



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Vectra Felis (EMA/V/C/002746/0000)

International non-proprietary name: pyriproxyfen / dinotefuran

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



Introduction

On 26 November 2012 the applicant CEVA Santé Animale submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Vectra Felis, through the centralised procedure falling within Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 16 May 2012 as Vectra Felis contains a new combination of two active substances (dinotefuran and pyriproxyfen) which was not authorised in the European Union (EU) on the date of entry into force of the Regulation. The rapporteur appointed was C. Ibrahim and co-rapporteur E. Lander Persson.

The veterinary medicinal product was approved for the following indication:

“Treatment and prevention of flea infestation (*Ctenocephalides felis*) on cats.

One application prevents flea infestation for one month. It also prevents the multiplication of fleas by inhibiting flea emergence in the environment of the cat for 3 months.

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

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

On 10 April 2014, the CVMP adopted an opinion and assessment report.

On 6 June 2014, the European Commission adopted a Commission Decision granting a marketing authorisation for this product.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The pharmacovigilance system as described by the applicant fulfils the requirements of Directive 2001/82/EC and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the EU or in a third country.

Manufacturing authorisations and inspection status

The finished product is manufactured and packaged (primary and secondary packaging) at the following manufacturing site outside the EU: Ei, Kannapolis (USA). The product is then shipped to Europe where batch testing and batch release for the EU will be carried out by CEVA Santé Animale, Libourne (France); this site also acts as an additional site for secondary packaging.

Both sites comply with good manufacturing practice (GMP) requirements; corresponding GMP certificates have been provided.

Overall conclusions on administrative particulars

The GMP status of the active substances and the dosage form manufacturing sites has been satisfactorily established and are in line with legal requirements.

The detailed description of the pharmacovigilance system is considered in line with legal requirements.

Part 2 - Quality

Composition

The finished product is a non-aqueous solution for spot-on use containing the active ingredients dinotefuran and pyriproxyfen dissolved in the non-aqueous solvent dimethyl sulfoxide (DMSO). The formulation contains no preservative or antioxidant, but this is justified. The product is available in a single strength (423 mg dinotefuran and 42.3 mg pyriproxyfen) unit dose spot-on applicator, containing a volume of 0.9 ml.

Container

The product is presented in a single dose spot-on applicator composed of a multi-layered complex of aluminium and polyethylene, with a neck and a shoulder made of high density polyethylene (HDPE). The spot-on applicators are top-sealed with an aluminium liner complex (aluminium/polyester/sealable polyethylene layer) and fitted with a tan-coloured polypropylene screw applicator tip.

Development pharmaceuticals

The aim of the product's development was a spot-on solution containing dinotefuran and pyriproxyfen. Previous experience of developing a similar product, already authorised and marketed in the United States (US), was used. However, an identical formulation to the US product could not be used for the EU product, as in order to ensure 30 day efficacy against fleas a higher concentration of both active substances, without an increase in the volume of the spot-on, was necessary.

DMSO was chosen as the solvent as both active substances are freely to very soluble in it.

The CVMP agreed that although brief, the information on the development of the product is sufficiently comprehensive and acceptable for such a simple solution formulation.

Method of manufacture

The finished product is a simple solution formulation with no complex processing or packaging operations. Dissolution of the two active substances is the most critical step in the manufacturing process but this is controlled by an in-process control on visible active substances. Furthermore, the solution is then filtered before filling.

Validation of the manufacturing process at the largest proposed production scale is still outstanding, however the CVMP considered it is sufficient to provide a recommendation for this to be conducted following the granting of a marketing authorisation for the product. A satisfactory validation scheme for this was provided.

Control of starting materials

Active substances

Active substance - dinotefuran

Dinotefuran [IUPAC: (RS)-1-methyl-2-nitro-3-(tetrahydro-3-furylmethyl)guanidine, CAS: 165252-70-0] is not described in either the European Pharmacopoeia (Ph. Eur.) or any other pharmacopoeia of the EU so is tested according to an in-house monograph.

The data for this active substance are presented in the form of an active substance master file (ASMF) held by the active substance manufacturer. The manufacturing process of dinotefuran is a chemical synthesis. The justification for the designation of the starting materials is considered appropriate.

Adequate specifications for the control of the active substance have been provided, and the analytical methods have been satisfactorily validated.

Results of several active substance batches were provided and were shown to meet the specifications.

Results of stability studies have been presented which justify the claimed retest period of 36 months.

Active substance - pyriproxyfen

Pyriproxyfen is not described in either the Ph. Eur. or any other pharmacopoeia of the EU so is tested according to an in-house monograph.

The data for this active substance are presented in the form of an ASMF held by the active substance manufacturer. The manufacturing process of pyriproxyfen is a chemical synthesis. The justification for the designation of the starting materials is considered appropriate.

Adequate specifications for the control of the active substance have been provided. The potentially genotoxic impurity 2-chloropyridine (CRP) is the subject of a separate test and limit in the specification and is adequately controlled. The assay and content of impurities is determined using high-performance liquid chromatography (HPLC).

All the analytical methods have been sufficiently validated.

Results of three recent production batches show that they meet the agreed specifications.

A retest period of 36 months has been substantiated by the results of stability studies.

Excipients

Dimethyl sulfoxide (DMSO) is described in the Ph. Eur. and is controlled according to the current monograph.

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

No material of animal origin is used in the manufacture of any of the ingredients in the finished product. Compliance of the active substance and all the excipients in the product with the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) has been confirmed.

Control tests during production

Not applicable.

Control tests on the finished product

The specification for release testing is appropriate to control the quality of the finished product and is in line with the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL39 on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances. Adequate specifications and routine tests have been described to ensure the appropriate and consistent quality of the finished product. Analytical methods are fully described and validated in accordance with VICH guidelines.

The shelf life specification is different from the release specification only with regard to lower content limits for the active substances and the limit for water content, but the differences are justified.

Results of the analysis of three consecutive batches of finished product (manufactured at the smallest of the proposed production scales of 39.4 kg) were presented which comply with the proposed specification.

Stability

The stability studies were conducted in accordance with the relevant stability guidelines.

Results covering periods of 24 months at both long term and intermediate conditions, and 6 months at accelerated conditions, are available. All results comply with the product's shelf life specification. The data provided justify a shelf life of 3 years with no special storage conditions.

Overall conclusions on quality

The data for each of the active substances is presented in an ASMF. Each includes comprehensive information on the starting materials, manufacture, characteristics and control of the relevant active substance. Neither of the actives are the subject of a monograph of the Ph. Eur. or a pharmacopoeia of any EU member state and therefore both are tested in accordance with in-house monographs, which are satisfactory.

The only excipient is a non-aqueous solvent, which is considered acceptable, and is the subject of an appropriate specification.

The rationale for the choice of the formulation is acceptable.

Appropriate information is provided for the packaging materials for these single dose spot-on applicators.

There are no concerns in relation to transmissible spongiform encephalopathy (TSE) for any of the ingredients of the product.

Manufacturing process validation for the largest proposed production scale batches is still outstanding but will be finalised before any such sized batches are placed on the market.

The finished product release specification is considered acceptable. The control methods have been validated and the specification is considered appropriate for a product of this type.

Suitable stability studies according to VICH guidelines have been carried out and the data provided support the shelf life of 3 years. No special storage precautions are considered necessary.

The quality data and documentation provided are in accordance with the relevant VICH and EU guidelines.

