered orally three times at eight week time intervals. In dogs receiving doses of 120 and 200 mg/kg bw, vomiting was observed in the 24 hours following treatment. Some dogs also exhibited diarrhoea. Female dogs in the treatment groups had lower food consumption compared to the control group, however no weight loss could be observed. Males and females in the group receiving 200 mg/kg bw had a lower food intake the first week after treatment (C_{max} was 21,600 ± 11,700 ng/ml). Haematology, serum chemistry and physical examination parameters did not demonstrate dose dependent changes.

Conclusions

Afoxolaner appears to have been well tolerated when administered to Beagle puppies (8 weeks of age at the start of the pivotal tolerance study at 1x, 3x and 5x the maximum exposure dose of 6.3 mg/kg bw at three, one-month dose intervals and three, two-week dose intervals. All puppies survived until the scheduled necropsy. Based on the data presented, there was no evidence of test article-related alterations in food consumption; body weight; physical examination variables (heart rate, respiratory rate, body temperature); anatomical or clinical pathology findings; or clinical abnormalities.

Additional tolerance data is available from a number of dose determination/confirmation studies along with tolerance data from four field studies. Tolerance to dose rates of up to 200 mg/kg bw has been investigated as well as a re-treatment interval less than that recommended. It would appear from the data presented that the candidate formulation was in general well tolerated (apart from sporadic vomiting and diarrhoea reported in a number of studies and more notably at higher dose rates:

diarrhoea and vomiting was observed at approximately 5x overdose (25 mg/kg bw) in Collies, and at higher doses (120 and 200 mg/kg bw) in Beagles.

Reproductive toxicity

Developmental toxicity studies were conducted in rats and rabbits. These studies were conducted in accordance with GLP and the relevant OECD guideline.

In two studies, administration of afoxolaner to rats daily from gestation Day 6 to Day 19 resulted in lower mean body weight gains, hair loss and reductions in food consumption during the treatment period at doses of 3, 5, 10, 25, 30 and 50 mg/kg bw/day. Two females (30 mg/kg bw/day) and one female (50 mg/kg bw/day) were euthanized due to body weight losses. Mean combined foetal weights in groups administered 25, 30 and 50 mg/kg bw/day were 11.1% lower than control values; however no significant differences in this parameter were found for groups administered 5 and 10 mg/kg bw/day. There was no evidence of foetal malformation at any dose tested. In this study, the NOAEL for embryo/foetal development was considered to be 10 mg/kg bw/day.

In two studies in rabbits, afoxolaner was administered at doses of 3, 10, 15, 30 and 45 mg/kg bw/day to females from gestation Days 7 through 28. Lower mean body weight gains together with reduced food consumption were noted in groups administered 10, 15, 30 and 45 mg/kg bw/day. Mean foetal weights were 19.4 and 18.5% lower than the control group in the 10 and 30 mg/kg bw/day groups respectively. Two females (45 mg/kg bw/day) and 1 female (3 mg/kg bw/day) aborted on gestation Day 28 as a result of marked body weight losses. There was no evidence of foetal malformation or developmental variations at any dose tested.

Reproductive toxicity studies were conducted in rats. These studies were conducted in accordance with GLP and the relevant OECD guideline.

Female rats were administered 1, 3, 5, 10, 20, 30 or 75 mg afoxolaner/kg bw/day from 7 or 14 days prior to mating until the end of lactation and males were administered the same doses during mating from 70 days prior to mating.

The 75 mg/kg bw/day group had marked weight losses and were euthanized in the first week. Sixty seven per cent of the females in 30 mg/kg bw/day group had total litter loss during lactation. In female rats receiving daily doses of 20 or 30 mg/kg bw/day, decreases in food consumption and mean body weight gain could be observed. Also a lower mean number of implantation sites were noted in these groups. Lower mean number of F1 pups born, lower body weights of the pups were noted, litter losses and lower live litter size were observed. No pathological findings on the pups that died during lactation were noted.

