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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for Cheristin (EMEA/V/C/004316/0000)

Common name: spinetoram

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

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Introduction

The applicant Elanco Europe Ltd submitted on 1 September 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Cheristin, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 8 October 2015 as Cheristin contains a new active substance (spinetoram) which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "for the treatment and prevention of flea infestations (*Ctenocephalides felis*) in cats". The target species is cats.

The active substance of Cheristin is spinetoram, a multicomponent tetracyclic macrolide of the spinosyn family, which has an insecticidal activity by activation of nicotinic acetylcholine receptors (nAChRs).

Cheristin spot-on solution contains 130 mg/ml spinetoram and is available as a unit dose pipette delivering 91 mg of spinetoram (in 0.7 ml of product). The product is presented in aluminium blister packs packed into carton boxes containing 3 or 6 pipettes.

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

On 29 March 2017, Elanco Europe Ltd withdrew the application during the clock-stop at day 120 of the procedure. In its letter notifying the Agency of the withdrawal of application, the applicant stated that the reason for the withdrawal is the nature of the major objections.

Scientific advice

The applicant received scientific advice from the CVMP on 13 December 2012. The scientific advice pertained to safety aspects of the dossier.

The applicant has in general followed the scientific advice provided by the CVMP, with each of the recommendations having been considered in the relevant parts of the application dossier.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (Version – October 2015) 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

Manufacture of the dosage form takes place outside the EEA. GMP certification, issued on 22 May 2014 by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), which confirms the date of last inspection to be March 2014 and shows that the site is authorised for the manufacture of such veterinary dosage forms, has been provided.

Batch release within the EU takes place at Eli Lilly and Company Limited, Liverpool, UK which holds a manufacturing authorisation issued on 15 December 2014 by the Medicines and Healthcare Products Regulatory Agency MHRA, UK confirming the date of last inspection to be September 2014.

A QP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site, stating that the active substance is manufactured in accordance with ISO 9000 standards, which is acceptable for this site given that the product is an ectoparasiticide, and as such standards other than EU GMP for starting materials may be applied. The declaration was based on an on-site audit by the manufacturing site responsible for batch release. However, the applicant's QP declaration of the compliance of the manufacture of the active substance with GMP requirements for starting materials, or with ISO 9000 standards, needed to be updated with respect to the re-designated starting material.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered to be in line with legal requirements.

The GMP status of the finished product manufacturing site has been satisfactorily established and is in line with legal requirements.

The GMP declaration of the active substance manufacturing sites remains unsolved.

Part 2 - Quality

Composition

Cheristin is presented as a spot-on solution in a single/unit dose 1 ml white polypropylene pipette delivering 0.7 ml, containing 91.1 mg spinetoram.

The active substance is spinetoram which is composed of two factors spinetoram J and spinetoram L.

Containers

The finished product is presented in a 1 ml white polypropylene pipette with a spike cap which is utilised to breach the pipette. The material of construction of the pipette complies with Regulation (EU) No 10/2011 detailing requirements for materials coming into contact with food. The choice of the container closure system has been supported by extractable/leachable migration studies and by stability data and is adequate for the intended use of the product.

The pipette is packaged into an aluminium foil/aluminium foil blister pack; one pipette per blister cavity. Each blister card contains three pipettes. One or two blister cards (3 or 6 pipettes) are packed per carton.

Development pharmaceutics

Formulation development focused on the formulation of an existing product containing spinetoram which has been marketed in the United States. The formulation of the product marketed in the USA contained a higher concentration of the active substance and different excipients. Changes to the formulation were made as hair loss was observed in some cats in clinical trials and following use of the commercially marketed product in the USA.

The role of each excipient in the formulation is described, and compatibility between the active substance and the excipients was observed in stability studies. All excipients are well known pharmaceutical ingredients and their quality is compliant with their respective Ph. Eur. or USP monographs.

Method of manufacture

The manufacturing process is a simple mixing process of the excipients and the active substance.

The solution is then filtered to clarify the solution and remove potential elemental impurities before being filled into 1.0 ml pipettes. Small overfill volumes are required to ensure accurate delivery of 0.7 ml from the 1.0 ml pipettes. In-process controls are well described and are adequate for this type of manufacturing process. A question relating to the classification of critical in-process control remained unsolved.

Process validation data is presented for two full scale batches and one batch of approximately 50% full scale. The manufacturing process has been satisfactorily validated.

Control of starting materials

Active substance

The active substance spinetoram is a member of the spinosyn class of insecticides. It is comprised of semi-synthetic derivatives of a fermentation product. Spinetoram is composed of two factors, spinetoram J and spinetoram L.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

No Ph. Eur. monograph exists for the substance, or a monograph in any pharmacopoeia of any EU member state. The active substance specification includes tests for appearance, identification (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (USP), and sulfated ash (Ph. Eur.). However, a test and limits for the nominal ratio of the active substance factors was not included in the specification.

Impurities present at higher than the qualification threshold according to VICH GL39 ‘Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances’ were justified by toxicological and clinical studies, given that, as a semi-synthetic product derived from a fermentation product, the active substance falls outside of the scope of VICH GL10 ‘Guideline on Impurities in New Veterinary Drug Substances’ with respect to the identification and qualification thresholds. However questions regarding the proposed limits for impurities, residual solvents and metal catalysts remain unsolved.

The analytical methods used have been sufficiently adequately described and non-compendial

methods appropriately validated in accordance with the VICH GL2 'Validation of analytical procedures: methodology'. Satisfactory information regarding the reference standards has been presented. Some batch analysis data for 2 commercial scale batches of the active substance have been provided. The results provided are within the specifications however complete batch analysis data is needed to demonstrate compliance with all tests in the proposed active substance specification.

In the Applicant's Part of the ASMF, further information has been provided. The manufacturing process of the active substance involves two phases, a fermentation phase to produce the intermediate, and then a chemical synthesis phase. However, the fermentation process is not considered to be part of the manufacturing process of the active substance, which is not acceptable. The absence of this phase from the manufacturing process constitutes a major concern and re-designation of the starting material is therefore required along with an update of the ASMF to include additional information necessary on all sites of manufacture and the extended manufacturing process. GMP for starting materials must be extended to include the fermentation. Detailed information on the manufacture of the active substance, in-process controls, specifications and control methods for intermediate products, starting materials and reagents have been provided in the Restricted Part of the ASMF. A number of issues remain unsolved.

The characterisation of the active substance is in accordance the CVMP Guideline 'Chemistry of new active substances' (EMEA/CVMP/541/03). Potential impurities are detailed, however questions regarding the proposed limits for impurities, residual solvents and metal catalysts remain unsolved.

The proposed ASMF specification is generally considered to be acceptable, and includes tests for appearance, identification, assay and related substances, water content and residual solvents. However there are questions relating to the identification test and tests for the nominal ratio of the active substance factors and for sulfated ash. There are also discrepancies between some of the tests included in the ASMF specification and that in the dossier. Questions relating to these discrepancies remain unsolved. Test methods are well described and are validated in accordance with VICH GL2, but there are issues to be addressed regarding system suitability criteria, and the validation of the related substances method. Batch analysis data is provided for 5 production-scale batches of the active substance and all results comply with the proposed specification. Satisfactory information regarding the reference standards has been presented.

Information has been provided on the container-closure system, however some issues regarding the specifications for the immediate packaging, and for the compliance of the immediate packaging with EU requirements remain unsolved.

Stability data are provided for 3 production-scale batches of the active substance. The samples on stability were packaged in a container closure system that simulates that used for the bulk active substance. Forced degradation studies were also carried out on a single batch of the active substance, which demonstrated that the related substances method used in the stability studies is stability indicating, but a forced degradation study should also be performed on the method currently used for stability. Method validation is also required for the assay method used in the stability studies. Data was provided following storage to 36 months at 25 ºC/60% RH, and for 6 months at 40 ºC/75% RH. The following parameters were tested: appearance, assay, related substances, water and microbial limits. All results were within specification with the exception of assay at one time-point for one batch. Tabulated results were requested for water content and microbial quality for the 3 batches on stability. The CVMP could not conclude on the acceptability of the proposed re-test period and storage conditions.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with their respective Ph. Eur. or USP monographs. There are no novel excipients used in the finished product formulation.

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

The product does not contain any materials derived from human or animal origin. The product is therefore out of scope of the relevant Ph. Eur. monograph and 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 on the finished product

The specifications proposed for use at release and at the end of shelf-life are generally considered appropriate to control the quality of the finished product although a number of questions relating to the control and qualification of impurities remain unsolved. In accordance with the CVMP Guideline 'Quality aspects of single-dose veterinary spot-on products' (EMEA/CVMP/QWP/54461/2007), the assay is expressed in terms of the quantity by mass of the active substance in a container of average delivered mass or volume. Limits of ± 5% of the declared content are applied to this parameter. The analytical methods used have been adequately described and appropriately validated in accordance with the VICH GL2 'Validation of analytical procedures: Methodology'. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis results are provided for two full scale and one laboratory scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Updated batch data were required once revisions to the specification and limits for impurities are completed.

Stability

Stability data is provided for two full scale and one laboratory scale batches of finished product stored under long term conditions for 6 months at 25 ºC/60% RH, intermediate conditions for 6 months at 30 ºC/60% RH and for 6 months under accelerated conditions at 40 ºC/75% RH in accordance with VICH GL3 'Stability testing of new veterinary drug substances and medicinal products'. The composition and manufacture of the batches used in stability studies are identical to those proposed for marketing and the primary packaging was identical to that proposed for marketing.

There were no adverse trends observed for any of the parameters tested, although results for active substance content in terms of mg/pipette and average weight of the pipettes are reported for the 6 month time point only, so trending for these parameters was not currently possible. One result for assay of the active substance in mg/pipette is out-of-specification at 6 months. Given that this is only time point at which results are reported in mg/pipette, it is not currently possible to conclude on the significance of this result. Results of further stability timepoints are needed before any conclusion can be drawn. A number of questions relating to impurities detected in the stability

studies and their qualification remain unsolved.

Photostability studies demonstrate that the product is sensitive to light and the pipettes should therefore be packaged in the secondary packaging (aluminium blisters) in order to provide sufficient protection from light.

Given the limited data currently available the CVMP could not agree a shelf life and storage precautions for the product.

Overall conclusions on quality

Information on the development, manufacture and the finished product has been presented in a generally satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The manufacturing method is a relatively simple standard process and satisfactory process validation data were provided.