Part 3 – Safety

Safety documentation

Dinotefuran is an active substance which was recently included for the first time in a veterinary medicinal product, Vectra 3D for dogs, from the same applicant. Full study reports to support the safety profile of this compound have been presented in the application. Dinotefuran has been tested in a number of laboratory animals in well executed good laboratory practice (GLP) studies, all of which have been conducted in line with the appropriate guidelines.

Pyriproxyfen has been included in veterinary medicinal products authorised in the EU and indicated for use in non-food producing species. It is also included in the product Vectra 3D (see previous paragraph). To complete the limited data available in the public domain, full study reports have been presented for pyriproxyfen. The data are relatively recent and the majority of the studies were conducted in accordance with GLP. Those studies which were not in conformance with GLP were however performed in accordance to modern protocols and were satisfactorily reported. These studies are considered adequate to ascertain the toxicity profile for pyriproxyfen.

The solvent DMSO has been included in several authorised veterinary and human medicinal products. Its characteristics are described in an Organisation for Economic Co-operation and Development (OECD) Screening Information Dataset dossier.

Pharmacodynamics

See Part 4.

Pharmacokinetics

After an oral dose of radiolabelled dinotefuran given to rats, nearly 100% of the radioactivity was absorbed. Absorption of dinotefuran is rapid, with wide distribution throughout the body. Additionally, it is rapidly transferred from maternal blood to milk and widely distributed in foetal tissues. After intravenous and oral administration of radiolabelled dinotefuran to rats, very little metabolism occurs as over 90% is excreted as the unchanged parent compound.

Pharmacokinetic data in neonatal rats indicate that the absorption and clearance of radioactivity were slower than in adults and suggest a slower metabolism of ¹⁴C-guanidine dinotefuran in pups, possibly due to the incomplete development of their liver function.

Systemic dermal absorption of dinotefuran in the rat was demonstrated to be very low, with only 1.04% of the dose measured in the systemic circulation.

For pyriproxyfen, absorption and distribution in the body were limited. Pyriproxyfen levels in tissues of rats (with the exception of fat) peaked 2 to 8 hours after oral administration, whereas the peak concentrations in fat were found 12 to 24 hours after dosing. Pyriproxyfen concentrations were found to be the highest in fat, without any evidence of accumulation. Pyriproxyfen was highly metabolised. Excretion into the faeces and urine was demonstrated to be rapid, with the major route of excretion being via the faeces.

The excipient DMSO is readily absorbed through the skin and after oral administration in rats, and is widely distributed to all body tissues. Metabolism of DMSO takes place primarily in the liver and the

kidneys. The principal metabolite is dimethyl sulfone (DMSO₂). Peak plasma levels of DMSO₂ in humans were observed 72 to 96 hours after dosing; they then declined with a half-life of about 60 to 72 hours. DMSO is excreted in the urine unchanged or as the metabolite DMSO₂.

In an *in vitro* percutaneous absorption study with the finished product, it was shown that maximum values of 23.32% for dinotefuran and 18.11% for pyriproxyfen diffused through the human skin, or remained in the skin or adjacent tissue.

Toxicological studies

Single dose toxicity:

GLP-conforming acute toxicity studies show that the acute oral, dermal and inhalation toxicities of dinotefuran and pyriproxyfen are low.

The excipient DMSO is also of low acute oral and dermal toxicity; however GLP-conforming studies were not available.

Repeated dose toxicity:

Dinotefuran:

Several repeat dose toxicity studies in rats and dogs were provided. From these it was not possible to attribute a target organ to dinotefuran toxicity. Clinical adverse signs consisted mainly of reduced food consumption and reduced bodyweights (dogs and rodents) at higher dose levels. In rats, alterations in adrenal histopathology were evident. With regard to studies conducted in dogs, emesis and loose stools were particularly prevalent after dinotefuran administration. The lowest no-observed-effect level (NOEL) for dinotefuran was found to be 34 mg/kg bodyweight (bw)/day in male rats, which was obtained from a 90 day oral repeat dose study, and 22.3 mg/kg bw/day in female dogs, which was obtained from a 52 week repeat dose oral study.

Dinotefuran did not exert systemic effects after repeated dermal application in rats. Exposure from inhalation is not considered to be a relevant route of exposure with respect to target animal and user safety when taking into account the formulation of the product and its intended topical application and use.

Pyriproxyfen:

Several repeat dose toxicity studies in rodents (mice and rats) and dogs were provided. Pyriproxyfen showed clear renal toxicity in mice and hepatotoxicity in rats. In dogs also, hepatotoxicity was noted which resulted in liver enlargement, chronic inflammation and repair fibrosis. In dogs which received pyriproxyfen at higher dose levels, emesis and diarrhoea occurred. Notably, following the administration of 1,000 mg pyriproxyfen/kg/day for 52 weeks, two dogs out of a group of eight had to be euthanized for animal welfare reasons, apparently as the result of pyriproxyfen-related hepatotoxicity. The lowest NOEL for pyriproxyfen was found to be 10 mg/kg bw/day in dogs, for both sexes. However, it was noted that this was the highest dose tested in this study.

After the repeated oral administration of pyriproxyfen in mice, a dose-dependent mortality was seen at 750 mg/kg bw/day and above. The main target organ was the kidney. Increases of liver enzymes and liver organ weights were not associated with histopathological findings. A NOEL was established at 38 mg/kg bw/day based on increased cholesterol values in females.

In rats, no mortality was seen up to the highest dose of 784 mg/kg bw/day. The liver was the target tissue and hepatotoxicity of pyriproxyfen was firstly seen at doses of 118 mg/kg bw/day in rats,

observed by changes in biochemistry parameters and increases in liver weight. Additionally, changes in red blood cell parameters were affected and histopathological changes were seen in the kidneys. A NOEL was established at 24 mg/kg bw/day in males and 28 mg/kg bw/day in females.

Pyriproxyfen did not exert systemic effects after dermal application in rats. Exposure by inhalation is not considered a relevant route of exposure in respect to target animal and user safety, taking into account the formulation of the product and its intended use.

DMSO:

The excipient DMSO is of low toxicity when administered by repeated oral or dermal administration. With the exception of a decrease in bodyweight gain and some haematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common observation was changes of the refractive power of the lens in some animal species. Species in which such lens alterations readily develop include the rat, rabbit, dog and pig, whilst primates are not sensitive.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

The applicant has provided GLP-compliant studies (dinotefuran and pyriproxyfen) and publications (DMSO) on the reproductive toxicity for all three substances. There were no treatment-related changes regarding reproductive parameters for pyriproxyfen and DMSO.

A two-generation study in rats and a preceding preliminary two-generation study were provided for dinotefuran. The preliminary study showed evidence that at 1,340 mg/kg bw/day and 1,507 mg/kg bw/day in males and females respectively, dinotefuran may cause increased post-implantation losses and decreased litter sizes. Other reproductive parameters were not affected. Possible treatment-related effects in the offspring included changes in organ weights and a reduction in bodyweight. The NOELs for the adults of the parental (P) and 1st filial (F1) generations, as well as for pup development, were 241 mg/kg bw/day in P males, 249 mg/kg bw/day in F1 males, 267.9 mg/kg bw/day in P females and 292.6 mg/kg bw/day in F1 females. The NOELs for reproductive effects and pup behaviour were 822.1 mg/kg bw/day in P males, 934.7 mg/kg bw/day in F1 males, 907 mg/kg bw/day in P females and 1,004.8 mg/kg bw/day in F1 females.

