9 September 2021
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for Felpreva (EMEA/V/C/005464/0000)

INN: tigolaner / emodepside / praziquantel

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

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Introduction

Bayer Animal Health GmbH submitted on 17 June 2020 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Felpreva, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope). During the procedure the MAH was transferred from Bayer Animal Health GmbH to Vetoquinol S.A., Magny-Vernois, 70200 Lure, France.

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 October 2019 as Felpreva contains a combination of existing active substances emodepside and praziquantel, and tigolaner which is not yet authorised as a veterinary medicinal product in the Union and so is a new active substance.

On 9 September 2021, the CVMP adopted an opinion and CVMP assessment report.

On 11 November 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Felpreva.

At the time of submission, the applicant applied for the following indication:

> "For cats with, or at risk from, mixed parasitic infestations. The veterinary medicinal product is indicated when ectoparasites, cestodes and nematodes are targeted at the same time.

Ectoparasites

- For the treatment and prevention of flea and tick infestations in cats providing immediate and persistent flea (*Ctenocephalides felis*) and tick (*Ixodes ricinus*) killing activity for 13 weeks. Fleas already on the animal prior to administration are killed within 12 hours. For newly infecting fleas the onset of efficacy is within 8 hours for 2 months after product administration and within 24 hours afterwards. The flea life cycle is broken due to the rapid onset of action and long-lasting efficacy against adult fleas on the animal. Ticks are killed within 24 hours after product administration. The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).
    - For the treatment of notoedric mange (*Notoedres cati*).
    - For the treatment of ear mite infestations (*Otodectes cynotis*)

Gastrointestinal roundworms (nematodes)

For the treatment of infections with:

- *Toxocara cati* (mature adult, immature adult, L4 and L3)
- *Toxascaris leonina* (mature adult, immature adult and L4)
- *Ancylostoma tubaeforme* (mature adult, immature adult and L4)

Lungworms (nematodes)

For the treatment of infections with:

- *Aelurostrongylus abstrusus* (adult)
- *Troglostrongylus brevior* (adult)

Tapeworms (cestodes)

For the treatment of tapeworm infections:

- *Dipylidium caninum* (mature adult and immature adult)
- *Taenia taeniaeformis* (adult)

- *Echinococcus multilocularis* (adult)".

Felpreva is a fixed combination of three antiparasitic active ingredients, containing tigolaner, an acaricide and insecticide belonging to the chemical class of bispyrazoles, emodepside, an antiparasitic belonging to the cyclic depsipeptide class and praziquantel, a pyrazino-isoquinoline. In combination these actives are proposed to treat endoparasite infestations as well as treatment and control of ectoparasites. The target species is cats.

Felpreva spot-on solution contains 9.79 % w/v tigolaner, 2.04 % w/v emodepside, 8.14 % w/v praziquantel and is presented in single dose applicators in packs containing 1, 2, 10 or 20 applicators. The applicant is proposing three strengths: 0.37 ml (36.22 mg tigolaner + 7.53 mg emodepside + 30.12 mg praziquantel), 0.74 ml (72.45 mg tigolaner + 15.06 mg emodepside + 60.24 mg praziquantel) and 118 ml (115.52 mg tigolaner + 24.01 mg emodepside + 96.05 mg praziquantel).

The rapporteur appointed is Andrea Golombiewski and the co-rapporteur is Bruno Urbain.

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

Scientific advice

Bayer Animal Heath GmbH received scientific advice from the CVMP on 13 September 2018 (EMA/CVMP/SAWP/419185/2018). The scientific advice pertained to efficacy and safety issues for the development of the veterinary product.

The applicant followed the scientific advice in most parts.

Deviations from the scientific advice are noted with regards to the justification of the dose-limiting cestode *Dipylidium caninum* and the strains used for dose-confirmation studies, and the inclusion of treatment groups which are not considered necessary. The deviations are addressed in the respective sections and can be accepted with regard to both the age of the studies and the additional treatment groups in dose confirmation studies. Data provided with the dossier show that tigolaner accumulates, but the data set does not allow for final conclusions on the extent of accumulation. In the studies provided, steady state following repeated dose has not been reached. Therefore, the target animal safety studies are not suitable to support unlimited repeated use.