Information on the active substance has also been provided in a generally satisfactory manner, however a number of issues remain unsolved particularly with respect to the re-designation of the starting material and regarding the proposed limits for impurities and their qualification.

The limits for impurities on the finished product release and shelf life specifications and qualification of these impurities were not satisfactorily addressed.

Additional stability data for the product is required before an appropriate shelf life and storage conditions for the product could be determined.

Part 3 – Safety

The active substance (spinetoram) of Cheristin, a multicomponent tetracyclic macrolide is a new active substance not authorised for a veterinary medicinal product in the EU before. A full safety file in accordance with Article 12(3)(j) has been provided.

Safety documentation

Pharmacodynamics

See part 4.

Pharmacokinetics

See Part 4 for pharmacokinetics in the cats.

A ^{14}C radiolabelled study in rats was provided to investigate the absorption, distribution, metabolism and elimination of spinetoram-J following oral administration. It was a GLP study conducted in accordance with OECD 417.

Absorption

Spinetoram-J is rapidly absorbed when administered by the oral route to rats, with a T_{max} of approximately 2 hours. The maximum concentrations (C_{max}) were 0.23–0.28 µg/ml in males and females, respectively, following a 10 mg/kg bw dose.

Spinetoram-J exhibited dose proportional pharmacokinetics over the range of 10 to 100 mg/kg bw in rats with a 7-fold higher C_{max} in the higher dose group. For plasma AUCs, the 100 mg/kg bw dose was approximately 14-fold greater than the 10 mg/kg bw dose. Elimination was faster at a dose of 10 mg/kg bw with half-lives of four hours in males and females compared to 9 and 11 hours for males and females in the 100 mg/kg bw groups.

In relation to bioavailability, based on the comparison of AUCs, 26 and 29% of spinetoram-J was systemically available in males and females given 10 mg/kg orally compared to intravenous (IV) administration. This rose to 37 and 36% in males and females given 100 mg/kg by the oral route. However, as spinetoram-J has a large molecular weight and rapid metabolism, estimating bioavailability using plasma AUC ratios is expected to underestimate the actual fraction that is orally absorbed. It was estimated that approximately 70% of the dose was absorbed from the gastrointestinal tract as indicated by the quantity of metabolites recovered in faeces and urine.

Tissue Distribution

In rats following oral administration of 10 mg/kg, the highest radioactivity was measured in fat followed by the kidney, lymph nodes, adrenals and gastrointestinal tract in males, whereas in females it was fat, kidney, ovaries, gastrointestinal tract and lymph nodes after dosing.

Metabolism

In rats, the major route of metabolism for the test material was found to be glutathione conjugation with the parent compound, as well as glutathione-pathway conjugates of metabolites arising from N-demethylation, O-deethylation, and hydroxylation of the parent compound. Spinetoram-J was highly metabolised.

It is unknown if the metabolites have pharmacodynamic activity.

Excretion

Excretion in faeces represented the major route of elimination following oral administration with an average of 86% excreted over the period. A similar profile was observed in the IV groups. Parent compound accounted for 7–40% of the total radioactivity eliminated in urine plus faeces, with seven metabolites comprising between 47.9–79.4%.

The plasma elimination half-life in rats averaged 4 hours following an oral dose of 10 mg/kg.

Based on the information presented, it is accepted that the pharmacokinetics of spinetoram-J have been adequately characterised. However, the absence of pharmacokinetic data on spinetoram-L or, for that matter, other constituents of the active substance (categorised as impurities) has not been justified. The applicant was requested to justify that the pharmacokinetic data relating to spinetoram-J reflects the pharmacokinetic characteristics of the active substance generally (all constituents).

Toxicological studies

Single dose toxicity

Single dose toxicity studies in rats investigating the acute toxic effects of spinetoram using the oral, dermal and inhalation routes of administration were conducted in accordance with GLP and relevant acute toxicity OECD guidance.

In the acute oral study in rats, a dose of 5000 mg/kg bw did not result in mortality. Watery faeces, perineal soiling and perioral soiling were observed following treatment and resolved within 7 days. The oral LD_{50} was determined to be >5000 mg/kg bw.

The acute dermal study conducted in rats resulted in perineal, perioral, perinasal, and/or periocular soiling in some of the animals. However, as no mortality was observed a dermal LD_{50} above 5000 mg/kg bw was determined.

In the acute inhalation study, rats exposed to a dose of 5.50 mg/l for 240 minutes exhibited combinations of periocular, perineal and/or extensive body soiling that resolved by the end of the 14-day observation period. In the absence of mortality an LC_{50} of >5.50 mg/l was determined.

In conclusion, it is accepted that the acute toxicity of spinetoram is low.

Repeat dose toxicity

The toxicity of spinetoram was investigated in repeat dose 28- and 90-day studies in rats, mice and dogs using the oral route of administration. In addition, a 1-year repeat dose oral study in the dog and a 28-day repeat dose dermal study in rats were also conducted. All studies, with the exception of the 28-day dog study, were conducted in accordance with OECD guidelines.

In the 90-day repeat dose-oral study the most sensitive endpoints for male rats were the histopathological effects. The histopathological changes observed in male and female rats were aggregates of macrophages/histiocytes in the lymph nodes (mediastinal and mesenteric), thymus, spleen, liver, intestinal tract (jejunum and ileum) and vacuolation of parenchymal cells of the kidneys and thyroid gland and degeneration of skeletal muscle (multiple sites) of males and females. These effects were observed in male rats at doses of 70.6 mg/kg bw/day and higher and in females at doses of 42.4 mg/kg bw/day and higher. These histopathological changes are similar to those seen in the 28-day rat study. At higher doses, elevated levels of aspartate aminotransferase were observed in males and females together with increased alanine aminotransferase in males. Based on these findings the NOEL of 34.7 mg/kg bw/day can be accepted for male rats. In the case of female rats, significant treatment related effects were observed as low as 42.4 mg/kg bw/day with decreases in triglycerides and T4 concentrations as well as histopathology changes. Therefore, for female rats, a NOEL of 10.1 mg/kg bw/day can be accepted.

For the mouse 90-day repeat dose oral study, the most sensitive end points where histopathological changes to the epididymides in males and increased white blood cells and splenic extramedullary haematopoiesis in females observed in the 22.8 and 29.6 mg/kg bw/day male and female groups. This resulted in a NOEL of 7.5 and 10.2 mg/kg bw/day for male and female mice, respectively. A dose of 89.9 mg/kg bw/day resulted in increased alanine aminotransferase and aspartate aminotransferase in female mice. In the case of male mice a dose of 70.5 mg/kg bw/day resulted in increased aspartate aminotransferase. Additional effects observed at the higher doses included a slight microcytic anaemia, increased liver weights, cytoplasmic vacuolation of parenchymal cells,

epithelial cells, macrophages and fibroblasts in numerous organs.

For the one-year dietary toxicity study in dogs, a NOEL of 2.5 mg/kg bw/day in female dogs was established based on an increase in mean absolute liver weights in the highest dose group. Arteritis lesions were also observed in the highest dose group although it is argued that these could be attributed to the use of Beagle dogs which can spontaneously exhibit polyarteritis. It is noted that in the 28-day repeat dose dog study elevated levels of aspartate aminotransferase, increased liver weights and decreased thymus weights were observed when doses of 27.1 and 31.0 mg/kg bw/day for males and females, respectively, were administered. Histopathological changes similar to those observed in the rat and mice studies were also noted at the higher doses.

In the case of dermal toxicity, the 28-day repeat dose study in rats identified a NOEL for systemic effects of 1000 mg/kg bw/day in males and females. As very slight or slight thickening of the epidermis with a very slight increase in the amount of keratin was observed at all dose levels a dermal NOEL could not be established. However, given the slight nature of these skin reactions it is argued that they are non-adverse. Therefore, a NOAEL of 1000 mg/kg bw/day is proposed.

The available data is suitable for use in the user safety risk assessment. Based on the totality of data presented, a chronic NOEL of 2.5 mg spinetoram/kg can be established (based on the one-year study in dogs).

Note: A risk assessment of spinetoram was conducted by EFSA evaluating its use as a pesticide. In this assessment, an ADI of 0.025 mg/kg bw per day was established based on the 1 year dog study and an NOAEL of 2.5 mg/kg bw/day. An acute reference dose of 0.1 mg/kg bw based on the rat multigeneration study was also established. An uncertainty factor of 100 was used in both cases (EFSA Journal 2013;11(5):3220).

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Study of the effect on reproduction

A reproductive toxicity study investigating the effects of spinetoram in rats using the oral route of administration was conducted in accordance with GLP and OECD guideline 416.

An increase in post implantation losses was observed at a dose of 75 mg/kg bw/day. Treatment related clinical signs of difficult birth/incomplete delivery were also observed in a small number of P1 and P2 females in the 75 mg/kg bw/day group. Additional signs in these females included vulvar discharge, perinasal or perioral soiling and/or pale skin/mucous membranes. In the absence of any effects at 10 mg/kg bw/day, a dietary NOEL of 10 mg/kg bw/day for parental and reproductive toxicity in rats could be derived from this study.

Study of developmental toxicity

Developmental toxicity studies were conducted in rats and rabbits. All studies were carried out in accordance with GLP and OECD guidelines.

In the rat developmental study maternal toxicity was observed at a dose of 300 mg/kg bw/day, but

no teratogenicity, embryo or foetal toxicity was observed at the doses tested. Based on the data provided a NOEL of 100 mg/kg bw/day for maternal toxicity and 300 mg/kg bw/day for embryo/foetal toxicity in the rat could be derived from the results of this study.

In the rabbit developmental study a maternal oral NOEL of 10 mg/kg bw/day was determined based on the increased liver weight, decreased food consumption and weight gain observed in the 60 mg/kg bw/day group. Although malformations were observed in all treatment groups, the available data do not show a dose-related increase in foetal alterations when compared to control animals. On this basis an embryo/foetal NOEL of 60 mg/kg bw/day in rabbits was established.

Based on the above described rat and rabbit studies, spinetoram showed no potential for teratogenicity.

Genotoxicity

The genetic toxicology potential of spinetoram was evaluated in a standard test battery in accordance with VICH GL23 on genotoxicity testing. This included an in vitro bacterial reverse mutation test, an in vitro HGPRT forward mutation assay in Chinese hamster ovary cells, an in vitro chromosome aberration assay using rat lymphocytes, and an in vivo mouse micronucleus test.