In 10 mg/kg bw/day group, females had lower mean body weight gain prior to mating and one animal (3 mg/kg bw/day) had a litter loss during lactation. Necropsy on these pups did not reveal any cause of death.

No test article effects were noted on reproductive performance, oestrus cycle length, gestation length, fertility (both females and males) or the process of parturition. No macroscopic or microscopic findings or effects were noted in both parents and in pups.

Based on the findings of these studies, afoxolaner has no effect on reproductive performance at doses up to 5 mg/kg bw/day. Doses of 20 mg/kg bw/day were associated with effects on implantation rate, litter size, litter loss during lactation and pup weight.

Mutagenicity/genotoxicity

Afoxolaner was negative in the bacterial reverse mutation test, and in the mouse lymphoma mutagenesis assay.

Afoxolaner was tested in a mouse bone marrow micronucleus test following oral administration at a dose of 500, 1,000 and 2,000 mg/kg bw (single dose). The study was performed in accordance with OECD guideline 474. Bone marrow was used, no data were available on the peripheral blood. Samples were taken at 24 and 48 hours. From the PCE/total erythrocyte ratio, it can be concluded that no bone marrow cytotoxicity occurred at any of the doses. Afoxolaner did not induce micronucleus formation at 500 and 1,000 mg/kg bw 24 hours (which is in general the standard sampling time for bone marrow). At 48 hours post dose, afoxolaner did not induce micronucleus formation at any dose. A statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (MPCEs) in bone marrow was observed at 2,000 mg/kg bw 24 hours post-dose, which did not fall within the spontaneous historical range. However, at the oral dose of 1,000 mg/kg bw elevated bone marrow MPCEs were not observed, while the systemic exposure to afoxolaner was similar for this dose when compared to the 2,000 mg/kg bw dose. Moreover, after 48 hours elevated bone marrow MPCEs were not observed, while prolonged exposure to afoxolaner (at least up to 36 hours) due to its long half-life *in vivo* was demonstrated.

Given that other genotoxicity tests with afoxolaner were negative, there are no structural alerts for afoxolaner, and it is acknowledged that induction of MNPCE may be caused by other factors than intrinsic genetic toxicity (although not proven for current test), it is concluded that afoxolaner is not genotoxic.

Carcinogenicity

Carcinogenicity studies have not been conducted with afoxolaner. This is acceptable as afoxolaner has no structural alerts and is not considered to be genotoxic.

Studies of other effects

Dermal irritation:

A dermal irritation study using the active substance was performed in rabbits. This study was performed in accordance with OECD guideline 404. Although the performed study showed some shortcomings, it suggests that afoxolaner is not an irritant.

Eye irritation:

An eye irritation study using the active substance was performed in rabbits. This study was performed in accordance with OECD guideline 405. Some eye irritating effects occurred after administration of afoxolaner, which were reversible within 72 hours. Therefore, it is concluded that afoxolaner may be slightly irritating to the eye.

Skin sensitisation:

A local lymph node assay using the active substance was performed in mice. This study was performed in accordance with OECD guideline 429. From this study, it can be concluded that afoxolaner does not have skin-sensitising activity.

Conclusions

Afoxolaner is not irritating to the skin of rabbits, and is not considered to have sensitising properties. Afoxolaner is considered to be slightly irritating to the eyes.

User safety

The applicant has presented a User Safety Risk Assessment which has been conducted in accordance with CVMP guideline EMA/CVMP/543/03-Rev.1.

Hazard characterisation:
Systemic toxicity of this product is determined by its active substance afoxolaner as the excipients are of low toxicity and/or present at low concentrations. Local reactions (i.e. irritation, sensitisation) are not expected taking into consideration the concentrations of the substances present in the product, the pharmaceutical formulation of this product (i.e. a tablet), and the anticipated level of exposure.