In a GLP-compliant two generation study in rats with pyriproxyfen, no treatment-related changes regarding reproductive parameters were observed. However, the study showed a possible treatment-related increase in chronic interstitial nephritis in males of the F1 generation. The parental NOEL was 200 ppm, the maternal and maternal reproductive NOEL was 5,000 ppm and the pup developmental NOEL (F1 and F2 generation) was 1,000 ppm.

No treatment-related changes regarding reproductive parameters were reported for DMSO.

The applicant has provided sufficient experimental data from developmental toxicity studies in rats and rabbits to conclude that each of the two active ingredients in the finished product have no teratogenic potential. However dinotefuran increased the rate of abortions in rabbits (at 1,000 mg/kg bw, NOEL 300 mg/kg bw), and pyriproxyfen provoked developmental effects at toxic maternal doses (300 mg/kg, NOEL 100 mg/kg bw) in rats.

Mutagenicity/genotoxicity

A comprehensive data set on mutagenicity was provided. Each of the three ingredients in the product, dinotefuran, pyriproxyfen and DMSO, proved to be non-mutagenic.

Since all three ingredients were tested individually and adequately, and revealed clear negative results, it can be assumed that Vectra Felis has no genotoxic potential.

Carcinogenicity

Dinotefuran:

In a carcinogenicity study in mice, a no-observed-adverse-effect level (NOAEL) of <3 mg/kg (for males) or <4 mg/kg (for females) bw/day, established by the US Environmental Protection Agency (EPA), was based on decreased spleen weights in males at termination, and on increased ovarian weights in females at week 53. Since there were no microscopic findings associated with the increases of the spleen weights, and the ovarian weights were not clearly dose-dependent and not seen at terminal sacrifice (78 weeks), these changes are considered not to be treatment-related. The proposed NOAEL of 345 and 441 mg/kg bw/day for males and females respectively can be supported.

In rats, the survival rate of the combined chronic carcinogenicity study (104 weeks) was below 50% in all groups treated with dinotefuran, except the highest dose group in males (53%), and did not show a dose-dependence. This is in agreement with published survival rates of this strain (compilation by Charles River Laboratories). However, it should be noted that pelvic mineralisation and ulceration clearly increased at 991 mg/kg bw/day in males during the carcinogenicity study and may be caused by the treatment.

It can be concluded from the GLP-compliant carcinogenicity studies that dinotefuran has not shown any carcinogenic potential in mice and rats.

Pyriproxyfen:

The chronic toxicity and carcinogenicity of pyriproxyfen was studied in GLP-compliant carcinogenicity studies in rats (2 year study) and in mice (78 week study). None of the studies showed any evidence of a carcinogenic potential.

The relevant NOEL in male mice was 16 mg/kg bw/day based on a reduced survival rate, increased severity of systemic amyloidosis and histopathological changes in the kidneys.

In rats, the main target organ was the liver. Increases in serum chemistry values (cholesterol, phospholipids) suggest a compound-related change which is likely to be associated with the liver during the first half of the study in the high dose groups. However, these effects were no longer manifest during the latter half of the study. No microscopic hepatic changes due to treatment were identified.

DMSO:

The excipient DMSO has not been assessed in a valid GLP-compliant carcinogenicity study. There are some contradictory results from initiation and promotion studies which do not allow a firm conclusion with regard to the carcinogenic potential of this solvent.

Studies of other effects

Dinotefuran has been found to be a mild ocular irritant in one GLP-compliant ocular irritation study in rabbits, leading to a classification of category 2 in accordance with Regulation (EC) No 1272/2008. The results of the second eye irritation study, conducted with a lower concentration, were negative. In a dermal irritation study dinotefuran demonstrated no dermal irritation. In addition, dinotefuran is not a dermal sensitizer. During an acute and sub-chronic neurotoxicity study, decreased motor activity was seen in high dose animals. However, as there were no correlative effects in the functional observational battery (FOB) data evaluations and macroscopic or microscopic examinations, this effect was not considered adverse or as a sign of neurotoxicity. Following monoclonal antibody assays, in both mice and rats, no effect on immune response function was seen, demonstrating that dinotefuran does not elicit an immunotoxic effect.

Dermal and ocular irritation studies (GLP-compliant) in rabbits show that pyriproxyfen is only minimally irritating to the eyes and is not a skin sensitizer or a skin irritant.

Studies conducted with the product demonstrated that Vectra Felis is irritating to the eyes and moderately irritating to the skin, but is not a skin sensitizer.

Topical application of the product resulted in low amounts of pyriproxyfen and dinotefuran residues dislodged from cats after petting (stroking) them over the whole sampling period (30 days). Sampling (by petting) was performed in three groups. Maximum residue levels were dislodged four hours after treatment. The amounts of dislodgeable substance declined significantly over time.

DMSO is of low oral and dermal toxicity. It has been sporadically reported to be irritating to the skin and it is slightly irritating to the eye. It is not a skin sensitizer.

Human use:

Dinotefuran and pyriproxyfen are not used in human medicinal products and no human data are therefore available for assessment.

The excipient DMSO has been used as a solvent for a wide variety of substances administered to humans and laboratory animals. Following topical application, DMSO enhanced the biological response of many kinds of substances, however the effect of some substances was reduced, and very few were unaffected (OECD, SIDS Initial Assessment Report for SIAM 26, 2008). DMSO can induce transient erythema, burning and itching, but these symptoms disappear after discontinuing its application.

User safety

A user safety assessment according to the current CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) has been submitted. Relevant exposure scenarios were considered for the veterinarian and the cat owner who apply the product, and also for other people (especially children) who have direct contact with a treated cat.

A quantitative risk assessment for both acute and chronic oral/dermal exposures was performed with the whole contents of one pipette (worst case). Eye exposure was also considered. Margins of exposure (MOE) were calculated for each of the two active substances and the solvent (DMSO) and each exposure scenario using equations from the latest standard operating procedure published by the US EPA in 2012. The following warning phrases were therefore included in the summary of product characteristics (SPC) and other product information and have been agreed as satisfactory:

- Wash hands thoroughly and immediately after use.
- The veterinary medicinal product is irritating to the eyes and skin.

- Avoid contact with the skin, eyes or mouth.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- If the veterinary medicinal product accidentally gets into the eyes, they should be thoroughly flushed with water.
- If skin or eye irritation persists, or in case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- People with known hypersensitivity to dinotefuran, pyriproxyfen or dimethyl sulfoxide should avoid contact with this veterinary medicinal product.

In the user safety evaluation of the potentially genotoxic impurity of pyriproxyfen, CRP, which is limited in the pyriproxyfen specification, it was concluded that users and children are dermally exposed to amounts of CRP exceeding the toxicological reference value of 0.15 µg per person/day or 0.0025 µg/kg bw/day in the first 8 hours after application. It is only this acute exposure which is of concern; chronic exposure is considered acceptable.

To address the risk of acute oral exposure of children to dinotefuran, warnings have been included in the SPC and other product information and agreed as satisfactory:

- Treated animals must not be handled for at least eight hours after application of the product. It is therefore recommended to treat the animal in the evening. Treated animals should not be allowed to sleep with their owners, especially children, on the day of treatment.

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP Guideline on environmental impact assessment for veterinary medicinal products – Phase I (CVMP/VICH/592/98-FINAL). The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used for non-food producing animals.