In the in vitro bacterial reverse mutation test, spinetoram was negative for induction of reverse mutations in four tester strains of *Salmonella typhimurium* and one *E. coli* tester strain in the presence and absence of metabolic activation.

Spinetoram did not induce mutations with or without metabolic activation in the CHO/HGPRT in vitro mammalian cell gene mutation test.

Spinetoram was non-genotoxic with or without metabolic activation in the in vitro chromosomal aberration assay.

Spinetoram did not induce chromosomal damage in an in vivo mammalian erythrocyte test.

Based on the above studies, it is concluded that spinetoram is not genotoxic.

Carcinogenicity

Spinetoram was tested for carcinogenicity in a two year chronic toxicity/oncogenicity study in rats and an eighteen month oncogenicity study in mice conducted in accordance with GLP and OECD guidelines and VICH GL28 on carcinogenicity testing.

In F344/DuCrl rats administered spinetoram at mean daily doses up to 32.9 mg/kg bw/day and 40.0 mg/kg bw/day in feed for 104 weeks of males and females, respectively, no evidence of carcinogenicity was found.

There was no evidence of carcinogenicity when spinetoram was administered in the diet for up to 18 months to mice in doses up to 37.5 and 46.6 mg/kg bw/day in males and females, respectively.

Studies of other effects

In order to investigate the potential for spinetoram to cause irritation to the skin and eyes an acute eye irritation study and acute dermal irritation study were conducted in rabbits.

Eye irritation:

An eye irritation study using spinetoram was performed in New Zealand rabbits. All three rabbits had slight to moderate conjunctival redness, slight chemosis, slight to marked discharge, and two of the rabbits had reddening of the iris. All ocular irritation resolved 24 hours after dosing demonstrating reversible ocular irritation.

The acute eye irritation potential of the 11.2% w/w spinetoram topical formulation was shown to be a moderate eye irritant in rabbits, reversible after seven days.

Dermal irritation:

The acute dermal irritation potential of spinetoram was evaluated in New Zealand White rabbits. The substance was found to be non-irritant. While the active substance may be classed as non-irritant to the skin, a dermal irritation study using the formulation proposed for marketing was not conducted. However, from the target animal safety studies, it is noted that there is the potential for local reactions at the application site (characterised by hair loss, erythema, scaling, scabbing).

Skin sensitisation:

In a guinea pig study spinetoram administered in a 39.6% w/w formulation tested at a concentration of 100% did not show any skin sensitisation potential. For the formulation tested, the active substance is present at a higher concentration and the excipient composition is different compared to the formulation that is the subject of the present application. Based on information reviewed and summarised by the expert, an increased risk of skin sensitisation with the new formulation is not expected.

Neurotoxicity:

The potential for spinetoram to cause neurotoxicity was investigated in acute and chronic rat studies.

In the acute neurotoxicity study, rats exposed to an oral dose of up to 2000 mg/kg bw exhibited no signs of neurotoxicity or neuropathological effects. An acute oral neurotoxicity NOEL of 2000 mg/kg bw was established.

A chronic neurotoxicity study conducted in accordance with OECD 424 was provided. In the absence of neurotoxic effects a chronic oral neurotoxicity NOEL of 36.7 and 44.3 mg/kg bw/day in males and female rats, respectively, was established.

Excipients

The excipients are commonly used pharmaceutical ingredients with acceptable toxicological profiles.

Impurities:

The batches of active substance used in the toxicological studies are broadly comparable to the proposed active substance specification in terms of limits of spinosyn impurities and ratio between spinetoram-J and L. As a consequence, the results of the toxicological studies can be considered representative of the active substance in the final formulation.

User safety

A user safety risk assessment was presented which was conducted broadly in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-

Rev.1).

The main potential routes of accidental contact with the product have been considered and it was concluded that exposure by the dermal, oral and ocular routes is possible.

Based on the information provided, the product has the potential for moderate eye irritation. An appropriate risk communication measure to mitigate the risk of eye irritation was proposed.

Sensitisation and dermal irritation studies have confirmed that the active substance does not cause these effects in the test animals used. However, from the target animal safety studies, it is noted that there is the potential for local reactions at the application site (characterised by hair loss, erythema, scaling, scabbing). Again, to address any concerns for local dermal effects following dermal exposure to the product, appropriate risk mitigation measures were proposed.

With regard to accidental oral exposure, it was considered that ingestion of an entire pipette's contents (91 mg spinetoram) by a small child (11 kg) should be used as a worst-case scenario. The exposure was compared to an LD_{50} value which is not accepted. When comparing the estimated exposure to the oral NOAEL from a 28-day repeat dose toxicity study, the margin of exposure is below the trigger value of 100. However, when the rarity of the exposure event is considered together with the use of a sub-acute toxicological reference value (TRV) for margin of exposure (MOE) estimation, it is accepted that this does not represent an unacceptable risk. Further, the risk can be controlled with appropriate risk mitigation measures.

A similar risk arising from hand-to-mouth exposure following a small child's contact with a treated animal shortly after treatment was identified with a margin of exposure of 36. As for the accidental oral exposure it is accepted that the risk can be controlled with appropriate risk mitigation measures.

As a result of the user safety assessment the following advice to users/warnings for the user are considered appropriate:

"Avoid direct contact with skin, eyes or mouth. In case of accidental spillage onto skin wash with soap and water.

This product can cause eye irritation. Contact with the eyes should be avoided. If the product accidentally gets into the eyes, they should be flushed thoroughly with water. If symptoms persist, seek medical advice immediately and show the package leaflet or the label to the physician.

Wash hands after use.

Treated animals should not be handled until the application site is dry, and children should not be allowed to play with treated animals until the application site is dry. It is therefore recommended that animals are not treated during the day, but should be treated during the early evening, and that recently treated animals should not be allowed to sleep with owners, especially children.

Only remove one pipette at a time from the blister and only when required, in order to prevent children from getting direct access to the product. Used applicators should be disposed of immediately. Return the blister pack into the carton after use and keep the product out of sight and reach of children."

In conclusion, the user safety warnings proposed are generally acceptable after the amendments in the text above have been made. The product when used as proposed including the amendments above is not expected to pose an unacceptable risk to the user.

Environmental risk assessment

An ERA was provided according to VICH GL6 on Environmental Impact assessment (EIAs) for Veterinary Medicinal Products – Phase I (CVMP/VICH/592/98-Final). Based on the data provided the ERA can stop at Phase I, as the veterinary medicinal product will only be used in non-food animals. Cheristin is not expected to pose a risk for the environment when used according to the proposed SPC.

Overall conclusions on the safety documentation

The product Cheristin contains a new active substance, spinetoram. Spinetoram has not previously been authorised for use in a veterinary medicinal product within the EU. A full safety file in accordance with Article 12(3)(j) has been provided.

Pharmacodynamics and pharmacokinetics relevant to the target species are addressed in Part 4. In the rat, spinetoram-J was rapidly absorbed with peak plasma times occurring at approximately two hours after oral administration. The increase in AUCs observed between the 10 mg/kg bw and 100 mg/kg bw oral groups was approximately dose proportional, being 14-fold greater. Elimination was faster in the 10 mg/kg bw groups with half-lives of four hours in males and females compared to 9 and 11 hours for males and females in the 100 mg/kg bw groups. When the excretion profile of the metabolites in faeces and urine are taken into account, an oral bioavailability of 70% was estimated. Metabolism of spinetoram-J occurred primarily by glutathione conjugation with metabolites arising from N-demethylation, O-deethylation and hydroxylation. Excretion in faeces represented the major route of elimination following oral administration with an average of 86% excreted over the period. Parent compound accounted for 7–40% of the total radioactivity eliminated in urine plus faeces, with seven metabolites comprising between 47.9–79.4%. The lack of pharmacokinetic data on spinetoram-L has not been justified.

A comprehensive set of studies investigating the toxicity of spinetoram has been provided.

- The most sensitive endpoint from the repeat dose oral toxicity studies was a NOEL of 2.5 mg/kg bw/day from the one-year dietary toxicity study in dogs. This was based on an increase in mean absolute liver weights in the highest dose group. Arteritis lesions were also observed in the highest dose group although it is argued that these could be attributable to the use of Beagle dogs which can spontaneously exhibit polyarteritis.
- In the case of dermal toxicity, the 28-day repeat dose study in rats identified a NOEL for systemic effects of 1000 mg/kg bw/day in males and females (that is, absence of systemic effects at the highest dose tested). As very slight or slight thickening of the epidermis with a very slight increase in the amount of keratin was observed at all dose levels a dermal NOEL could not be established. However, given the mild nature of these skin reactions they may be classed as non-adverse. Therefore, a NOAEL of 1000 mg/kg/day is proposed.
- A NOEL of 10 mg/kg bw/day for parental and reproductive toxicity in rats was established for spinetoram. In the case of embryo/foetal developmental toxicity a NOEL of 60 mg/kg bw/day for rabbits and 100 mg/kg bw/day in rats was observed.
- Spinetoram did not show genotoxic activity.
- Spinetoram is not considered to have carcinogenic potential based on the results of two carcinogenicity studies.

- In the rat, the chronic NOEL for neurotoxicity was 36.7 mg/kg bw/day in males and 44.3 mg/kg bw/day in females, in the absence of neurological effects the NOEL were based on the highest doses tested.
- Cheristin spot-on solution for cats (11.2% spinetoram) was found to be a mild eye irritant with effects fully reversible within seven days of exposure.
- Spinetoram was non-irritant in a dermal irritation study. Spinetoram is a non-sensitiser based on the results from a dermal sensitisation study. While a dermal irritation study using the formulation proposed for marketing has not been conducted, it is noted based on the findings of the safety/efficacy studies in that target species that there is the potential for local reactions at the application site (characterised by hair loss, erythema, scaling, scabbing). This would suggest that there is the potential for similar local effects to occur in the user. Based on the available information it is accepted that Cheristin spot-on solution for cats is unlikely to be a skin sensitiser.

The data presented are considered adequate to characterise the toxicity profile of the active substance.