Exposure assessment:
Exposure may occur during opening or accessing the product and administration of the product to the animal. Anticipated users are pet-owners (administering the product) and children (which may accidentally get access to the product). The most relevant routes are dermal exposure for adults and oral ingestion for children. Also eye contact due to hand-to-eye contact and oral contact due to hand-to-mouth contact may occur if personal hygiene measures (i.e. wash hands after administration) are not maintained. Adults can become exposed every time they administer the tablets, which is at monthly intervals according to the treatment schedule.

Given that the tablets should not be broken/split, the potential for inhalation of dust is considered negligible. Children may become exposed by ingesting the product; however, the packaging (blister pack containing one to six individually sealed tablets) will likely limit child access and the tablets are usually not removed from the packaging until immediately prior to administration. The anticipated (external) dose caused by accidental intake of a large size tablet (136.1 mg afoxolaner) by a child (15 kg) is 9.1 mg afoxolaner/kg bw.

No quantitative risk characterization is performed for dermal exposure after handling the product by adults.

User risk/safety assessment:
The single oral study in rats is considered the most relevant study for the risk characterization of accidental intake of a tablet by a child. The NOAEL for this study was 300 mg/kg bw. This would result in a margin of exposure (MOE) of 33 (300/9.1), which is below the acceptable MOE of 100. However, for this substance it is acknowledged that the adverse effects are not severe or irreversible and most probably related to the decreased food consumption. Therefore, the calculated MOE of 33 is acceptable. Furthermore, the blister packaging and advice for removal/storage minimise the risk of accidental ingestion by children.

Considering the infrequent administration of the product (once a month), the consequent infrequent user exposure and the toxicological profile of afoxolaner, the potential for dermal exposure to result in adverse effects is considered negligible.

Risk management and risk communication:
The packaging of the product and the recommendation with respect of removing/storing the tablet (only removing one tablet for use from blister/return blister with remaining tablets to carton) is considered sufficient to prevent accidental exposure by children.

Conclusions:
Based on the data presented, the product does not pose an unacceptable risk to the user, which are pet-owners (administering the product) and children (when getting accidentally access to the product), when used in accordance with the SPC.

Environmental risk assessment

A Phase I environmental impact assessment was provided in line with the Guideline on Environmental Impact Assessment for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-FINAL). According to the Phase I decision tree, no Phase II assessment is required since the product is intended for the treatment of non-food producing animals only, and furthermore, the treatment is given on an individual basis; therefore exposure of the environment to the product is considered insignificant.

The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Pharmacodynamics: Afoxolaner is a potent inhibitor of the GABA receptor function with a high binding to arthropod receptors, blocking pre- and post-synaptic transfer of chloride ions across cell membranes. This results in uncontrolled activity of the central nervous system and death of insects or acarines. Binding of afoxolaner to mammalian GABA receptors is expected to be low.

Pharmacokinetics: Following oral administration, afoxolaner is rapidly absorbed with a mean C_{max} in plasma after 2–4 hours. Tissue distribution is moderate, and plasma clearance is low; the terminal plasma $T_{1/2}$ is approximately 2 weeks in dogs. Metabolites and parent compound are eliminated mainly via faeces. At 10 times the recommended treatment dose, C_{max} and $T_{1/2}$ were markedly higher in Collies with deficient multidrug-resistance-protein 1 than compared to Beagles (although this had no clinical implications).

Single dose toxicity: An oral LD_{50} of > 1,000 mg afoxolaner/kg bw and an NOAEL of 300 mg/kg bw in rats could be derived, concluding that afoxolaner has a low acute toxic potential.

Repeat-dose toxicity: Both the oral and dermal NOAEL can be established at 10 mg/kg bw/day.

Target animal tolerance: Dogs tolerated afoxolaner well, even at 5x RTD, at an age of 8 weeks for 6 consecutive treatments with 1-month or 2-week interval.