The product is a spot-on formulation for topical (spot-on) use containing a combination of a third generation neonicotinoid, dinotefuran with flea adulticidal activity, and pyriproxyfen, a second generation insect growth regulator (IGR). The active ingredients are well known active substances and any exposure of the environment is likely to be via transfer from the cat's fur to the terrestrial environment; while transfer from the cat's fur to the aquatic environment is considered unlikely. Pyriproxyfen is known to adversely affect aquatic organisms. Therefore, the recommendations agreed for inclusion in the SPC and other product information relating to disposal specifically address the risk to the aquatic environment:

- Vectra Felis should not enter water courses as it is dangerous for fish and other aquatic organisms. Do not contaminate ponds, waterways or ditches with the veterinary medicinal product or with used containers.

In conclusion, based on the data provided, the ERA can stop at Phase I. Vectra Felis is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on safety

The acute toxicity of dinotefuran is low following dermal and oral exposure. After repeated oral administration in rodents and dogs, no target tissue could be identified. The lowest NOEL was 34 mg/kg bw/day in male rats in a 90 day oral repeated dose study and 22.3 mg/kg bw/day in female dogs in a 52 weeks oral repeat dose study. Repeated dermal application of dinotefuran revealed no signs of systemic toxicity up to the highest tested dose (1,000 mg/kg bw/day). Reproductive toxicity studies showed increased post-implantation losses and decreased litter sizes at high doses (1,340 mg/kg bw/day and 1,507 mg/kg bw/day in males and females respectively) and reduction in bodyweights during lactation in the offspring. Dinotefuran is not teratogenic, however it increases the rate of abortions in rabbits (at 1000 mg/kg bw/day). Dinotefuran is not genotoxic and not carcinogenic. Dinotefuran is minimally irritating to the eye. It is not a skin sensitizer.

The acute toxicity of pyriproxyfen is low following dermal or oral exposure. After the repeated administration of pyriproxyfen, the main target tissues are the kidney, liver and blood. Hepatotoxicity was noted in rats and dogs and resulted in liver enlargement, chronic inflammation and fibrosis. The lowest NOEL was 10 mg/kg bw/day in dogs in a 52 week oral repeat toxicity study. Repeated dermal application of pyriproxyfen revealed no signs of systemic toxicity up to the highest tested dose (1,000 mg/kg bw/day). There were no treatment-related changes regarding reproductive parameters for pyriproxyfen, and no teratogenic potential was observed. However, pyriproxyfen provoked developmental effects at toxic maternal doses (300 mg/kg bw/day) in rats. Pyriproxyfen is not genotoxic and not carcinogenic. It is not irritating to the eyes or skin, and it is not a skin sensitizer.

The solvent DMSO is of low acute toxicity after dermal or oral application, and is of low toxicity following repeated oral or dermal administration. With the exception of a decrease in bodyweight gain and some haematological effects (which could be secondary to an increased diuresis) at very high dose levels, the most common finding observed in some species is changes of the refractive power of the lens. Species in which such lens alterations readily develop include the rat, rabbit, dog and pig, while primates are not sensitive.

DMSO shows no genotoxic potential, has no negative effects in any of the reproductive parameters tested and is not teratogenic. DMSO shows a variable influence on the human immune system in several different assays. The carcinogenic potential of DMSO has not been tested.

Each of the components included in the final product has been shown to be of varying ocular and dermal irritation, and the entire product has been shown to be irritating to the eyes and moderately irritating to the skin, although it is not classified as irritating to the skin according to the criteria of Regulation (EC) No 1272/2008 on the classification, labelling and packaging of substances and mixtures.

In the user safety evaluation of the potentially genotoxic impurity of pyriproxyfen, CRP, which is limited in the active substance specification, a risk was identified regarding the dermal exposure of users and children in the first 8 hours after application. Appropriate warning phrases are included in the SPC (and other product information). The CVMP concluded that the user safety for this product is acceptable when used as recommended, and taking into account the safety advice given in the SPC.

Based on the data provided, the ERA can stop at Phase I. Vectra Felis is not expected to pose a risk for the environment when used in accordance with the SPC. Adequate risk mitigation measures reflecting the known toxicity of pyriproxyfen for fish and other aquatic species are included in the SPC and other product information.

Residues documentation

Not applicable.

Part 4 – Efficacy

Pharmacodynamics

Vectra Felis includes two active ingredients, dinotefuran and pyriproxyfen.

Pyriproxyfen is already authorised and widely used as an active substance in several different ectoparasiticide veterinary medicinal products authorised within the EU, and its mode of action has been well described. It is a photo-stable insect growth regulator that targets the insect endocrine system by mimicking juvenile hormone activity which results in inhibiting embryogenesis, metamorphosis and adult formation. Pyriproxyfen has been proven to act as a larvicide and ovidicide.

Dinotefuran is a new third generation member of the nicotinoid class of insecticides. Its structure is based on the acetylcholine molecule. It disrupts the insect nervous system by mimicking the action of acetylcholine on the postsynaptic nicotinic acetylcholine receptor. Dinotefuran binds to the acetylcholine receptor, however, its exact binding site is still unknown. Dinotefuran has adulticidal activity against a wide spectrum of insects, including fleas.

Justification of the fixed combination

The fixed combination of dinotefuran and pyriproxyfen is considered to be justified based on the widened spectrum of activity providing for insecticidal, ovidicidal and larvicidal activity, and in line with the recommendations of the CVMP Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005).

The durations of activity of the two active substances included in the fixed combination differ significantly, with persistent efficacy periods of 4 weeks for the adulticide dinotefuran, and 12 weeks for the larvicide pyriproxyfen. Appropriate information and advice regarding re-treating any cats which are likely to be re-infested, according to the assessment of the responsible veterinarian, is included in section 4.9 of the SPC.

Development of resistance

Dinotefuran: From the available published literature provided, there is no evidence of resistance of the cat flea against neonicotinoids (that is, nitenpyram, imidacloprid or dinotefuran) and, therefore, no warnings in the SPC or other product information on resistance are considered necessary at the current time.

Pyriproxyfen: Information available from published literature reveals no resistance to pyriproxyfen in developing insect stages of ectoparasites which infest companion animals. Hence, no warnings or limitations of use for this product appear necessary at the current time.

Pharmacokinetics

Pharmacokinetic studies in cats include one bioavailability study and one study on the hair coat distribution of dinotefuran and pyriproxyfen.

A GLP-compliant study on the bioavailability of dinotefuran and pyriproxyfen was conducted following single intravenous, oral and topical administrations. After oral administration to cats the bioavailability

was about 80% for dinotefuran and 40% for pyriproxyfen. After topical administration to cats, the bioavailability was about 30% for dinotefuran and 12% for pyriproxyfen.

The results of a GLP-compliant study on hair coat distribution indicate that dinotefuran and pyriproxyfen are well distributed in the fur after administration of the final product formulation to cats, and are still measurable in different zones of the hair coat of the treated animal one month after treatment.

Dose determination/justification

Dose determination

A series of 6 dose determination studies has been provided to evaluate the efficacy of the adulticidal neonicotinoid dinotefuran, either alone or in fixed combination with pyriproxyfen against fleas. In these studies different preliminary spot-on formulations of C660 (the final formulation) were applied to cats as a single spot-on treatment at the base of the neck.

Dose finding of the active substances in Vectra Felis is generally based on the body surface area (BSA) of cats because the BSA of an animal is considered as a more accurate measure of the dose needed considering that a spot-on treatment against fleas acts primarily by distribution over the skin and through the hair coat. The conversion of bodyweights into BSA was conducted by means of the formula $BSA = K_{cat} \times W^{2/3} \times 10^{-4}$, where K is a constant, specific for each animal species (for cats: $K_{cat}=10$) and W corresponds to the bodyweight (expressed in grams). The calculation of the BSA of cats is based on a published conversion table (Merck Veterinary Manual, 2012). Thus, both the dose per cat (in mg/kg bw) and the dose (expressed in mg/m² BSA of a cat) was given.