A user safety risk assessment conducted broadly in accordance with current guidance has been presented. The most likely routes of exposure would be accidental dermal exposure, ocular exposure, repeated dermal exposure to dislodgeable residues, accidental oral ingestion and hand-to-mouth transfer of dislodgeable residues. A risk to children following acute oral exposure was identified. An additional risk to the user will arise from ocular (and possibly dermal) exposure to the product. It is considered that the identified risks can be addressed by suitable risk mitigation measures.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the proposed SPC.

Part 4 – Efficacy

This application is for the product 'Cheristin' containing 130 mg spinetoram/ml (11.2% w/w). The product is to be indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) on cats. The active substance spinetoram has not previously been authorised for use in a veterinary medicinal product within the EU. Spinetoram is a member of the spinosyn family of fermentation-derived insecticides produced by the actinomycete *Saccharopolyspora spinosa*. It consists of two active factors (spinetoram J and spinetoram L).

Spinetoram was authorised as a (420 mg spinetoram/ml) spot-on veterinary medicinal product in the USA in 2010. However, it is reported that due to a high frequency of post-marketing reports of hair loss at the application site, the product was reformulated (lower level of spinetoram and change to excipients) and has been marketed since 2013 under the tradename 'Cheristin'. The latter formulation is the subject of the present application.

Given the fact that many studies included in the application relate to the original higher strength formulation, scientific advice from the CVMP was sought in respect of the data package required for the new formulation.

The candidate formulation includes a lower concentration of spinetoram and different excipients.

Each pipette contains 0.7 ml of the candidate formulation (equivalent to 91 mg spinetoram).

Pharmacodynamics

The mode of action of spinosyns in insects is believed to primarily involve nicotinic acetylcholine receptors (nAChRs). The spinosyn based products, spinosad and spinetoram, share the same mode of action. The mechanism by which spinosyn exerts its insecticidal action is different from other agents and it does not interact with the known nAChRs binding sites of other classes of insecticides such as neonicotinoids. However, some interaction with γ-aminobutyric acid (GABA) receptors is believed to occur.

Three published studies were cited in support of the pharmacodynamic effects of spinosyns in various insects, as measured using electrophysiological techniques. However, all studies were conducted using spinosyn A (active factor of spinosad and not spinetoram). Insects treated with spinosyns initially show involuntary muscle contractions and tremors resulting from activation of motor neurons. Prolonged spinosyn-induced hyper-excitation results in prostration, paralysis and death. Spinosyns have very low mammalian toxicity. The reason for the selective toxicity in insects over mammals has not been fully elucidated but is believed to be due to the differential sensitivity of the insect versus vertebrate nACh and/or GABA receptors.

According to the EPAR for a product containing spinosad, this active substance hardly penetrates through the insect cuticle and therefore, spinosad exerts its insecticidal activity orally rather than by contact (the product is administered orally to dogs and cats).

However, no information/discussion on the method by which spinetoram exerts its insecticidal effect has been presented, particularly given the fact that the candidate formulation is to be administered topically (as opposed to the oral administration of the product containing spinosad).

Given the route of administration proposed for the candidate formulation (topical), information how the target ectoparasite (*Ctenocephalides felis*) becomes exposed to the insecticidal action of spinetoram (spinetoram factors J and L) following topical application to cats remains unclear; that is, how the product exerts its pulicidal effect.

Development of resistance

Prior to the granting of a marketing authorisation in 2011 for a product containing spinosad, there were no pulicidal products containing spinosyns as active substance for use on cats in Europe. A literature review did not highlight any reports of *Ctenocephalides felis* resistance to spinosad.

Spinosad and spinetoram exert their insecticidal activity through a dual mode of action involving both nicotinic- and GABAergic pathways, primarily targeting the insect-specific nAChR Dα6 subunit. This particular target site differs from the mode of action of other chemical classes, including the neonicotinoids such as imidacloprid. It is therefore concluded that target-site mediated cross-resistance between spinosyns and other insecticides, including the neonicotinoids, is highly unlikely to develop.

Given that spinosyns are a relatively new class of insecticide for use in animals in Europe and the comparatively unique mode of insecticidal activity when compared with other available insecticides, it can be concluded that resistance development of *C. felis* to spinetoram is not of concern at present.

Pharmacokinetics

A ^{14}C radiolabelled study in cats to investigate the surface spread as well as dermal penetration of spinetoram following topical application to cats (at the base of the neck, between shoulder blades) was performed using a different formulation, which includes a higher concentration of the active ingredient (420 mg spinetoram/ml) and slightly different excipients compared to the candidate formulation.

Results demonstrated that ^{14}C-spinetoram reached peak concentrations in plasma, hair and skin at one, two and seven days, respectively, with concentrations decreasing thereafter. It was determined that only 0.04% of the applied dose was detectable in plasma, suggesting very limited dermal penetration of the product, with an apparent association with hair follicles and sebaceous glands.

As it was unclear how the reformulated product might influence the surface spread and dermal penetration of spinetoram, a further study was conducted using the candidate formulation (130 mg spinetoram/ml).

In that study, 0.7 ml of spinetoram 11.2% w/w was applied at the base of the skull as a single dose, spot-on treatment to six domestic shorthair cats (3 male and 3 female). Blood samples were collected periodically (4, 8, 12, 24, 30, 96 and 168 hours and 14, 21, 28, 35 and 42 days post-application). Hair samples were collected periodically (24 and 96 hours and 14, 28, and 42 days post-application). One animal per gender was euthanised on each of study Days 14, 28 and 42. Following euthanasia, skin blocks and skin stripping samples were collected from selected sites on the animals. All samples were analysed for total ^{14}C using LSC techniques.

Measurement of radioactivity on the skin and hair from selected areas of the body at various time points permitted assessment of the movement and dissipation of ^{14}C-spinetoram. Measurement of ^{14}C-spinetoram equivalents in plasma and visualisation of radioactive residues in skin sections (by micro-autoradiography (MARG)) permitted assessment of dermal absorption of topically applied spinetoram in cats.

The radiolabelled component of the test article contained spinetoram factor-J (but not factor-L). This radiolabelled component was subsequently combined with 11.2% w/w spinetoram. Recovery ranged from 90% to 110% for plasma and from 86% to 102% for hair and skin samples. Results demonstrated that ^{14}C-spinetoram reached peak concentrations in plasma, hair and skin at 30 hours, one day and 7 days, respectively, with concentrations decreasing thereafter.

The concentration of spinetoram in the plasma was found to be lower for the lower strength formulation. Whilst lower dermal concentrations of spinetoram were also observed following application of the lower strength formulation, the mean concentrations of spinetoram in hair were higher for up to 28 days post-application (possibly resulting from the different application sites between studies and consequently the reduced opportunity for oral ingestion (via self-grooming) of the test article in the latter study.

As the radiolabelled component of the test article only contained spinetoram factor-J (but not factor-L), it is unclear how the ^{14}C-spinetoram equivalents measured (associated with spinetoram factor-J) may be considered to adequately characterise the fate of spinetoram factor-L and any impurities; that is, whether the pharmacokinetic profile of spinetoram factor-L differs significantly. How the findings of this study permit concluding on the fate of spinetoram factor-L and any impurities remains unclear.

Dose determination / finding studies

Four dose determination studies were conducted.

One study was a GLP dose determination and speed of kill study conducted outside the EU and was designed to investigate both the pulicidal effect and the speed of kill of spinetoram against *Ctenocephalides felis*, following a single application to adult cats with various hair lengths. The formulation was not the final one but instead was the higher strength formulation (39.6% w/w equivalent to 420 mg spinetoram/ml). Sixty-three cats aged 7–195 months and in the bodyweight range 2.3–6.0 kg, were infested with 100 unfed newly emerged adult *C. felis* fleas and were randomly allocated to one of three treatment dose volumes: 0 ml/cat (no treatment), 0.5 ml (210 mg spinetoram)/cat and 0.7 ml (294 mg spinetoram)/cat. Results indicate an onset of pulicidal effect that met minimum efficacy requirements (≥95%) from 24 hours post-treatment in cats treated with 0.7 ml (294 mg spinetoram) of the product but not in cats administered 0.5 ml (210 mg spinetoram) of the product. An acceptable level of persistent pulicidal effect (≥95%) was observed for both treatment groups for up to 50 days.

The second study was a GLP-compliant study conducted outside the EU. The formulation was not the final one but instead was the higher strength formulation. Thirty adult short-hair cats of both genders were randomly allocated to one of 5 treatment groups. The pulicidal effect of three doses was investigated in this study (0.3 ml - 126 mg spinetoram; 0.5 ml - 210 mg spinetoram; 0.7 ml - 294 mg spinetoram) with the product applied to the base of the skull. An acceptable level of efficacy (≥95%) was not demonstrated in any of the treatment groups at 12 hours post-treatment application. However, an acceptable level of efficacy was demonstrated in all three treatment groups from 48 hours until 37 days post-treatment application. The results of this study do not indicate any difference in efficacy between the three doses investigated.

A third study was a GCP-compliant study conducted within the EU (Ireland) to determine the efficacy of the higher strength 39.6% w/w; 420 mg spinetoram/ml formulation following topical administration at dose rates of 0.15 ml (63 mg spinetoram), 0.5 ml (210 mg spinetoram) and 0.85 ml (357 mg spinetoram) to the skin at the base of the skull on cats infested with adult-stage cat fleas (*Ctenocephalides felis*). Twenty-four domestic short-hair cats (14 male and 10 female) in the age range 9–58 months old and in the bodyweight range 2.2–5.8 kg were randomly allocated to one of four treatment groups. All cats were treated once on study Day 0. Adequacy of infestation of control animals did not meet guideline requirements, therefore the results of this study may only be considered as supportive. Results suggest that an acceptable level of pulicidal effect at all three dose levels, from 48 hours to 30 days post-treatment application, with the two higher dose levels (210 mg and 357 mg spinetoram) showing evidence of a slightly longer persistent pulicidal effect. Local reactions of a cosmetic nature were observed (spiking, clumping, greasy appearance and yellow discolouration).