Reproductive toxicity: Besides litter losses during lactation, afoxolaner at low doses (3–5 mg/kg bw/day) seems relatively unharmful for reproduction and foetal development. However, in higher doses (20–30 mg/kg bw/day) effects were noted in female rats (weight loss and reduced food consumption) and their off-spring (lower mean numbers of implantation sites, F1 pups born, lower body weights of the pups, litter losses and lower live litter size).

Genotoxicity: Afoxolaner is considered to be non-genotoxic.

Carcinogenicity: Carcinogenicity studies have not been conducted with afoxolaner which is acceptable as afoxolaner has no structural alerts and is not considered to be genotoxic.

Other effects: Afoxolaner was non-irritating to the skin of rabbits, and is considered to have no sensitising properties. Afoxolaner is considered to be slightly irritating to the eyes.

User safety: When used in accordance with the SPC, the product is not expected to pose an unacceptable risk to the user.

Environmental risk assessment: The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

See Part 3.

Development of resistance

Afoxolaner is a new active substance; there is no known resistance to the substance among the target tick and flea species listed. No studies were provided. This was considered acceptable.

Pharmacokinetics

See Part 3.

Palatability

A study was provided investigating the palatability of two experimental formulations, one being essentially similar in this respect to the final formulation. Thirty mixed breed dogs were randomised to one of five treatments (Heartgard Plus, two placebos or two test formulations). The tablets were palatable to most dogs.

Pre-clinical studies

General study design

All preclinical efficacy studies in dogs were performed according to the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.2).

For ticks: The test product was administered on Day 0. Infestations, using approximately 50 unfed adult ticks, were conducted on Day –1 and every week after treatment. Ticks were counted and removed approximately 48 hours after treatment (therefore 3 days after first infestation) and 48 hours after subsequent infestations. During counting, the dog was completely palpated for ticks.

For fleas: Infestations, using approximately 100 unfed adult fleas, were conducted one day prior to treatment (Day 0) and every week after treatment. 12–24 hours after treatment or infestation, fleas were counted and removed by combing the entire dog for at least 10 minutes. Flea eggs were counted by using a collecting pan placed under the pen of each dog. The pans were left in place for approximately 12 hours or 24 hours before counting.

Efficacy assessment

In all performed efficacy studies, calculation of efficacy has been conducted using the Abbott's formula and was based on arithmetic mean counts.

The efficacy assessment for fleas was conducted in line with recommendations of the CVMP guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.2) and accepted as appropriate.

However, for ticks, the assessment of efficacy deviated from the standard approach described in the CVMP guideline in that the assessment does not take account of attached engorged dead (Category 6) ticks. The current CVMP guideline only addresses the evaluation of acaricides that are topically applied, and not those for systemic use. The applicant therefore proposed an alternative approach for assessment of efficacy to that detailed in the current CVMP guideline, in line with proposals outlined in the published The World Association for the Advancement of Veterinary Parasitology (WAAVP) "Guidelines for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestations on dogs and cats (Marchiondo et al., 2013)". This approach does not follow the categorisation outlined in the above CVMP guideline, but only focuses on live (failure) and killed (success) ticks (i.e. excluding category 6 ticks).

The CVMP considered this approach and agreed that it could in principle be accepted for orally administered acaricides provided that the product information clearly states that: the use of the product is for treatment only (not preventive use); ticks and fleas must attach to the host and commence feeding in order to be exposed to the active substance; and parasites need to start feeding on the host to become exposed to afoxolaner (therefore, the risk of the transmission of parasite-borne diseases cannot be excluded).