Dinotefuran:

Dinotefuran is the adulticidal insecticide active substance in Vectra Felis.

To evaluate the adulticidal efficacy of dinotefuran, cats were infested with 100 unfed fleas before treatment, and then weekly for at least 4 weeks, which is in accordance with the relevant CVMP Guideline on the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2). Comb counts were performed approximately 24 hours after treatment or infestation, apart from one study where efficacy calculations based on comb counts were performed 48 hours after treatment or infestation.

The insecticidal efficacy in these studies was usually calculated based on the geometric means of the flea counts. The efficacy was also calculated based on the arithmetic means.

Two initial good clinical practice (GCP)-compliant dose determination studies were undertaken in the USA but were largely in accordance with the relevant CVMP Guideline (see above). In both preliminary studies dinotefuran was tested in cats as a spot-on test formulation without pyriproxyfen present.

In the first study, three dosing groups, each of 6 cats, were compared with an untreated control at 24 hours post-treatment (D1) or flea infestation (D8 to D30). The experimental formulation used consisted of dinotefuran (5.0% w/w) dissolved in 70% ethanol, and this was applied topically to groups of cats using single doses of 2 ml (low dose group), 2.5 ml (mid) and 3 ml (high), respectively. The test formulation showed >95% efficacy for one day (D1=100%, D8=80.9%) in the low dose group (325–370 mg dinotefuran/m² BSA), and for up to one week (D1 and D8=100%) in the mid dose group (365–480 mg dinotefuran/m² BSA) based on the arithmetic means. The high dose group (325–370 mg dinotefuran/m² BSA) showed high initial treatment insecticidal activity (100% at D1) but again

insufficient persistent adulticidal activity after one week (92.7% at D8), based on the arithmetic means.

In the second study, three dosing groups, each of 6 cats, were compared with a solvent (only) control at 24 hours post-treatment (D1) or flea infestation (D8 to D30). An experimental formulation of dinotefuran (15.0% w/w dissolved in ethyl lactate) was applied topically onto the neck of the cats using single doses of 1.5 ml (corresponding to 740–815 mg dinotefuran/m² BSA), 1.8 ml (corresponding to 835–990 mg dinotefuran/m² BSA) and 2 ml (corresponding to 1,025–1,170 mg dinotefuran/m² BSA), respectively. The low dose group showed >95% efficacy for two weeks, as did both the mid and high dose groups for three weeks (>95% efficacy) based on arithmetic means. Insufficient persistent efficacy rates were calculated for the low dose group at D23 (87.7%) and at D30 in the mid (86.7%) and high dose (93.5%) groups. Several cats, however, showed pooling of the experimental formulation at the application site. Some loss of the material was also noted. These shortcomings substantially limit interpretation of the final study results.

In a comparative efficacy study, which was GLP-compliant, the US formulation of Vectra Felis (dinotefuran 22% w/w and pyriproxyfen 3% w/w) was compared with a veterinary medicinal product containing 9% imidacloprid (0.4 ml topically to cats). Originally, the dosages of dinotefuran were not calculated according to the cat's BSA. Instead, a fixed dose of 0.8 ml of the experimental formulation, corresponding to a dose range of 825–1,050 mg dinotefuran/m² BSA, was applied onto the neck of the cats. The study results demonstrated that a mean topical dose of 924 mg dinotefuran/m² BSA in fixed combination with a mean topical dose of 124 mg pyriproxyfen/m² BSA exhibited 74.2% pulicidal activity as early as 2 hours after treatment, 100% efficacy 6 or 12 hours after treatment, and ≥95% efficacy after one month, 24 hours after weekly challenge with 100 fleas. Treatment of cats with the comparator product containing 9% imidacloprid achieved 97.3% efficacy within 6 hours post-treatment on D0, and persistent efficacy above 95% up to and including D9. Thereafter, efficacy did not exceed 90% until D30, when 94.4% efficacy was calculated based on arithmetic means. The intrinsic activity of pyriproxyfen was not proven in this study. However, the data revealed that addition of pyriproxyfen to the solution does not negatively interact with the neonicotinoid dinotefuran.

To determine the persistent pulicidal efficacy of the formulation authorised in the US and referred to in the previous paragraph, a GCP-compliant dose determination study was undertaken in Ireland using point doses of (1) 750 mg dinotefuran and 102 mg pyriproxyfen/m² BSA (low dose group), (2) 900 mg dinotefuran and 123 mg pyriproxyfen/m² BSA (mid dose group), and (3) 1,500 mg dinotefuran combined with 102 mg pyriproxyfen/m² BSA (high dose group). The product was applied once onto the cat's neck. The flea comb counts were performed either at 48 hours post-treatment on D2, or at 48 hours post-infestation on D9, D16, D23 and D30. At the low dose the insecticidal activity persisted for 16 days above the threshold of ≥95% based on arithmetic means. Thereafter, efficacy decreased to 93.8% and 89.9% on D23 and D30 post-treatment respectively. At both the mid and the high point doses the product demonstrated efficacy consistently above the threshold of >95% for 30 days. The activity of pyriproxyfen was not considered in this study.

Based on the study results and considering a cat weighing 10 kg equates to a BSA of 0.47 m², the applicant calculated a treatment dose of 0.47 m² x 900 mg/m² which is equal to 423 mg per cat (corresponding to 42.3 mg dinotefuran/kg bw).

Pyriproxyfen:

Pyriproxyfen is the insect growth regulator (IGR) contained in this product.

The SPC of an authorised spot-on product for cats containing pyriproxyfen only as the single active substance (Cyclio 60 mg spot-on solution for cats) was provided in addition to two publications (reporting on the field efficacy of a 10% pyriproxyfen spot-on for the prevention of flea infestations on

cats, and on insect growth regulators as new products and new approaches for flea control on dogs) to identify the appropriate minimum topical dose of pyriproxyfen for cats needed to inhibit flea development for a three month period of activity. According to the SPC of the already authorised product (Cyclo), the spot-on administration of 60 mg pyriproxyfen to cats with a bodyweight range of 1–6 kg prevents *C. felis* flea multiplication for 3 months. This topical dose equates to a minimum dose of 10 mg/kg bw in cats. Furthermore, according to the publication on insect growth regulators as new products and new approaches for flea control on dogs, the single spot administration of just 4.5 mg pyriproxyfen/kg bw achieved 100% inhibitory efficacy for 92 days, which corresponds to a minimum dose of 45 mg pyriproxyfen in Vectra Felis when calculated for a 10 kg cat. (This equates to 95.7 mg pyriproxyfen/m² BSA.)