A fourth study was conducted using an interim formulation and was not GLP-compliant. The study was conducted to determine the efficacy and local tolerance of a spinetoram solution (9.8% w/w, approximately 104 mg/ml) following topical administration at dose rates of 0.5 ml (52 mg spinetoram), 0.7 ml (73 mg spinetoram), 0.9 ml (94 mg spinetoram) and 4.5 ml (468 mg spinetoram) to the skin at the base of the skull on cats infested with adult-stage cat fleas (*Ctenocephalides felis*). Twenty domestic short-hair cats aged at least 8 months and in the bodyweight range 2.2–5.4 kg were randomly allocated to one of five treatment groups. Insufficient information has been provided to confirm whether adequacy of infestation in control animals was achieved. Results suggest that doses of 52 mg and 73 mg spinetoram per cat have an acceptable pulicidal effect from 24 hours to 30 days post-treatment application. Application of a higher dose of

94 mg spinetoram was reported to have a slightly longer persistent pulicidal effect (37 days post-treatment). Application site changes of a cosmetic nature (hair clumping and residues) were evident on study Day 1 for all spinetoram dose levels.

None of the dose determination studies were conducted using the candidate formulation - three of the studies used the a higher strength formulation (39.6% w/w; 420 mg spinetoram/ml) while a fourth study used an interim formulation.

Whilst some studies failed to meet guideline requirements in terms of adequacy of infestation of control animals, results suggest that a dose of 62 mg spinetoram per cat may be efficacious against fleas from 48 hours to 30 days post-treatment application and that higher doses are required for an earlier onset of pulicidal effect (294 mg was the lowest dose that showed evidence of an acceptable pulicidal effect 24 hours post-treatment application) and for a longer persistence in pulicidal effect (126 mg spinetoram was the lowest dose that showed evidence of an acceptable pulicidal effect at 37 days post-treatment application).

Dose confirmation studies

Results of dose determination studies suggest that a dose of 62 mg spinetoram per cat may be efficacious against fleas from 48 hours to 30 days post-treatment application. The dose selected for investigation in the dose confirmatory studies is 50% higher (91 mg per cat).

Seven dose confirmation studies have been provided in support of the proposed dose of 91 mg spinetoram per cat. All seven studies used the final formulation of Cheristin and in all but one study, the product was applied in accordance with the recommendation included in the proposed SPC (base of the skull).

One of the studies was GCP-compliant and the candidate formulation was used. This study was conducted to confirm the immediate and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered to cats at a dosage of 0.7 ml (91 mg spinetoram) per cat. Sixteen cats (8 male and 8 female) in the bodyweight range 2.37–5.54 kg were randomly allocated to one of two treatment groups (placebo (light mineral oil) 0.7 ml per cat, or 11.2% (w/w) solution 0.7 ml (91 mg spinetoram) per cat). Flea infestation was on study days -2, 7, 14, 21, 28 and 35 with flea counts on study days 2, 9, 16, 23, 30 and 37. An acceptable level of pulicidal effect (≥95%) was demonstrated from 48 hours to 37 days post-treatment application of 91 mg spinetoram per cat. Application site changes of a cosmetic nature were observed in the majority of cats.

A second GCP-compliant study was conducted within the EU (Ireland) using the candidate formulation to confirm the immediate and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered to cats at a dosage of 0.7 ml (91 mg spinetoram) per cat. Sixteen mixed-breed short-haired cats (8 male and 8 female) aged 14–74 months and in the bodyweight range 2.0–4.9 kg were randomly allocated to one of two treatment groups (0.7 ml of light mineral oil, or 0.7 ml of 11.2% (w/w) solution containing 91 mg spinetoram). Flea infestation was on study days -1, 7, 14, 21, 28 and 35 with flea counts on study days 2, 9, 16, 23, 30 and 37. An acceptable level of pulicidal effect (≥95%) was demonstrated from 48 hours to 30 days post-treatment application of 91 mg spinetoram per cat. Application site changes of a cosmetic nature (hair clumping/spiking, oily appearance) were observed in the majority of cats administered spinetoram.

A third GLP-compliant study was conducted outside the EU (USA) using the candidate formulation to

confirm the immediate and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered to cats at a dosage of 0.7 ml (91 mg spinetoram) per cat. Sixteen mixed-breed short-haired cats (6 male and 10 female) aged 36–184 months and in the bodyweight range 2.97-6.94 kg were randomly allocated to one of two treatment groups (0.7 ml of vehicle control, or 0.7 ml of 11.2% (w/w) solution containing 91 mg spinetoram). Flea infestation was on study days -1, 7, 14, 21, 28 and 35 with flea counts on study days 2, 9, 16, 23, 30 and 37. Based upon the data provided, an acceptable level of pulicidal effect (≥95%) appears to have been demonstrated from 48 hours to 30 days post-treatment application of 91 mg spinetoram per cat. However, results can only be considered supportive as adequacy of infestation of control animals at all flea count time points could not be confirmed. Further, the relevance of the flea strain used in this study (originating from outside the EU) is unclear. Application site changes of a cosmetic nature (wetness, hair clumping, residue) were observed in cats administered spinetoram. One cat was observed to have focal alopecia at the application site following application of spinetoram.

Another GLP-compliant study was conducted outside the EU (USA) using the candidate formulation to confirm the immediate post-treatment speed of kill and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered at a dosage of 0.7 ml (91 mg spinetoram) per cat. Forty-eight mixed-breed short-haired cats (21 male and 27 female) aged 7.5–109 months and in the bodyweight range 2.2–5.9 kg were randomly allocated to eight treatment groups. Based upon the data provided, an acceptable level of pulicidal effect (≥95%) appears to have been demonstrated from 12 hours following product application (study Day 0) i.e. against an existing flea infestations. However, a similar speed of kill (from 12 hours) following re-infestation with fleas was only observed on study Days 7 and 14 but not on study Days 21, 28, 35 or 42. An acceptable pulicidal effect at 24 hours post-infestation was only demonstrated for up to 21 days post-treatment application. Application site changes of a cosmetic nature (wetness, hair clumping, residue) were observed in cats administered spinetoram.

A non-GLP study was conducted outside the EU (Australia) using the candidate formulation to confirm the immediate and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered at a dosage of 0.7 ml (91 mg spinetoram) per cat. Sixteen mixed-breed short-haired cats were randomly allocated to two treatment groups (untreated or 11.2% (w/w) solution 0.7 ml (91 mg spinetoram) per cat). Flea infestation was on study days -3, 7, 14, 21, 28 and 35 with flea counts on study days -1, 2, 9, 16, 23, 30 and 37. Adequacy of infestation of control animals was not achieved on study Days 2, 9, 16, 23, 30 and 37. Based upon the limited data provided and notwithstanding the concerns in respect of adequacy of infestation of control animals, results would suggest that an adequate level of pulicidal effect (>95%) was demonstrated from 48 hours to 30 days following product application.

Another GLP-compliant study was conducted outside the EU (USA) using the candidate formulation to confirm the immediate and persistent efficacy of spinetoram 11.2% topical formulation against fleas (*Ctenocephalides felis*) when administered at a dosage of 0.7 ml (91 mg spinetoram) per cat. Sixteen mixed-breed short-haired cats (6 male and 10 female) aged 12–29 months and in the bodyweight range 2.04–6.3 kg were randomly allocated to two treatment groups (vehicle control 0.7 ml per cat or 11.2% (w/w) solution 0.7 ml (91 mg spinetoram) per cat). Flea infestation was on study days -1, 7, 14, 21, 28 and 35 with flea counts on study days 2, 9, 16, 23, 30 and 37. Insufficient data was provided to confirm whether an adequate infestation of individual control animals was achieved at all time points. Based upon the limited data provided, results would suggest that an adequate level of pulicidal effect (>95%) was demonstrated from 48 hours to 37 days following product application.

A GCP-compliant study was conducted outside the EU (USA) using the candidate formulation to document the speed of kill efficacy against cat fleas (*Ctenocephalides felis*) on cats, at various time points after dosing or infestation on study Days 0, 7, 14, 21 and 28. Ninety-six mixed-breed short-haired cats (both genders) aged 12–29 months and in the bodyweight range 2.2–6.6 kg were randomly allocated to four treatment groups. Insufficient data was provided to confirm whether an adequate infestation of individual control animals was achieved at all time points. Based upon the data provided, an acceptable level of pulicidal effect was not demonstrated 12 hours following product application.

Based upon the data provided from the seven dose confirmatory studies, an acceptable level of pulicidal effect (≥95%) was demonstrated consistently from 48 hours to 30 days post-treatment application of 91 mg spinetoram per cat. Although earlier onset (from 12 hours) and longer persistence (up to 42 days) of pulicidal effect was reported in some studies, the data provided in two of the studies is considered inadequate to support the proposed claim for 'elimination of fleas within 12 hours' as the acceptance of such a claim is dependent upon the same speed of kill having been demonstrated for the entire treatment interval being claimed (one month) which was not demonstrated by the study data provided. Furthermore, adequacy of infestation of control animals in those studies has not been confirmed.

The adequacy of infestation in 5 of the studies provided in relation to guideline requirements remains unsolved.

In 2 of the studies a European strain of *Ctenocephalides felis* was used and therefore it can be accepted that adequate confirmatory data (using European flea strains) is available to support the proposed claim against *C. felis*. However, the strain of *Ctenocephalides felis* used to artificially infest study animals in the other dose confirmatory studies originated from outside the EU. The relevance (in terms of both geographical representativeness and sensitivity) of the flea strain used in these additional supportive studies given the geographical location (Europe) where the product is intended to be marketed remains unclear.

Application site changes of a cosmetic nature (wetting, hair clumping/matting, residues) were observed in cats administered spinetoram. Only one animal in the dose confirmatory studies was reported to have evidence of alopecia at the application site.

In further support of the selected dose (91 mg spinetoram per cat), the results of two additional studies were provided – the first investigating the impact of water showering and shampooing on the efficacy of the formulation and the second investigating effectiveness under a simulated home environment.

The first study was a GCP-compliant study conducted outside the EU (Republic of South Africa) to investigate the effect of repeated exposure to wetting (on five occasions at weekly intervals commencing two days post-treatment application) or shampooing (once 16 days post-treatment application). The formulation was not the final one but instead was the higher strength formulation (39.6% w/w; 420 mg spinetoram/ml). Forty-eight (9 male and 39 female) domestic short-hair cats aged >6 months and in the bodyweight range 2.2–4.9 kg were included. The investigational product had a yellow/amber colouration and caused temporary discolouration of the hair coat when applied to white/light coated cats. Signs of hair loss/thinning at the application site were observed in all cats treated with spinetoram. Based upon the results of this study, it can be concluded that efficacy of the higher strength formulation was not affected by repeated weekly water exposure from 2 days post-treatment application or shampooing once 16 days post-treatment application. However, the relevance of this study's findings for the reformulated lower strength formulation is unclear and

consequently, the findings cannot be extrapolated to the reformulated lower strength candidate formulation in the absence of further justification.