Dose selection

The findings from pharmacokinetics/pharmacodynamics studies (see Part 3) suggest that all dogs administered a single chewable tablet at a dose of 2.5 mg afoxolaner/kg bw will have afoxolaner plasma concentrations above the EC_{90} for fleas (*Ctenocephalides felis (C. felis)*, > 25 ng/ml), and most dogs will have afoxolaner plasma concentrations above the EC_{90} for ticks (*Rhipicephalus sanguineus (R. sanguineus) (*> 91 ng/ml*)* and *Dermacentor variabilis (D. variabilis)*, (> 110 ng/ml)) on Day 28 after administration. These data suggest that a dose of 2.5 mg afoxolaner/kg bw is appropriate to take forward to clinical efficacy testing. In addition, these results suggest that *Dermacentor* may be the least sensitive ectoparasite, and *Dermacentor reticulatus* was therefore chosen for the pivotal dose finding study.

The pivotal dose finding study, investigating oral doses of 0, 1, 2.5 and 4 mg afoxolaner/kg bw over 37 days, demonstrated that 4 mg afoxolaner/kg bw was effective when treatment is conducted at an interval of 28 days, with ticks being killed within 48 hours after infestation. In this dose finding study, a dose of 2.5 mg/kg bw showed sufficient efficacy against *Dermacentor* spp. for 23 days.

Dose confirmation

Fleas

Four studies were conducted in accordance with Guideline EMEA/CVMP/EWP/005/2000-Rev.2 to investigate the efficacy of an oral dose of 2.5 mg afoxolaner/kg bw against *C. felis* and *C. canis*. In all

studies, efficacy against fleas exceeded 95% within 24 hours after infestation and this effect persisted for in excess of 30 days.

Speed of kill:
Based on the speed of kill studies submitted with the original dossier, efficacy against fleas approaches 100% at 8 hours and thereafter.

Egg counts:
Two studies included the evaluation of efficacy of afoxolaner to reduce egg production both in *C. felis* and *C. canis*. For all counts performed at or beyond Day 7, efficacy was 100% for all time points through Day 35 for *C. canis*. It was also the case for *C. felis* except for Day 14 (99.8%).

Ticks

The applicant provided a number of dose confirmation studies investigating the efficacy of afoxolaner (2.5–3.1 afoxolaner/kg bw) in different European tick species.

When efficacy is evaluated based simply on the live/dead status of ticks and using arithmetic mean data, the following can be concluded from the dose determination/confirmation studies conducted in those species of tick:

Ixodes ricinus
Two dose confirmation studies were provided.

In both studies, immediate efficacy was confirmed. Persistent efficacy was confirmed for 30 days (one study) and 37 days (one study).

Rhipicephalus sanguineus
Two dose confirmation studies were provided.

In both studies, immediate efficacy was confirmed. Persistent efficacy was confirmed for 37 days.

Dermacentor reticulatus
One dose determination study and three dose confirmation studies were provided.

In all four studies, immediate efficacy (> 90% by 48 hours after treatment) was confirmed. Given that persistent effect for up to 30 days was demonstrated in two dose confirmation studies (three studies, if the 72 hour observation is taken into account) and this was confirmed for ticks generally (including *D. reticulatus*) in the European field study, CVMP accepted a claim for persistent effect of 30 days for *D. reticulatus*.

In conclusion, the following tick indication can be accepted:

> "Treatment of tick infestation in dogs (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus).* One treatment kills ticks for up to one month."

In addition to the European tick species, the applicant also provided studies investigating the efficacy of afoxolaner (2.5–3.1 afoxolaner/kg bw) against tick species exotic to Europe.

- For *D. variabilis* and *Ixodes scapularis,* two dose confirmation studies were provided for each tick species. In all studies, immediate efficacy was confirmed. Persistent efficacy was confirmed for 30 days for *D. variabilis and* 37 days for *I. scapularis*.
- For *Amblyomma americanum*, four dose confirmation studies were provided, although three studies were considered inadequate for efficacy assessment as tick counts were conducted at 72 hours (rather than the 48 hours recommended in the guideline) and/or inadequate infection in the

control group. For the one remaining study, immediate efficacy was confirmed and persistent efficacy was confirmed for 23 days.