MUMS/limited market status

The initial applicant Bayer Animal Heath GmbH requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted as the indications for the treatment of notoedric mange (*Notoedres cati*) and for the treatment of infections with *Troglostrongylus brevior* (adult) in cats are considered a minor use.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant changed from Bayer Animal Health GmbH to Vetoquinol S.A. and a new electronic application with Vetoquinol S.A. as the applicant was required. Accordingly, the latest version of Vetoquinol´s DDPS was submitted which was already assessed and approved in former procedures as indicated by the applicant. 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 bulk solution takes place outside the EEA in the United Kingdom. The site has a valid manufacturing authorisation issued by Veterinary Medicines Directorate of UK. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided, the site was considered appropriately certified as complying with GMP requirements.

Importation, primary and secondary packaging and quality control testing release within the EU takes place in Germany which holds a manufacturing authorisation issued by State Social Services Agency Schleswig-Holstein, Germany for which GMP compliance was confirmed by the competent national authority State Social Services Agency Schleswig-Holstein, Germany.

Batch release takes place at Vetoquinol S.A., Magny-Vernois, 70200 Lure, France. The site has a valid manufacturing authorisation issued by the French Agency for veterinary medicinal products. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms, has been provided.

A QP declaration concerning GMP compliance for the active substance manufacturing site of emodepside was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by a third party which has taken into consideration the GMP certificates available for the active substance sites issued by Federal Agency for Medicines and Health Products, Belgium following inspection.

A QP declaration concerning GMP compliance for the active substance manufacturing sites of tigolaner was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit and on a remote audit due to COVID-19 travel restrictions which has taken into consideration the GMP certificates available for the active substance manufacturing site issued by the Ministero della Salute, Italy as well as the AGENZIA ITALIANA DEL FARMACO, Italy and the GMP certificate available for the active substance micronisation site issued by Swissmedic, Switzerland following inspection.

A QP declaration concerning GMP compliance for the active substance manufacturing site of praziquantel was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by a third-party following inspection.

Overall conclusions on administrative particulars

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

The GMP status of the active substance manufacturing sites for praziquantel, tigolaner and emodepside as well as of the finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a non-aqueous spot-on solution containing 97.90 mg/ml tigolaner, 81.40 mg/ml praziquantel and 20.35 mg/ml emodepside as active substances. Three different single-dose

volumes are proposed: 0.37 ml (36.22 mg tigolaner, 30.12 mg praziquantel and 7.53 mg emodepside), 0.74 ml (72.45 mg tigolaner, 60.24 mg praziquantel and 15.06 mg emodepside) and 1.18 ml (115.52 mg tigolaner, 96.05 mg praziquantel and 24.01 mg emodepside). 0.37 ml and 0.74 ml are filled in 1 ml spot-on tubes. 1.18 ml are filled in 2.5 ml spot-on tubes.

The active substances are dissolved in 1,2-isopropylidene glycerol containing 0.3 % of the antioxidant butylhydroxyanisole (E320). Butylhydroxytoluene (E321) is additionally included in the formulation as an antioxidant. (S)-lactic acid is used for pH-value adjustment.

Containers

The primary packaging is a white polypropylene applicator of 1 ml or 2.5 ml with a cap. The 1 ml applicator contains 0.37 ml or respectively 0.74 ml spot-on solution, the 2.5 ml applicator contains 1.18 ml spot-on solution.

Secondary packaging consists of an aluminium blister. The blister packs containing 1, 2, 10 or 20 unit dose pipettes are packaged in a cardboard box.

The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Development pharmaceutics

The product is formulated as a spot–on solution in a non-aqueous vehicle. Development of Felpreva is based on the already authorised Profender spot-on solution which contains the active substances emodepside and praziquantel. During the procedure the MAH of Profender also changed from Bayer Animal Heath to Vetoquinol S.A. As such Vetoquinol S.A. now owns, and has full access to, the Profender data. Formulation of Profender spot-on solution was essentially transferred, with the new product now also containing the active substance tigolaner (micronised). A minor change in quantity of the solvent 1,2-isopropylidene glycerol already containing the antioxidant butylhydroxyanisol was implemented.

Addition of a second antioxidant, butylhydroxytoluene, to the formulation enhances stability of all three active substances. As a result, less of the antioxidant butylhydroxyanisole is necessary compared to Profender spot-on solution. (S)-lactic acid was already included in Profender spot-on solution to stabilise the active substances. Liquid (S)-lactic acid is used to avoid variability in water intake.