A GLP-compliant dose determination study was conducted in South Africa to assess the therapeutic and persistent efficacy of a test topical solution, containing 35% dinotefuran and 5% pyriproxyfen dissolved in the non-aqueous solvent n-methylpyrrolidone, in cats. The study was conducted on 4 groups, each of 6 animals. One group served as a (vehicle only) control. The test formulation was administered topically using single doses of 0.6 ml (equivalent to 635–1,325 mg dinotefuran/m² BSA and 91–189 mg pyriproxyfen/m² BSA), 0.8 ml (equivalent to 985–1,890 mg dinotefuran/m² BSA and 141–270 mg pyriproxyfen/m² BSA), and 1.0 ml (equivalent to 1,215–2,135 mg dinotefuran/m² BSA and 174–305 mg pyriproxyfen/m² BSA), respectively. All cats were artificially infested with fleas, once before treatment and then after treatment on D7, D14, D21 and D28 (adulticidal efficacy) and on D2, D9, D16, D23 and D30 (flea egg inhibition assessment). Adult fleas were comb counted pre-treatment and then on D1, D8, D15, D22 and D29 post-treatment. Flea eggs were collected 3 days after the second weekly infestation, and egg hatching was recorded 72 hours after incubation. Emergence to adult fleas was recorded 35 days after each seeding. No clear dose-related response was observed in relation to efficacy against adult fleas. The immediate treatment efficacy on D1 (24 hours post-treatment) was 99.9–100% in all dosing groups. Adequate persistent efficacy of >95% efficacy was seen for 1 week (99.4%) in the low dose group, for 3 weeks (96.8%) in the mid dose group, but only for 2 weeks (98.7%) in the high dose group, based on arithmetic means. In the 4th week, efficacies of 74.7%, 89.2% and 80% in the low, mid and high dose groups respectively, were reported. With regard to the ovicidal efficacy of the test formulation, all dose ranges tested showed 100% efficacy in inhibiting larvae hatching from flea eggs collected at all time points up to one month (D33).

A further GLP-compliant laboratory efficacy study was submitted comparing the efficacy of the US spot-on formulation, which contains dinotefuran (22% w/w) and pyriproxyfen (3% w/w), with that of another US-authorised spot-on product for cats containing the tetracyclic macrolide spinetoram (39.6%). The study was conducted using 2 treatment groups, each of eight adult cats, which received 1.2 ml Vectra Felis (corresponding to 759–1,116 mg dinotefuran/m² BSA and 103–152 mg pyriproxyfen/m² BSA) and 0.57 ml of the spinetoram-containing product, respectively. One additional group of eight cats served as untreated controls. Results revealed that 1.2 ml of the Vectra Felis spot-on formulation exhibited >95% insecticidal efficacy 24 hours post-infestation and after weekly challenges (D7, D14, D21, D28) for 1 month, based on the arithmetic means. Furthermore, the immediate treatment efficacy at D0 (speed of killing fleas) was considered high, with an 81% insecticidal efficacy as early as 4 hours post-treatment. This speed of kill activity decreased slowly during the study period, resulting in calculated activities of 63% and 41.8% at 4 hours after each challenge infestation on D28 and D35 respectively. Commencing firstly on D36 at 24 hours post-infestation and then for the next 24 hours, flea eggs were collected and incubated (according to the state of the art) for 35 days. The resulting activity of pyriproxyfen was high, showing 99.6% inhibition of adult flea emergence when incubated for 35 days, while in the control dishes there was a 95.4% emergence of the eggs to adult fleas.

Dose confirmation studies

Dinotefuran:

Three GCP-compliant dose confirmation studies were conducted in Ireland. In these studies the designs followed the recommendations of the CVMP Guideline on the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMA/CVMP/EWP/005/2000-Rev.2).

In the first study, one group of cats were treated with a test formulation (C660 DTE) containing 22.3% dinotefuran and 3.0% pyriproxyfen, and each cat received a topical dose equivalent to point doses of 1,000 mg dinotefuran/m² BSA and 135 mg pyriproxyfen/m² BSA. Another group of cats were treated topically with C660 DTF (the final formulation) with calculated point doses of 1,000 mg dinotefuran/m² BSA and 100 mg pyriproxyfen/m² BSA, respectively. In the group treated with the test formulation (C660 DTE) the residual efficacy at 48 hours after weekly flea (*Ctenocephalides felis*) challenge on D2, D9, D16, D28 was >95% for 3 weeks (D23), and below the threshold (85%) on D30, based on arithmetic means. The efficacy in the study group treated with the final formulation (C660 DTF) persisted above the threshold of ≥95% at 48 hours after each infestation for the entire 4 week activity period claimed. The efficacy of the insect growth regulator pyriproxyfen was not investigated in this study.

In a second dose confirmation study each cat in the treatment group received the final formulation (C660 DTF) at individual point doses equivalent to 900 mg dinotefuran/m² BSA and 90 mg pyriproxyfen/m² BSA. This corresponds to a spot-on dose of 0.4 ml to 0.7 ml per cat, depending on the individual bodyweights. A group of 8 infested cats served as untreated controls. At a point dose of 900 mg dinotefuran/m² BSA the insecticidal efficacy against fleas (*Ctenocephalides felis*) persisted for 4 weeks (D30) above the threshold of ≥95%, based on the arithmetic mean after each weekly (D2, D9, D16, D28) flea challenge infestation, and when the flea comb counts were performed at 48 hours after each challenge. By study D37 the persistent insecticidal activity had decreased to 88% in the treatment group. In this study the number of dead fleas falling off the treated animal was also monitored. One to 3 dead fleas, out of the 100 fleas used for infestation, were collected within 30 minutes on D0 (cumulative means n=1) and a mean of 4.2 fleas were collected 5 minutes after infestation on D7. Thereafter, the fall off of the fleas remained low within the next 30 minutes. In the untreated control cats no dead fleas dropped within the first 30 minutes of infestation on D0, but 1 to 4 fleas (mean number: 2.1) were already collected within the first 5 minutes after the second challenge infestation on D7.

A further GCP-compliant dose confirmation study was performed to evaluate the speed of kill (efficacy) of Vectra Felis on cat fleas. A total of 48 European cross breed cats were allocated to three treatment and three control groups. Approximately 100 unfed adult fleas were applied to the animals prior to treatment, and again on D7. Effectiveness in the three treatment groups was calculated at different time points post-infestation showing approximately 55% at 1 hour, 93.4% at 2 hours, and ≥95% (threshold) from as early as 3 hours post-infestation (3–12 hours), based on the arithmetic means of the live and moribund fleas counts. As a secondary outcome the cumulative falling-off rate of fleas immediately after treatment was also recorded by collecting dislodged live, dead and moribund fleas from cats (in pans, as detailed below) on D0 and D7 days at 5, 15, 30 and 60 minutes post-treatment or post-infestation. Based on the total number of 2,400 fleas used for each infestation, the cumulative falling off rate was below 1% (0.4–0.8%) up to 15 minutes post-treatment or post-infestation, and increased to 12.1% at 1 hour on D0, and 7.1% at 1 hour on D7.

A clinically meaningful falling-off of fleas (>95%) was demonstrated within 2 hours after administration of the product, but not within 5 minutes (and even 60 minutes) after application.

Information consistent with these study results is included in section 5.1 of the SPC ("Fleas are killed by dinotefuran within 2 hours after treatment or infestation.").

Pyriproxyfen:

In a GCP-compliant dose confirmation study carried out in South Africa, sixteen cats were randomised either to a treatment or control group. Each cat in the treatment group received one 0.9 ml pipette of C660 (final formulation) topically on D0, corresponding to a mean dose of 190 mg pyriproxyfen/m² BSA and 1,910 mg dinotefuran/m² BSA. All cats were infested with 100 *C. felis* on D-12 (pre-treatment ranking), D10, D21, D28, D35, D46, D53, D60, D81 and D90. The dropped flea eggs were collected (up to 50 eggs on each occasion) from pans beneath the individual cat cages 3 days later. Egg hatching was measured by counting the number of larvae after a 3 day incubation period. Adult flea emergence was assessed 35 days after egg collection. The efficacy of the final formulation in preventing adult flea emergence was 100% for eggs collected up to and including D49 after treatment, based on the arithmetic means. Thereafter, the inhibitory activity remained consistently >97% for eggs collected up to and including D93. Both egg hatching and emergence to adult fleas were otherwise high in the controls, with rates of 74–95% and 47.5–65.5%, respectively, throughout the entire study period. To evaluate the speed of killing fleas after distribution of the product through the cat's fur, additional flea infestations were carried out on D3 and D4. The efficacy of the final formulation (C660) against adult fleas was 70.2% 1 hour post-infestation on D3 and 91.9% at 2 hours post-infestation on D4, based on the arithmetic means. Since the mean dose applied was twice the minimum recommended dose when related to the body surface area (BSA) of cats, no final conclusion on the efficacy at the minimum recommended dose of 90 mg pyriproxyfen/m² BSA can be drawn from this study.