Overall conclusions on dose finding/confirmation:
Afoxolaner is a potent insecticide and acaricide. Based on the data provided, the CVMP considered that a dose of at least 2.5 mg afoxolaner/kg bw was effective in the treatment of flea and tick infestations.

The following can be accepted as part of the indication:

Treatment of flea infestation in dogs (*Ctenocephalides felis* and *C. canis*) for at least 5 weeks. For fleas (*C. felis*), the onset of effect is within 8 hours of attachment.

Treatment with afoxolaner effectively killed fleas, and resulted in a reduction of egg counts in the environment of the dog. Consequently, the product can be recommended to be used as part of the treatment strategy against flea allergy dermatitis (FAD).

Treatment of tick infestation in dogs (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus).* One treatment kills ticks for up to one month.

Field trials

Four field trials were conducted, one located in Europe, one in the USA, and two studies in Japan. For evaluation of efficacy, the European study is considered pivotal.

European field efficacy study – flea and/or tick infestation

The pivotal GCP study in fleas and/or ticks was conducted in Europe in 2012 at 7 locations in 4 countries (Albania, Hungary, Germany and France). The study followed a positive control, partially blinded randomized block design. The positive control was a topical administration of pyriprol. 146 dogs (pure breeds and crossbreeds; 68 males and 78 females. Age: 3 months–16 years. Weight: 3.4–48.2 kg on Day 0) with natural infestation of fleas and/or ticks were enrolled in this study.

One dog per household was randomly selected to be treated with either afoxolaner (at the recommended dose of 2.7–6.7 mg/kg bw) or a positive control, pyriprol. Any co-housed animals were treated with another product containing fipronil and methoprene. In total 146 dogs with natural flea and/or tick infestations enrolled this study.

Approximately the same number of dogs were natural infested with fleas (*C. canis* (41 dogs treated with afoxolaner versus 38 dogs treated with pyriprol), *C. felis* (26 and 18), *Archaeopsylla erinacei* (2 and 2), and *Pulex irritans* (5 and 6)) and ticks (*Dermacentor reticulatus* (13 and 13), *I. ricinus* (10 and 6) and *R. sanguineus* (12 and 11)).

Study design: One treatment was conducted on Day 0. The primary variable was efficacy at Day 30 compared to baseline. Fleas and ticks were counted and removed at the Day 7, 14, and 21 visits, and were also compared to baseline.

Results: No test article related adverse events were observed.

At all-time points (Day 7, 14, 21 and 30), per cent efficacy of afoxolaner against ticks was more than 98%, and against live fleas efficacy was at least 97.9%. Afoxolaner was not inferior to the positive control containing pyriprol.

Based on the findings of this study, it was concluded that NexGard chewable tablets for dogs were efficacious for 30 days against ticks (*D. reticulatus, I. ricinus* and *R. sanguineus*) and fleas (*Ctenocephalide*s spp.) on naturally infested dogs.

US study – fleas

The GCP study, conducted in 2012 in the USA, was a positive controlled, blinded, multicentre, clinical safety and efficacy study using a randomized block design, focussing on flea efficacy. Dogs were naturally infested with *C. felis*. It was noted that data from a number of animals was excluded from efficacy calculations thus an intention-to-treat analysis has not been followed and consequently, results may be biased. As positive control spinosad was used, dosed and orally administered according to the label. In multiple dog households all dogs were treated with either afoxolaner or spinosad.

Dogs were treated on Day 0, 30 ± 4 and 60 ± 4. Flea counts were performed and fleas removed prior to treatment at Day 0, and on Days 30 ± 4, 60 ± 4 and 90 ± 4.

Afoxolaner was in general well tolerated. Afoxolaner was administered in conjunction with anthelminthics, antibiotics, vaccines, steroids, NSAIDs and other veterinary products. None of these medications impacted the efficacy or safety results of afoxolaner.