All excipients are known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Packaging material of Profender spot-on solution was transferred to the new product.

Development reports have been provided regarding physico-chemical characteristics of the product, amount of antioxidant to be included, water content in the formulation, influence of nitrogen-aeration on water uptake during manufacture, order of addition of ingredients, homogenisation, filtration of the solution, developmental stability studies, confirmation of overfill of the pipettes and the manufacturing process. Compatibility of the different active substances and excipients was shown. The overfill of the applicators has been sufficiently justified.

Besides micronisation of tigolaner, a homogenisation step is applied during manufacture of the bulk solution to ensure complete dissolution of tigolaner. Stirring and homogenisation steps lead to water uptake to the solvent. Therefore, nitrogen aeration is applied to reduce water uptake during manufacture of the bulk solution and thus minimising hydrolysis of the solvent 1,2-isopropylidene glycerol.

The formulation used during clinical studies is the same as that intended for marketing. However, tigolaner produced by a different active substance manufacturer than now used for manufacture of commercial batches was used. Furthermore, order of addition of ingredients was changed for manufacture of VICH stability batches as it was observed that solubility of tigolaner can be further enhanced by addition of praziquantel and emodepside first.

Method of manufacture

The manufacturing process consists of two main steps: manufacture of the bulk solution and filling into commercial packaging.

Manufacture of the bulk solution is performed under nitrogen-flushing and protected from light and consists of sequential addition and mixing of the ingredients until fully dissolved. The mixture is homogenised until the last ingredient is completely dissolved and finally, the solution is filtered and filled into a tightly closed stainless steel bulk storage container. The solution is overlaid with nitrogen.

The process is considered to be a standard manufacturing process and therefore only process validation schemes have been provided for both main steps of manufacture. Given the nature of the product, being a solution, the manufacturing of the product is not expected to be critical, even though the product is a unit dose product containing the active substance emodepside in low content of less than 2 % of composition. This is supported by the production of three VICH batches at commercial scale of 100 L manufactured at the production site where bulk compounding, fill and blistering was conducted showing consistent results for all three active ingredients being dissolved in the solution. Process validation will be conducted for bulk compounding, fill and blistering prior to the launch of the product. Validation plans have been provided.

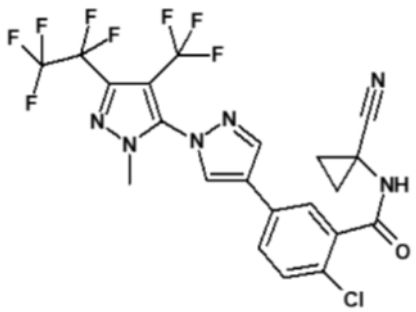
The in-process controls are adequate for this type of manufacturing process. A holding-time of 6 months for the bulk product at max. 25°C has been established.

Control of starting materials

Active substance

Tigolaner

Tigolaner is a new active substance for veterinary medicinal products. The active substance is not a derivative or complex of an already authorised substance. The chemical name of tigolaner is 2-chloro-N-(1-cyanocyclopropyl)-5-[2'-methyl-5'-(pentafluoroethyl)-4'-(trifluoromethyl)-2'H-[1,3'-bipyrazol]-4-yl]benzamide and has the following structure:



The active substance is a white to yellow, crystalline powder which is practically insoluble in water. Tigolaner has a non- chiral molecular structure. Polymorphism has been observed for tigolaner. Two modifications have been identified. Under the manufacturing conditions applied to isolate the final active substance, modification I is obtained.

The information on the active substance is included in full detail within the dossier.

Tigolaner is not subject of a monograph in either the European Pharmacopoeia (Ph. Eur.) or any other pharmacopoeia.

The active substance specification includes tests for appearance, identity, water, related substances, assay, residual solvents, palladium and particle size distribution. The proposed specification for the active substance tigolaner controls relevant parameters. The specification includes limits for single identified impurities, single unspecified impurities and total impurities. The identification, reporting and qualification thresholds according to VICH GL10 are met. In addition, the three mutagenic impurities pyrazoleboronic ester (PBE), pyrazoleboronic acid (PBA) and cyanocyclopropylammoniumchloride (CCPAC) are routinely controlled in tigolaner. They are known mutagens with unknown carcinogenic potential. The applicant applied the less than life-time concept to justify increased acceptable intakes of mutagenic impurities. This is considered acceptable since the active substance tigolaner is used in cats (companion animal). The specified limit for the sum of PBE + PBA + CCPAC is considered acceptable. The specified range for the assay of tigolaner is considered appropriate.