A further GCP-compliant dose conformation study was carried out to show that the minimum recommended dose of Vectra Felis (90 mg pyriproxyfen/m² BSA and 900 mg dinotefuran/m² BSA in fixed combination) prevents both egg hatching and development to adult fleas for a period of 3 months. In the first month after treatment either no eggs, or only low numbers of eggs, were collected from treated cats. This impeded calculation of the growth inhibition. As the activity of dinotefuran decreased in the 2nd month after treatment, the number of eggs collected also increased substantially in the treated cats, allowing collection of up to 50 flea eggs per cat pan three days after infestation. After an incubation period of further three days the egg hatch rate was recorded. Additionally, adult flea counts for each Petri dish were made 28 days following seeding. Vectra Felis showed 100% inhibition of flea egg hatching in the 2nd month and 94.5–99% in the 3rd month at the minimum recommended dose, compared with the control group. The development to adult fleas was inhibited to >96.5% for three months post-treatment.

Use of a single size of spot-on applicator in cats:

The proposed use of a single size of spot-on applicator which contains a minimum treatment dose calculated for a 10 kg bodyweight cat was specifically considered because such heavy cats are not representative of the European cat population. Hence, the use of such an applicator size was considered to lead to routine overdosing for the majority of European cats, without adding to the benefits. The data provided by the applicant did not however indicate any serious safety concern for cats and kittens at topical doses up to 4 times the recommended maximum treatment dose, or after oral administration of the recommended treatment dose to young kittens (see below). Consequently, the CVMP considered the single size of the spot-on applicator in cats to be acceptable. Appropriate information of the range of the treatment dose, when administered to cats weighing 0.6 kg to 10 kg, is included in the SPC and other product information.

Target animal tolerance

One study on target animal safety and two oral gavage safety studies in cats and kittens were provided. Additionally, target animal safety information could be derived from studies primarily conducted for other purposes.

The three studies were conducted in accordance with GCP requirements and took into account the relevant VICH GL43 on target animal safety for pharmaceuticals (EMA/CVMP/VICH/393388/2006). The intended final formulation was used during the tolerance studies.

The first oral tolerance study on cats of 3.2 to 5.5 kg and aged 7 to 8 months investigated different doses by oral gavage until a dose volume of 0.3 ml/kg body weight (141 mg dinotefuran/kg and 14.1 mg pyriproxyfen/kg). However, since no product-related adverse clinical signs, other than from salivation and cosmetic signs, were recorded during the study, a maximum tolerated dose has not been determined. The applicant carried out a new study in 7 week old kittens in order to determine the safety of the final formulation following administration of escalating oral (gavage) doses, until the maximum recommended treatment dose. Abnormal faeces, salivation and/or emesis, generally reversible within 3 to 4 hours, were observed after administration of 1.5 ml/kg (716.4 mg dinotefuran/kg and 72.2 mg pyriproxyfen/kg). Following the recommendations of the VICH GL43 Guideline on target animal safety for pharmaceuticals (EMA/CVMP/VICH/393388/2006), the oral safety has been adequately characterised with respect to the target population intended to be treated.

The safety of Vectra Felis after repeated topical use was investigated in a margin of safety study, in accordance with the relevant VICH Guideline GL43. Vectra Felis was administered at doses corresponding to 0, 1X, 3X and 5X the recommended treatment dose at 14 day intervals for a total treatment period of 15 weeks. At the time of enrolment cats were 7–8 weeks old and the mean bodyweight in the 1X, 3X and 5X groups was 744 g, 834 g and 773 g, respectively, in males, and in females 771 g, 795 g, and 791 g, respectively.

The safety of the maximum recommended dose (1X) has therefore not actually been investigated, and the safety of the product has been investigated at doses up to 4X the recommended maximum treatment dose. The CVMP considered this as acceptable because the product proved to be well-tolerated at all dosages under these study conditions. Cosmetic effects and rare local adverse reactions at the application site, such as slight scaling, transient erythema and alopecia, are adequately addressed in section 4.6 of the SPC, and in other product information (the package leaflet). The information on overdoses has also been adequately addressed, in section 4.10 of the SPC, taking into account the results of the second oral gavage safety study.

The potentially genotoxic impurity of pyriproxyfen, CRP, was not considered as a risk to the target animal species.

Field trials

A GCP-compliant controlled, randomised, fully blinded multicentre field study was performed in 6 European countries according to current scientific standards, and the results largely confirm the results of the laboratory efficacy studies. At the time of enrolment, all cats in both treatment groups showed adequate and comparable flea infestations and, although no negative control group was included, it was considered that flea challenge would have prevailed during the study period. *Ctenocephalides felis* was the most frequently identified flea species at baseline in all European countries involved. The final formulation of Vectra Felis (C660) was administered at the recommended treatment dose at monthly intervals for a total of three times. An authorised product, Frontline Combo (fipronil plus (S)-methoprene), was used as the control. The mean percentage flea count reduction over the entire study

period (84 days) was 90.85% in the C660 group and 90.66% the control group (per protocol (PP) population). C660 proved to be non-inferior compared to the control product. Similarly to the PP population, the non-inferiority of C660 compared to the control product was also demonstrated for the intention-to-treat (ITT) population.

Although the occurrence of flea allergic dermatitis (FAD) prior to treatment was very low (only one cat per treatment group showed signs of FAD at the time of enrolment), the use of Vectra Felis as an aid in the treatment strategy of FAD was agreed by the CVMP.

Vectra Felis proved to be well tolerated in the cats.

Other studies

None.

Overall conclusion on efficacy and target animal safety

Vectra Felis is intended for the treatment and prevention of flea infestations (*Ctenocephalides felis*) on cats. The mode of action and the spectrum of activity of the two active substances, dinotefuran and pyriproxyfen, are well described. There is currently no evidence for any resistance in fleas to either of the two active substances.

The fixed combination is considered justified based on the widened spectrum of activity providing for insecticidal, ovicidal and larvicidal activity, and this is in line with the recommendations of the CVMP Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005).

The durations of activity of dinotefuran and pyriproxyfen differ substantially, with persistent efficacy periods of 4 weeks for the adulticide dinotefuran, and 12 weeks for the larvicide pyriproxyfen. Appropriate advice for the re-treatment of any cats which are likely to become re-infested, according to the assessment of the responsible veterinarian, is included in the SPC and package leaflet.

A series of six dose determination studies with experimental spot-on formulations has been provided to evaluate the efficacy of dinotefuran, either alone or in fixed combination with pyriproxyfen. Dose-finding of the active substances in Vectra Felis is based on the body surface area (BSA) of cats rather than on the cat's bodyweight because the body surface area of an animal was considered as a more accurate measure of the dose needed. In a dose determination study with a test formulation it was demonstrated that a minimum recommended dose of 900 mg dinotefuran/m² BSA is necessary to achieve ≥95% immediate and persistent adulticidal efficacy for 4 weeks against *Ctenocephalides felis*. Based on the study, and considering a maximum cat weight of 10 kg (0.47 m² BSA), a treatment dose of 0.47 m² x 900 mg/m² = 423 mg (equates then to 42.3 mg dinotefuran/kg bw of a cat) was calculated.