The second study was a GCP-compliant study conducted outside the EU (Republic of South Africa) to investigate the effectiveness of the product under simulated home environment surroundings (approximately one third of the cubicle floor area was covered with carpet suitable for the development of fleas, blankets were placed in clean litter trays on the carpeted area for the cats to sleep on and a minimum of two and a maximum of three cats were housed per cubicle). The formulation was not the final one but instead was the higher strength formulation. The investigational product had a yellow/amber colouration and caused temporary discolouration of the hair coat when applied to white/light coated cats. Signs of hair loss/thinning at the application site were observed in the majority of cats treated with spinetoram. Adequacy of infestation of control animals and consequently the validity of the results of this study cannot be confirmed. Given that the candidate formulation was not used in this study, the findings of this study were not considered further.

Target animal tolerance

In support of target animal tolerance, results of fifteen studies have been provided. Many of the studies were conducted using the original formulation granted a marketing authorisation in the USA(420 mg spinetoram /ml). The candidate formulation includes a lower concentration of spinetoram (130 mg/ml) and different excipients.

The original formulation was authorised in the USA at a dose volume of 0.5 ml per cat (equivalent to 210 mg spinetoram) whereas the candidate formulation is to be applied at a dose volume of 0.7 ml (equivalent to 91 mg spinetoram).

Given the results of the radiolabelled PK studies where it was demonstrated that application of the candidate formulation does not result in any difference in the extent of dermal spread or any increase in dermal penetration of spinetoram compared with the higher strength formulation, it can be accepted that the target animal tolerance data generated using the higher strength formulation represents more than a ‘worst case’ scenario in terms of target animal tolerance. The only aspect of the candidate formulation not assessed in the radiolabelled studies was the differences in excipients.

Five studies were conducted using the original higher strength 420 mg spinetoram/ml) formulation. In those studies, local and systemic tolerance in cats from as young as 8 weeks of age to application of doses of up to 16.2x the dose of spinetoram in the candidate formulation repeated once after one month or up to 11.5x the dose of spinetoram in the candidate formulation repeated on seven occasions at monthly intervals was investigated.

Alopecia, erythema, scaling, scabbing, abrasion and yellowing of the hair at the application site were reported in some cats in addition to changes of a cosmetic nature (spiking/matted hair and crystallisation). Some cats showed evidence of salivation and/or vomiting (assumed to be from oral ingestion of the formulation via self-grooming).

One of the studies investigated tolerance following oral administration of the formulation. Results suggest that oral ingestion of 0.2x recommended treatment dose (RTD) via self-grooming is likely to elicit salivation in the majority of cats.

Two tolerance studies were conducted using transitional formulations. Application site reactions of a cosmetic nature (e.g. spiking, wet appearance of hair and crystallisation) were reported in all cats. Dermal reactions (erythema, scaling and scabbing) were observed in addition to hair loss. All of the

above reactions were reported to occur at the lower dose of 52 mg spinetoram per cat, but tended to occur with higher frequency at the higher (210 mg spinetoram) dose.

Eight studies were conducted using the final formulation (130 mg spinetoram/ml). In those studies, local tolerance in cats from as young as 8 weeks of age to application of the recommended treatment dose (0.7 ml of 130 mg spinetoram/ml) applied either at the base of the head or at the base of the neck on a single occasion was investigated. Local tolerance findings considered related to product application included mild erythema, scaling and hair loss in addition to observations of a cosmetic nature (spiking and crystallisation).

A non-GLP laboratory study was conducted to evaluate the local tolerance of two spinetoram spot-on formulations containing 420 mg spinetoram /ml and 130 mg spinetoram/ml (Cheristin) and to compare them to a positive control (fipronil - (s)-methoprene for cats). Sixty adult domestic short hair cats were treated on study day 0 with either one unit dose (0.5 ml) of the 420 mg spinetoram /ml formulation, 0.7 ml of 130 mg spinetoram /ml formulation, or one unit dose of fipronil - (s)-methoprene, with all doses applied directly to the skin from the base of the neck to the inter-scapular region. Hair loss, eschar formation and epidermal reactions were reported in cats administered the candidate formulation, but at a lower frequency than cats administered the higher strength formulation.

Another GCP-compliant study evaluated the local tolerance of adult cats to 130 mg spinetoram/ml spot-on solution applied at the base of the head, however, no comparator group was included. Forty-eight healthy, male and female adult (>6 months) European domestic short hair cats in the bodyweight range 2–5.03 kg (twenty-three of which had displayed local tolerance reactions in previous studies). On study Day 0, all cats were treated with 0.7 ml of 130 mg spinetoram/ml spot-on solution applied directly to the skin at the base of the head. Local tolerance findings considered related to product application included mild erythema, scaling and hair loss in addition to application site changes of a cosmetic nature (spiking and crystallisation).

A GCP-compliant study evaluated the local tolerance of 130 mg spinetoram/ml spot-on solution applied topically at the base of the head on adult cats in comparison to fipronil and s-methoprene for cats. Forty-eight (19 male and 29 female) healthy, adult (>18 months) European domestic short hair cats in the bodyweight range 2.27–5.47 kg were included (fourteen of which had displayed local tolerance reactions in previous studies). On study Day 0, all cats were randomly allocated to one of two treatment groups and received either 0.7 ml of 130 mg spinetoram/ml spot-on solution (n= 24) or the positive control product (n=24), applied directly to the skin at the base of the head. Local tolerance findings considered related to product application were limited in this study to mild scaling and observations of a cosmetic nature (spiking and crystallisation) in one animal.

Another GCP-compliant study evaluated the local tolerance of kittens (>8 weeks old) and adult cats (>6 months old) to topical administration of 130 mg spinetoram/ml spot-on solution applied at the base of the head. Seventy-one (29 male and 42 female) healthy, domestic short-hair cats in the bodyweight range 0.48–4.93 kg, including 23 kittens older than 8 weeks and 48 adults older than 6 months. On study Day 0, each kitten or cat was treated with 0.7 ml of 130 mg spinetoram/ml spot-on solution applied directly to the skin at the base of the head. Local tolerance findings considered related to product application included scaling, erythema, hair loss and observations of a cosmetic nature (spiking and crystallisation). The frequency of occurrence of these findings was higher in the kittens.

A non GLP-compliant study evaluated the local tolerance of 130 mg spinetoram/ml spot-on solution compared to fipronil - (s)-methoprene on adult cats. Two hundred (male and female) domestic

short-hair, adult (>12 months) cats were treated on study Day 0 with either 0.7 ml of 130 mg spinetoram/ml spot-on solution (n=135 cats) applied directly to the skin at the base of the head using a pipette, or one unit dose of fipronil - (s)-methoprene for cats(n=65) applied at the base of the neck. Local tolerance findings considered related to product application included hair loss (n=1) and observations of a cosmetic nature (spiking and crystallisation; n=3) in animals administered spinetoram.

Another non GLP-compliant study evaluated the local tolerance of 130 mg spinetoram/ml spot-on solution when applied topically on cats at two different administration sites - either at the base of the head or at the base of the neck between the shoulder blades. One hundred and thirty (male and female) domestic short-hair, adult (>12 months) cats in the bodyweight range 2.2–7.12 kg were treated on study Day 0 with 0.7 ml of 130 mg spinetoram/ml spot-on solution applied directly to the skin at the base of the head (n=65 cats), or at the intrascapular region (n=65). Local tolerance findings considered related to product application included hair loss, scaling and observations of a cosmetic nature (spiking and crystallisation). Although only occurring at a low frequency, incidence of hair loss appeared to be lower when the product was applied at the base of the head.

A non-GCP compliant study assessed the local tolerance of 130 mg spinetoram/ml spot-on solution at the application site in a field (client-owned) population of cats when compared with a positive control (fipronil - (s)-methoprene product for cats). 125 adult (>6 months), mixed gender, mixed breed cats were recruited from households across Sydney, Australia. Cats were randomly allocated to one of two treatment groups and received either a single topical application of 0.7 ml of 130 mg spinetoram/ml spot-on solution (n=75) or 0.5 ml fipronil - (s)-methoprene product for cats (n=50) in a 3:2 ratio on study Day 0 (visit 1). Products were applied directly to the skin at the dorsal base of the head. No adverse events were reported. Unlike previous studies, there were no reports of local reactions at the application site (alopecia, erythema) or cosmetic changes frequently reported in the studies conducted under laboratory conditions using the same formulation.

Another non-GCP study was conducted to determine the rate of adverse events (particularly alopecia) associated with the application of 130 mg spinetoram/ml spot-on solution in a field (client-owned) population of cats and to compare the adverse events rate of the candidate formulation with fipronil - (s)-methoprene product for cats. 208 adults (>6 months), mixed gender, mixed breed cats were recruited from households located in two geographically different regions of Australia. On study Day 0 (visit 1), cats were randomly allocated into one of three treatment groups (2:2:1 ratio) and received either a single topical application of the candidate formulation at the base of the skull (Group 1, n = 78 cats), a single topical application of the candidate formulation at the base of the neck (Group 2, n = 77 cats), or a single application of the control product fipronil - (s)-methoprene at the base of the neck (Group 3, n = 53 cats). Two cats experienced excessive salivation and frothing from the mouth within 30 minutes of treatment application at the base of the neck (Group 2 – candidate formulation). Symptoms resolved within one hour. Slight alopecia was observed in 1/78 cats (1.3%) treated with the candidate formulation at the base of the head (Group 1). The incidence of alopecia was 0.6% in all 155 cats treated with the candidate formulation (applied at either the base of the head or neck). Unlike previous studies, there were no reports of cosmetic changes frequently reported in the studies conducted under laboratory conditions using the same formulation. In this study, only one cat administered the candidate formulation (at the base of the head) was reported to have alopecia at the application site.

In addition to the fifteen aforementioned tolerance studies, tolerance data is also available from seven dose confirmation studies and four clinical field trials.

Concerning the dose confirmatory studies, application site changes of a cosmetic nature (wetting,

hair clumping/matting, residues) were observed. Only one animal in the dose confirmatory studies was reported to have shown evidence of alopecia at the application site.