Study results showed that efficacy was more than 95% at all-time points (Day 30, 60 and 90) following treatment.

In addition to the European and US studies, the applicant also provided further studies undertaken in Japan to investigate efficacy of afoxolaner compared to spinosad in dogs with natural flea infestations (both *C. felis* and *C. canis*) or natural tick infestations (*Haemaphysalis flava*, *H. longicornis, H. ias, H. campanulata and Ixodes ovatus*). Although the studies showed non-inferiority towards the positive control, the tick species are not common in Europe, and the study was therefore only considered as supportive.

Overall conclusion on efficacy

Based on the data presented, it is evident that afoxolaner is a potent insecticide and acaricide.

A palatability study demonstrated that the product is palatable to most dogs.

Afoxolaner was well tolerated.

In all field studies afoxolaner given at the recommended dose (single treatment with 2.7–6.7 mg/kg bw) was non inferior to the positive control (either spinosad or pyriprol). Efficacy of afoxolaner, comparing ectoparasite-counts on Day 2 or Day 30 with baseline counts on Day 0, was more than 95% against fleas and more than 90% against ticks, meaning that the efficacy was sufficient according to the CVMP guideline EMEA/CVMP/EWP/005/2000-Rev.2.

Treatment with afoxolaner effectively killed fleas, and resulted in a reduction of egg counts in the environment of the dog. Consequently, the product can be recommended to be used as part of the treatment strategy against FAD.

Part 5 – Benefit-risk assessment

Introduction

NexGard chewable tablets contain a new active substance afoxolaner and are presented in four strengths (11.3, 28.3, 68.0 and 136.0 mg) in blisters of 1, 3 or 6 tablets per carton. The product is indicated for the treatment of tick and flea infestations in dogs, the route of administration is oral use.

Benefit assessment

Direct therapeutic benefit

Afoxolaner is a potent insecticide and acaricide.

When administered to dogs at the recommended dose (2.7–6.9 mg/kg bw), there is immediate efficacy against fleas (*Ctenocephalide*s spp.) within 8 hours after treatment, and this effect persisted for up to 5 weeks.

For ticks (*D. reticulatus, I. ricinus* and *R. sanguineus*), the onset of effect is within 24 hours of attachment, lasting up to 4 weeks.

Additional benefits

Additionally, the effective control of fleas on treated dogs will directly benefit the risk of infestation of other animals in contact with infested dogs.

NexGard may administered by the animal owner at home. The presentation is a chewable tablet formulation which has been designed to be palatable for most dogs. The method and route of administration of the product may be considered an additional benefit in that there is limited potential for the user to be exposed to the active substance.

Risk assessment

The product is well tolerated when administered to the target species at the recommended treatment dose. At large overdose (5x) only mild adverse events like diarrhoea and vomiting can be observed.

It is not expected that the product will pose an unacceptable risk to the user when used in accordance with SPC recommendations.

It is not expected that the product will pose a risk to the environment when used in accordance with SPC recommendations.

Risk management or mitigation measures

Warnings and other risk management measures have been included in the SPC to mitigate possible risks to the user, target animal and the environment.

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 indication:

"Treatment of flea infestation in dogs (*Ctenocephalides felis* and *C. canis*) for at least 5 weeks. Can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Treatment of tick infestation in dogs (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus).* One treatment kills ticks for up to one month.

Ticks (and fleas) must attach to the host and commence feeding in order to be exposed to the active substance. For fleas (*C. felis*), the onset of effect is within 8 hours of attachment. For ticks, the onset of effect (death) is within 48 hours of attachment."

The formulation and manufacture of NexGard is well described and specifications set will ensure that product of consistent quality will be produced.

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings have been included in the SPC.

Conclusion on benefit-risk balance

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of NexGard are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended. The overall benefit-risk evaluation is deemed positive with sufficiently clear and complete product information.