The analytical methods used have been sufficiently adequately described and non-compendial methods appropriately validated in accordance with the VICH guidelines VICH GL 2. Sufficient information regarding the reference standards used for assay and impurities testing has been presented.

Detailed information on the manufacturing of the active substance has been provided. The synthesis is carried out in 3 chemical steps followed by purification and micronisation and uses four starting materials. Appropriate critical process parameters and in-process controls were identified by the manufacturer.

The specifications for intermediate products, starting materials and reagents have been presented. The chosen starting materials are considered justified. The name and address of the manufacturer and the route of synthesis have been provided for each starting material. The proposed specifications of the starting materials are in general considered acceptable. The carry-over of potential impurities from the starting materials to the final substance has been discussed. Detailed specifications have been provided for the intermediates. Analytical methods have been described.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on the chemistry of active substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017). The discussion on the impurity profile of the drug substance is thorough. Information about the structural formula, nomenclature and origin of potential impurities in the starting materials, intermediates and final drug substance have been provided by the applicant. An extensive analysis of potential impurities that may be generated at each stage of the manufacturing process, their fate and values found has been presented. In addition, potential, suspected and known mutagenic and carcinogenic impurities identified in tigolaner are summarised with their genotoxic assessment. The control strategy of these impurities has been discussed. The control approach chosen for some potentially genotoxic impurities in the starting materials was sufficiently justified.

The discussion on residual solvents is in general considered acceptable. A risk assessment on elemental impurities was performed. Palladium is used as catalyst in the manufacturing process of the substance after introduction of the starting materials. The specified limit for residue palladium in non- micronized tigolaner is considered acceptable.

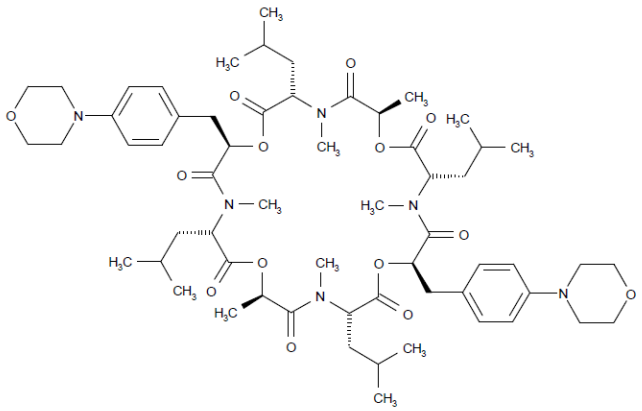
Batch analysis data for three full scale batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on three full scale batches of active substance from the proposed manufacturer(s), stored in the intended commercial package for 3 months under long term conditions at 25 ºC/60 % RH, and, for up to 3 months under accelerated conditions at 40 ºC/75 % RH according to the VICH guidelines were

provided. Additional stability data on three pilot scale batches of active substance from the former manufacturer stored in the intended commercial package for 18 months under long term conditions at 25 ºC/60 % RH and for up to 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines were provided. The following parameters were tested: appearance, particle size distribution, water, related substances and assay. The analytical methods used were the same as for the active substance specification and were stability indicating. All tested parameters were within the specification demonstrating comparability between both manufacturing sites. No trend of degradation can be observed. Results on stress conditions heat (70 °C – 7 days), humidity (40 °C/75 % RH – 7 days), light (200 Watth/m2 – 8.9 hours and 21.8 hours, white light 1.2 MLux/h – 8.9 hours and 21.8 hours), acid (HCl in methanol), alkaline (NaOH in methanol) and oxidizing conditions (H_2O_2 in methanol) were also provided on one batch. The stability results indicate that the active substance tigolaner manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 3 years in the proposed container without any storage restriction.