Concerning the four field studies, a number of adverse events (including changes of a cosmetic nature) were reported in the field studies; namely, pruritus, hypersalivation, frothing, vomiting, stickiness at the application site, shaking/flicking heads, irritation/scratching/licking at the application site and/or behavioural changes (excessive grooming/biting/scratching, hyperactivity/agitation, lethargy).

Clinical field trials

In support of the efficacy of the candidate formulation under field conditions of use, the results of four field studies were provided.

A pivotal GCP-compliant blinded and controlled multi-site field study was conducted in 11 clinics in Germany, 9 in France and 3 in Spain using the candidate formulation. Three hundred client-owned cats aged 8 weeks or older and weighing at least 0.82 kg bodyweight were enrolled (145 (48.3%) from Germany and 155 (51.7%) from France and Spain). Cats were randomised to either spinetoram or a control product containing fipronil and (s)-methoprene in a ratio of approximately 2:1 and were treated on study Days 0 and 30 and were clinically examined (including scoring for Flea Allergy Dermatitis (FAD)) on study Days 0, 30 and 60.

This study was designed to demonstrate non-inferiority to a comparator product (as opposed to meeting classical guideline requirements of ≥95% efficacy for laboratory studies), by demonstrating ≥90% reduction in flea counts from pre-treatment to post-treatment time points.

For assessment of efficacy, cats had to be infested with at least five live fleas. Co-habiting cats were also treated with Cheristin and co-habiting dogs were treated with a product containing spinosad authorised for dogs. The primary effectiveness variable was the flea count data. Six signs of FAD (pruritus, papules, erythema, alopecia, scaling and dermatitis/pyodermatitis) were examined as secondary effectiveness variables, along with a composite score consisting of the average of these variables. Each FAD sign was assessed using a visual analogue scale (VAS) from 0 to 10, and scored as a single point on the line. Treatment with the candidate formulation resulted in statistically significantly higher reductions in arithmetic mean flea counts at all time points when compared to the comparator product.

Based on the data provided, it can be accepted that the candidate formulation demonstrated an acceptable level of effectiveness against flea infestation under field conditions of use. Cats administered spinetoram showed statistically significant improvements in overall FAD score and scores for three out of the six symptoms (pruritus, papules and alopecia) as assessed on study Days 30 and 60. Further, statistically significant improvements in scores for two additional symptoms (erythema and dermatitis) were observed by Day 60. Consequently, the proposed indication for use of the product as part of a treatment strategy for the control of FAD is considered to have been adequately supported. An acceptable level of tolerance under field conditions of use is also considered to have been adequately supported.

A non-GCP single-arm, unblinded, field study was conducted outside the EU (Australia) using the candidate formulation. A total of 24 cats from 17 households were enrolled. Cats were of various breeds and weighed from 1.65 to 7.70 kg. At visits 1, 2 and 3 cats were treated topically with a single dose (one pipette applicator) of the candidate formulation regardless of bodyweight. Treatment

was applied to the back of the neck by the study investigator. This study included cats as young as 15 weeks old.

Households were selected based on the presence of a flea infestation (≥10 fleas) on at least one cat. Co-habiting cats were also treated with Cheristin and co-habiting dogs were treated with a product containing spinosad authorised for dogs. The study involved four visits to each household at approximately monthly intervals over a three-month period. Visit 1 occurred on Day 0, then visits 2, 3 and 4 at approximately one, two and three months respectively.

The main deficiency of this study's design is the absence of a control group. Consequently, the conclusions that may be drawn from the study's findings are somewhat limited. Results suggest arithmetic mean percent reductions in flea counts of approximately 85%, 95% and 98% after 1, 2 and 3 months treatment. Findings from this study suggest a reduction in symptoms of FAD, however, only 5 animals were considered to have FAD at enrolment. Consequently, the findings must be interpreted with caution. The findings of this study are in general supportive of the effectiveness of the candidate formulation in reducing flea infestation in cats under field conditions and that improvement in symptoms of FAD and pruritus can be expected. An acceptable level of tolerance under field conditions of use is considered to have been adequately supported.

A single-arm, unblinded, single-region GCP-compliant field study was conducted outside the EU (Australia) and used the final formulation. Fifteen households were selected based on the presence of a flea infestation (≥10 fleas) on at least one cat. A total of 24 cats from 15 households were enrolled. Cats were aged 0.6–14 years, of various breeds and weighed from 2–9 kg. Co-habiting cats were also treated with Cheristin and co-habiting dogs were treated with a product containing spinosad authorised for dogs. At visits 1, 2 and 3 cats were treated topically with a single dose (one pipette applicator) of the candidate formulation. Treatment was applied to the back of the neck, close to the base of the head. Efficacy parameters measured were percent reduction in flea counts and alleviation of pruritus and flea allergy dermatitis.

The main deficiency of this study's design is the absence of a control group. Consequently, the conclusions that may be drawn from the study's findings are somewhat limited. Results suggest arithmetic mean percent reductions in flea counts of 91.5%, 98.8% and 95.5% after 1, 2 and 3 months treatment, respectively, when calculated using average flea counts at each counting time point. Arithmetic mean percent reductions in flea counts were also broadly similar when calculated using the average of percent reduction in each individual cat (91.8%, 98.4% and 94.4% after 1, 2 and 3 months treatment, respectively). No cats were reported to have had symptoms of FAD in this study. The findings of this study are in general supportive of the effectiveness of the candidate formulation in reducing flea infestation in cats under field conditions. One study animal showed evidence of irritation/scratching at the application site immediately after product application. Other study animals were reported to have displayed behavioural changes such as excessive grooming, hyperactivity, commonly associated with the topical application of veterinary medicinal products (VMPs) on cats. An acceptable level of tolerance under field conditions of use is considered to have been adequately supported.

A single-arm, unblinded, single-region field study was conducted outside the EU (Australia) and used the final formulation. Seventeen households were selected based on the presence of a flea infestation (≥10 fleas) on at least one cat. A total of 24 cats from 17 households were enrolled. Cats were aged 0.25–13 years, of various breeds and weighed from 1.7–7 kg bodyweight. Co-habiting cats were also treated with Cheristin and co-habiting dogs were treated with a product containing spinosad authorised for dogs. At visits 1, 2 and 3 cats were treated topically with a single dose of the

candidate formulation. Treatment was applied to the back of the neck, close to the base of the head. Parameters measured were percent reduction in flea counts and flea allergy dermatitis score.

The main deficiency of this study's design is the absence of a control group. Consequently, the conclusions that may be drawn from the study's findings are somewhat limited. Results suggest arithmetic mean percent reductions in flea counts of 68.8%, 98.6% and 96.8% after 1, 2 and 3 months treatment, respectively. The 68.8% reduction in mean flea count (compared to pre-treatment) reported in this study at 30 days post-treatment application was suggested to have arisen due to one cat having a marked increase in fleas between visits 1 and 2 resulting from higher risk of re-infestation for this particular animal. No cats were reported to have had symptoms of FAD in this study. Based upon the data provided, it can be accepted that the effectiveness of the candidate formulation in reducing flea infestation in cats under field conditions has been generally supported. Vomiting (n=2) and frothing (n=1) were observed after product application. Other study animals were reported to have displayed behavioural changes such as excessive grooming, hyperactivity/agitation, commonly associated with the topical application of VMPs on cats.

An acceptable level of tolerance under field conditions of use is considered to have been adequately supported.

Overall conclusion on efficacy

Pharmacodynamics:

Spinetoram is a member of the spinosyn family of fermentation-derived insecticides produced by the actinomycete *Saccharopolyspora spinose* and consists of two active factors (spinetoram J and spinetoram L. The mode of action of spinosyns in insects is believed to primarily involve nicotinic acetylcholine receptors (nAChRs).

In the opinion of the CVMP, additional information should have been provided to characterise how the target ectoparasite (*Ctenocephalides felis*) becomes exposed to the pulicidal action of spinetoram (spinetoram factors J and L) following topical administration to cats.

Resistance:

Spinosad and spinetoram exert their insecticidal activity through a dual mode of action involving both nicotinic- and GABAergic pathways. This target site differs from the mode of action of other chemical classes, including the neonicotinoids such as imidacloprid. Given that spinosyns are a relatively new class of insecticide for use in animals in Europe and the comparatively unique mode of insecticidal activity when compared with other available insecticides, it can be concluded that resistance development of *C. felis* to spinetoram is not of concern at present.

Pharmacokinetics:

Two ^{14}C radiolabelled studies to investigate the surface spread as well as dermal penetration of spinetoram following topical application to cats have been conducted. Results demonstrated that ^{14}C-spinetoram reached peak concentrations in plasma, hair and skin at 30 hours, one day and 7 days, respectively, with concentrations decreasing thereafter.

Results suggest very limited dermal penetration of the product, with an apparent association with hair follicles and sebaceous glands. However, the fate of spinetoram factor-L and any impurities following application of the formulation to cats was not adequately characterised.

Tolerance:

In support of target animal tolerance, results of a total of fifteen target animal tolerance studies were provided.

Five studies (including one pivotal study) were conducted using the original higher strength (420 mg spinetoram/ml) formulation. In those studies, local and systemic tolerance in cats from as young as 8 weeks of age to application of doses of up to 16.2x the dose of spinetoram in the candidate formulation repeated once after one month and up to 11.5x the dose of spinetoram in the candidate formulation repeated on seven occasions at monthly intervals was investigated.

Alopecia, erythema, scaling, scabbing, abrasion and yellowing of the hair at the application site were reported in some cats in addition to changes of a cosmetic nature (spiking/matted hair and crystallisation). Some cats showed evidence of salivation and/or vomition (assumed to be from oral ingestion of the formulation via self-grooming).

One of the studies investigated tolerance following oral administration of the formulation. Results suggest that oral ingestion of 0.2x RTD via self-grooming is likely to elicit salivation in the majority of cats.

Two studies were conducted using transitional formulations with similar findings of application site reactions of a cosmetic nature (e.g. spiking, wet appearance of hair and crystallisation) being reported. Dermal reactions (erythema, scaling and scabbing) were observed in addition to hair loss.

Eight studies (including two with client-owned cats) were conducted using the candidate formulation. In those studies, local tolerance in cats from as young as 8 weeks of age to application of the recommended treatment dose (0.7 ml of 130 mg spinetoram/ml) applied either at the base of the head or at the base of the neck on a single occasion was investigated. Local tolerance findings considered related to product application included mild erythema, scaling and hair loss in addition to observations of a cosmetic nature (spiking and crystallisation).