With respect to the pyriproxyfen, 100% efficacy for the inhibition of flea larvae hatching was demonstrated for one month in a dose determination study using a test formulation containing dinotefuran and pyriproxyfen at all doses tested (low: 635–1,325 mg dinotefuran/m² BSA and 91–189 mg pyriproxyfen/m² BSA, mid: 985–1,890 mg dinotefuran/m² BSA and 141–270 mg pyriproxyfen/m² BSA, high: 1,215–2,135 mg dinotefuran/m² BSA and 174–305 mg pyriproxyfen/m² BSA). There was no dinotefuran interference on pyriproxyfen activity.

In a further laboratory study, a dose of 759–1,116 mg dinotefuran and 103–152 mg pyriproxyfen/m² BSA using the authorised US formulation, showed an inhibition of flea emergence of >99% on D36 after treatment.

Two dose confirmation studies were conducted. In the first study the final formulation was applied at point doses of 1,000 mg dinotefuran/m² BSA and 100 mg pyriproxyfen/m² BSA per cat. The insecticidal activity (>95%) persisted for 4 weeks. In the second study, each cat in the treatment group received Vectra Felis at the recommended treatment dose of 900 mg dinotefuran/m² BSA and 90 mg pyriproxyfen/m² BSA calculated for a 10 kg bodyweight cat. The insecticidal efficacy of >95% against fleas persisted for 4 weeks.

Another dose confirmation study was undertaken to evaluate the "speed of kill" activity of Vectra Felis. The flea adulticidal efficacy was 55% at 1 hour, 93.4% at 2 hours, and ≥95% from 3 hours onwards. The cumulative falling-off rate of fleas was below 1% at 15 minutes post-treatment or re-infestation, and 12.1% (D0) and 7.1% (D7) at 1 hour, respectively. A clinically meaningful falling-off (approximately 95%) of fleas has been demonstrated at 2 hours after application of the product. Information consistent with these study results is included in section 5.1 of the SPC.

Two dose confirmation studies were carried out to check the pyriproxyfen activity in Vectra Felis. In the first study each cat received Vectra Felis at a mean topical dose of 190 mg pyriproxyfen/m² BSA and 1,910 mg dinotefuran/m² BSA. The inhibitory activity on flea eggs collected up to and including D93 after treatment remained above 95%. In the second study the minimum recommended dose (90 mg pyriproxyfen/m² BSA and 900 mg dinotefuran/m² BSA) was tested. Vectra Felis showed 100% inhibition of flea egg hatching for 2 months, and 94.5–99% in the 3rd month compared to the controls. Development to adult fleas was inhibited (>96.5%) for three months post-treatment.

A GCP-compliant controlled, randomised and blinded multicentre field study performed in six European countries, and according to current scientific standards, largely confirmed the results of the laboratory efficacy studies. Vectra Felis was administered at the recommended treatment dose at monthly intervals for three times, and it proved to be non-inferior in the PP population (flea count reduction was 90.85% over 84 days) compared to a control product containing fipronil and (S)-methoprene (90.66%). Although only one cat per treatment group showed signs of FAD prior to treatment, the use of Vectra Felis as an aid in the treatment strategy of FAD was agreed by the CVMP. Vectra Felis proved to be well tolerated in the cats.

In the absence of serious safety concerns for the target species, the proposed use of a single size of spot-on applicator, which contains a minimum treatment dose calculated for a 10 kg bodyweight cat, was accepted by the CVMP.

Part 5 – Benefit-risk assessment

Introduction

The application is for Vectra Felis spot-on solution for cats, including kittens, for the treatment and prevention of flea infestations. The product contains a combination of dinotefuran and pyriproxyfen. The route of administration is spot-on use. The product is presented in one 0.9 ml unit dose pipette containing 423 mg dinotefuran and 42.3 mg pyriproxyfen dissolved in dimethyl sulfoxide. The application is supported by a full dossier submitted in accordance with Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The fixed combination of dinotefuran and pyriproxyfen in Vectra Felis is justified based on the broadened spectrum of activity against fleas, i.e., a combination of active substances which lead to insecticidal plus ovicidal and larvicidal activity.

The efficacy of Vectra Felis in the treatment and prevention of flea infestations, at the proposed dosage, was demonstrated in a large number of clinical efficacy studies performed according to current scientific standards.

Following a single administration, Vectra Felis will prevent flea infestations for up to one month. The product will also prevent further flea multiplication, by inhibiting flea emergence in the environment of the cat, for up to 3 months. The re-treatment of cats which are likely to become re-infested has been addressed.

Additional benefits

None identified.

Risk assessment

Main potential risks:

Quality:

As regards quality, the formulation and manufacture of Vectra Felis is well described and controlled, and adequate specifications have been defined.

For the target animal:

Safety after accidental oral ingestion has been adequately addressed taking into account a worst case scenario, that is, oral ingestion of the treatment dose for cats aged 7 to 8 months, and oral ingestion for cats aged 7 weeks.

In a margin of safety study the product proved to be generally well tolerated up to 4 times the recommended maximum topical treatment dose. At the recommended treatment dose, the most frequently observed adverse effects were cosmetic effects, and on rare occasions transient erythema and alopecia at the application site. After overdose, oedema and dry skin at the application site were observed in rare cases. Salivation was observed after oral administration of the product. All observed adverse effects are adequately addressed in sections 4.6 and 4.10 of the SPC (and other product information).

A potentially genotoxic impurity was not considered a risk to the target animal species.

For the user:

Risks for the user consist mainly of acute dermal or oral exposure to the whole product or its dislodged residues, and chronic dermal or oral exposure to dislodged residues of the medicinal product from the treated animal. The risk of irritation to the eyes and moderate irritation of the skin due to the product has been adequately addressed.

A risk with regard to dermal exposure to the product of adult users and children has been identified, but it is only the acute exposure, in the first eight hours after administration of the product, which is of concern. This risk is however considered to be adequately mitigated by appropriate warnings in section

4.5 of the SPC (and other product information). The user safety for this product is therefore acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

The product is for individual treatment of companion animals. The product is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

The re-treatment of any cats which are likely to become re-infested has been satisfactorily addressed in the SPC and package leaflet.

Evaluation of the benefit-risk balance

The combination of the insecticide, dinotefuran, and pyriproxyfen, an insect growth inhibitor, is justified based on the broadening of the spectrum of activity.

The formulation and manufacture of Vectra Felis spot-on solution is well described, and the specifications set will ensure that product of an appropriate and consistent quality will be produced.

The product has been shown to be efficacious for the indication:

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

One application prevents flea infestation for one month. It also prevents the multiplication of fleas by inhibiting flea emergence in the environment of the cat for 3 months.

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

Vectra Felis presents an acceptable risk for users and the environment when used as recommended.

Appropriate warnings have been included in the SPC and other product information.

The product has been shown to have a positive benefit-risk balance.

Conclusion on the overall benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete product information.

Conclusion

Based on the original and complementary data presented, the CVMP concluded that the quality, safety and efficacy of Vectra Felis were considered to be in accordance with the requirements of Directive 2001/82/EC.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Vectra Felis.