Emodepside

Emodepside is a semi-synthetic known active substance for veterinary medicinal products. The chemical name of emodepside is cyclo-[D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl)phenyl]-D-2-hydroxy-propanoyl-N-methyl-L-leucyl-D-2-hydroxypropanoyl-N-methyl-L-leucyl-3-[4-(4-morpholinyl) phenyl]-D-2-hydroxypropanoyl-N-methyl-L-leucyl] and has the following structure:



The active substance emodepside is a white to yellowish-white powder which is insoluble in water. Emodepside exhibits stereoisomerism due to the presence of 8 chiral centres. The specific optical rotation of emodepside is routinely controlled. Polymorphism has been observed for emodepside. Under the manufacturing conditions applied to isolate the final drug substance, modification I is obtained.

The information on the active substance is included in full detail within the dossier.

Emodepside is not described in any pharmacopoeia. The active substance specification includes tests for appearance, identity, water, specific optical rotation, heavy metals, sulphated ash, residual solvents, related substances, assay, appearance of solution colour and appearance of solution clarity. The proposed limit for m,p-isomer impurity is based on toxicity studies performed at the time of development of early emodepside finished products. The limits applied for residual solvents methanol (class 2), toluene (class 2) and ethyl acetate (class 3) are consistent with VICH GL18 limits.

The analytical methods used have been sufficiently adequately described and non-compendial methods appropriately validated in accordance with the VICH guidelines VICH GL 2. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Emodepside is synthesised in 4 steps using a well-defined starting material with acceptable specification. The starting material for the chemical synthesis is produced by fermentation of the fungus Mycelia sterilia. Detailed information on the manufacturing of the active substance has been provided and it was

considered satisfactory. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on the chemistry of active substances for veterinary medicinal products (EMA/CVMP/QWP/707366/2017). Potential impurities arising from the route of synthesis/production/purification are discussed, identified, and levels obtained from 10 batches are detailed. With the exception of one isomer, all impurities are below the VICH qualification threshold of 0.5 %.

Batch analysis data three batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data on three full scale batches of active substance from the proposed manufacturers stored in double polyethylene bags, placed in a metal drum as proposed for routine use, for 36 months under long term conditions at 25 ºC/60 % RH and for up to 6 months under accelerated conditions at 40 ºC/75 % RH according to the VICH guidelines were provided. In addition, 11 batches have been introduced in the on-going stability program. The following parameters were tested: appearance, identification, melting point, water, assay and related substance. The analytical methods used were the same as for the active substance specification and were stability indicating. All tested parameters were within the specification. No trend of degradation could be observed. The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period of 3 years in the proposed container.

Praziquantel

The chemical name of praziquantel is (11bRS)-2-(Cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one and is used as racemate. The active substance praziquantel is a white or almost white, crystalline powder which is very slightly soluble in water. Polymorphism has been observed for praziquantel. As the active substances are in solution in the finished product, polymorphism is not relevant for this dosage form.

There is a monograph of praziquantel in the Ph. Eur., and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia for praziquantel, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The manufacturer's specification for praziquantel refers to the tests included in the Ph. Eur. monograph for praziquantel (0855). Additional specifications have been set for nickel and palladium as stated on the CEP and for the particle size. All additional methods have been adequately described. The active substance specification is in general considered acceptable.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. Batch analysis data for three batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

A re-test period of 2 years if stored in double polyethylene bags is claimed by the applicant. The absence of use of material of human or animal origin in the manufacture of the substance is declared on the CEP. A risk management summary for elemental impurities has been provided.

Excipients

All excipients are well known pharmaceutical ingredients. The quality of lactic acid and butyl-hydroxytoluene is compliant with Ph. Eur. A monograph for 1,2-isopropylidene glycerol is not included in the Ph. Eur, however an acceptable specification for 1,2-isopropylidene glycerol has been provided controlling identity, physical characteristics, purity and assay of the excipient.

No novel excipients are used in the finished product formulation. An acceptable specification for 1,2-isopropylidene glycerol has been provided controlling identity, physical characteristics, purity and assay of the excipient.

The list of excipients is included in section 6.1 of the SPC.

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. None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Valid TSE declarations from the manufacturers of the active substances, excipients and of the finished product have been provided.

Control tests during production

The specification for the bulk product is in general appropriate to control the quality of the bulk product.