In addition to the fifteen aforementioned tolerance studies, tolerance data is also available from seven dose confirmation studies and four clinical field trials.

Concerning the dose confirmatory studies, application site changes of a cosmetic nature (wetting, hair clumping/matting, residues) were observed. Only one animal in the dose confirmatory studies was reported to have shown evidence of alopecia at the application site.

Concerning the four field studies, a number of adverse events (including changes of a cosmetic nature) were reported in the field studies; namely, pruritus, hypersalivation, frothing, vomiting, stickiness at the application site, shaking/flicking heads, irritation/scratching/licking at the application site and/or behavioural changes (excessive grooming/biting/scratching, hyperactivity/agitation, lethargy).

In the opinion of the CVMP, the scientific advice provided by the CVMP was in general followed. It can be concluded that the candidate formulation is unlikely to elicit systemic toxicity but may result in salivation and vomition if ingested orally. Local tolerance reactions that are to be expected include hair loss, erythema, scaling and scabbing at the application site in addition to changes of a cosmetic nature (e.g. spiking, wet appearance of hair and crystallisation). Behavioural changes commonly associated with topical application of spot-on products to cats that may be expected include excessive grooming/biting/scratching, hyperactivity/agitation.

In order to more accurately qualify the hair loss reported in cats following application of the final formulation and to ensure that all relevant adverse reactions likely to be observed following application of the final formulation are indicated in the proposed SPC, the frequency of occurrence of

adverse events in each of the studies in which the final formulation was used should be summarised and alternative wording for inclusion in section 4.6 of the SPC should be proposed that more accurately reflects the range of findings (pruritus, hypersalivation, frothing, vomiting, behavioural changes (excessive grooming/biting/scratching, hyperactivity/agitation, shaking/flicking head), local reactions at the application site (hair loss, erythema, scaling, scabbing) as well as changes to the clinical chemistry parameters [e.g. BUN] from the target animal safety, dose confirmatory and field studies provided with this application.

In addition, the range of changes solely of a cosmetic nature (spiking, wetting/matting, crystallisation) reported in those studies should also be mentioned, but an indication of their frequency of occurrence is considered unnecessary.

At the same time, the information proposed for inclusion in section 4.10 should also be reviewed to more accurately reflect the findings reported following application of overdose.

Efficacy:

The proposed indication is:

"For the treatment and prevention of flea infestations (*Ctenocephalides felis*) on cats.

Elimination of fleas within 12 hours. One treatment prevents flea infestations for at least one month. This product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) on cats."

In total, seven GCP-compliant dose confirmatory studies were conducted using the final formulation (one within the EU and six outside the EU).

In the one study conducted within the EU, an acceptable level of pulicidal effect against *C. felis* (≥95%) was demonstrated from 48 hours (immediate efficacy) to 30 days (persistent efficacy) following application of 91 mg spinetoram per cat.

In another study conducted outside the EU, a European strain of *C. felis* was used and an acceptable level of pulicidal effect (≥95%) was demonstrated from 48 hours (immediate efficacy) to 37 days (persistent efficacy) following application of 91 mg spinetoram per cat.

Consequently, it may be concluded that two dose confirmatory studies have demonstrated an acceptable level of efficacy of the product against *C. felis* in terms of both immediate and persistent pulicidal effect. However, the proposed indication is for the treatment and prevention of flea infestations. In the opinion of the CVMP, the study designs included in this application are considered appropriate to support only a treatment (immediate and persistent pulicidal effect) but not a preventative effect.

In another study, the final formulation was not used and counted fleas were applied directly back on to the study animals and therefore prevention of infestation was not investigated. In all four field trials, co-habiting cats and dogs were concurrently treated for fleas thereby reducing/eliminating infestation challenge from the environment. In the absence of acceptable justification/further study data, the proposed preventative claim was considered unacceptable.

Although earlier onset (from 12 hours) and longer persistence (up to 42 days) of pulicidal effect was reported in some studies, the data provided is considered inadequate to support the proposed claim for 'elimination of fleas within 12 hours' as the acceptance of such a claim is dependent upon the same speed of kill having been demonstrated for the entire treatment interval being claimed (one month) which was not demonstrated by the study data provided.

Furthermore, apart from two dose confirmation studies, the strain of *Ctenocephalides felis* used to artificially infest study animals originated from outside the EU. Further justification should be provided for the relevance (in terms of both geographical representativeness and sensitivity) of the flea strain used in these studies given the geographical location (Europe) where the product is intended to be marketed.

Notwithstanding the above, it can be accepted that the results of two dose confirmatory studies support an indication for the treatment of flea infestations (*C. felis*) for one month. However, the proposed indication as worded, suggests that pulicidal effect lasts more than one month, without any upper limit to duration of effect specified. In the opinion of the CVMP, the wording "…for at least one month" should be amended to "…for one month".

Application site changes of a cosmetic nature (wetting, hair clumping/matting, residues) were observed in cats administered spinetoram. Only one animal in the dose confirmatory studies was reported to have shown evidence of alopecia at the application site.

Results of a study investigating the impact of water showering and shampooing on the efficacy of the higher strength formulation (39.6% w/w; 420 mg spinetoram/ml) were provided. Although efficacy of the formulation tested was not affected by repeated weekly water exposure from 2 days post-treatment application or shampooing once 16 days post-treatment application, the relevance of these findings for the re-formulated lower strength formulation remains unclear. In the absence of acceptable justification/additional data, the statement "*The shampooing or showering of cats has no effect on the immediate and persistent effectiveness of the veterinary medicinal product*" was considered unacceptable.

In support of the effectiveness of the product under field conditions of use, results of four field studies were provided, with one pivotal study conducted within the EU.

The pivotal field study was a GCP-compliant study conducted in France, Germany and Spain, therefore addressing the guideline requirements to conduct field studies in more than one geographical region with at least 50 animals per geographical area included. It can be accepted that the candidate formulation demonstrated an acceptable level of effectiveness against flea infestation under field conditions of use for up to 30 days post-treatment application. Given the level of effectiveness demonstrated against fleas and the statistically significantly lower scores for the majority of FAD symptoms assessed in this study, the proposed indication for use of the product as part of a treatment strategy for the control of FAD is considered to have been adequately supported.

The three other field studies were conducted outside the EU and none included a control group. Although the level of effectiveness was sometimes less than 95% (based on arithmetic mean calculations) at some of the flea count time points, the results are considered to generally support the findings from the dose confirmatory studies.

A number of adverse events (including changes of a cosmetic nature) were reported in the field studies; namely, pruritus, hypersalivation, frothing, vomiting, stickiness at the application site, shaking/flicking heads, irritation/scratching/licking at the application site and/or behavioural changes (excessive grooming/biting/scratching, hyperactivity/agitation, lethargy). Such information should be summarised (see conclusion on target animal tolerance) in order to conclude on the most appropriate information to be included in section 4.6 of the proposed SPC.

Based on the information presented to date, it is not possible to conclude on the efficacy of the product.

Part 5 – Benefit-risk assessment

Introduction

Cheristin is a spot-on solution containing 130 mg/ml spinetoram. The product is available as a single/unit dose pipette delivering 91 mg of spinetoram in 0.7 ml of product and presented in aluminium blister packs packed into carton boxes containing of 3 or 6 pipettes.

The active substance spinetoram is a new active substance, a multicomponent tetracyclic macrolide of spinosyn family which has an insecticidal activity by activation of nicotinic acetylcholine receptors (nAChRs). The product is intended for use in cats for the treatment and prevention of flea infestations (*Ctenocephalides felis*) in cats.

The effective dose of 91 mg spinetoram per cat (one unit dose pipette of 0.7 ml) applied once topically to the base of the neck is considered to have been adequately supported.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Cheristin is its efficacy in treating flea infestations with *Ctenocephalides felis* on cats, which was investigated in a number of well-designed laboratory studies conducted in accordance with GLP and field studies conducted in accordance with GCP to an acceptable standard.

However, the proposed claims for the prevention of flea infestations and elimination of fleas within 12 hours were not considered to have been adequately supported.

A number of clarifications were required in terms of how fleas become exposed to the product, the relevance of the flea strains used in some of the studies, the adequacy of the pharmacokinetic characterisation of spinetoram factor L and any impurities, the adequacy of infestation in some studies and the relevance of the data provided in support of the absence of any impact of shampooing and showering on effectiveness of the product.

Additional benefits

The product has shown to be beneficial when used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD) on cats.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented in a generally satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. However, there remain questions relating to the active substance regarding re-designation of the starting material and the proposed limits for impurities and their qualification. In relation to the

finished product, questions are raised regarding the limits for impurities in the finished product release and shelf life specifications and the qualification of these impurities.

Deficiencies also arise from concerns over the (confidential) restricted part of the ASMF.

Based on the data presented an appropriate shelf life and storage precautions for the product cannot be determined.

Safety:

Risks for the target animal:

Risks for the target animal have been identified in the various studies conducted and principally relate to pruritus, hypersalivation, frothing, vomiting, behavioural changes (excessive grooming/biting/scratching, hyperactivity/agitation, shaking/flicking head) and local reactions at the application site (hair loss, erythema, scaling, scabbing). The final wording to be included in the SPC concerning adverse events, their frequency of occurrence and signs of overdose could not be finalised in the absence of additional information.

Risk for the user:

Risks to the user were adequately characterised and the proposed risk mitigation measures/advice was considered to be generally acceptable. However, some amendments to the advice were requested. Should the proposed amendments be implemented the CVMP could conclude that the product would not present an unacceptable risk for the user when handled, administered, stored and disposed of in accordance with the recommendations on the proposed SPC.

Risk for the environment:

Cheristin is not expected to pose a risk for the environment when used according to the proposed SPC recommendations.

Risk management or mitigation measures

The proposed risk management or mitigation measures are generally acceptable; however, some amendments to SPC statements are still necessary for final acceptance.

Evaluation of the benefit-risk balance

At the time of the application's withdrawal major concerns had been raised regarding quality and the proposed preventative claim.

In the presence of outstanding major and other concerns, the benefit-risk balance of the application was therefore inconclusive.

Conclusion

Based on the original data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Cheristin is not approvable at the present time as the data presented was not considered to be in accordance with the requirements of Directive 2001/82/EC.

The CVMP considers that no conclusions could therefore be taken on the benefit-risk balance in the

absence of additional information/data.