The bulk specification includes the following tests: material, clarity and colour of solution, pH, identity and assay of each active substance water content, identity and assay of the antioxidants BHA and BHT, praziquantel impurity B, acetone, water as well as unspecified and total impurities respective to the active substances.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines.

Batch analysis results on three pilot scale (25L) and three commercial scale bulk batches (100L) are provided, confirming the consistency of the manufacturing process and its ability to manufacture to the intended bulk product specification.

Bulk stability data on three pilot scale batches (25L) of the finished product manufactured with tigolaner from the manufacturer of development batches and stored under long term conditions for up to 12 months at 25 ºC/60 % RH and for up to 6 months under accelerated conditions at 40 ºC/75 % RH and on three commercial scale batches (100L) of the finished product manufactured with tigolaner from the manufacturer of commercial batches stored under long term conditions for up to 3 months at 25 ºC/60 % RH and accelerated conditions at 40 ºC/75 % RH according to the VICH guidelines GL3 were provided. The batch size of the pilot scale batches was different to those proposed for marketing and they were packed in smaller bulk storage containers (5L instead of 25L stainless steel drums UN) than proposed for commercial scale batches. Samples were tested against the bulk specification. Additional tests for density, assessment of packaging material and microbiological quality were performed.

During testing of the commercial scale batches manufactured with tigolaner from the manufacturer of commercial batch at accelerated conditions OOS results were found for colour of solution after one month for all three batches, for acetone content after two months in all three batches and for content of BHT after one month in one batch. The colour of solution changed to an intense red colouration. The root cause of the strong colouration was investigated and the active substance emodepside was found to form coloured complexes with traces of multivalent metal ions like Fe2+ or Ni2+ due to its cyclic amide structures. In addition, the sentence "Change in colour may occur during storage. This phenomenon does not affect product quality." was added to the SPC and the package leaflet.

The analytical procedures used are stability indicating, no significant changes have been observed. The bulk holding time of 6 months in 25 L stainless steel drums UN with the storage conditions 'Do not store above 25 °C/ 60 % RH' is accepted. The expiry date of the finished product is calculated from the date of production of the bulk solution in accordance with the 'Note for guidance on the start of shelf-life of the finished dosage form' (EMEA/CVMP/453/01). An applicator holding time of 3 months in the aluminium blisters for the 0.74 and 1.18 ml pipettes is considered acceptable based on a holding time study. A holding-time cannot be granted for the 0.37 ml applicator due to OOS results during the holding time study over 9 months.

Control tests on the finished product

The specification proposed for use at release is appropriate to control the quality of the finished product. In addition to the tests already included in the bulk specification the release and end of shelf-life specification include the tests for content of the active substances per pipette and uniformity of dosage units.

The analytical methods used have been adequately described. Method for determination of assay of emodepside, praziquantel, tigolaner, butylhydroxytoluene (BHT) and butylhydroxyanisole (BHA) was already validated in the bulk product.

Information regarding the reference standards used for assay and impurities testing have been provided.

Batch analysis results on the finished product are provided for 3 pilot batches of 23 kg confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Tigolaner sourced from the former active substance manufacturer was used for production of these batches. Comparability of tigolaner manufactured by the two manufacturers was proven by comparative batch analysis data on batches of tigolaner sourced from both active substance manufacturers.

Stability

The specification proposed for use during shelf-life is appropriate to control the quality of the finished product. All acceptance criteria in the end of shelf-life specification except for content of BHT and acetone remain the same as included in the finished product release specification.

Stability data up to 24 months at 25°C / 60 % RH and 30°C / 75 % RH show stability of clinical trial batches.

Stability data on three batches per applicator size corresponding to 9 pilot applicator batches manufactured from three pilot bulk batches (23.1 kg) stored at long term conditions for up to 18 months at 25 ºC/60 % RH, for up to 18 months at intermediate conditions of 30 ºC/75 % RH and for up to 6 months at accelerated conditions of 40 ºC/75% RH according to the VICH guideline GL3 were provided. The batches of product are representative of those proposed for marketing and are packed in the commercial packaging material.

Additionally, three batches per pipette size corresponding to 9 applicator batches manufactured from three commercial scale bulk batches (100 L) were stored for 3 months at long term conditions of 25 ºC/60 % RH, intermediate conditions of 30 ºC/75 % RH and at accelerated conditions of 40 ºC/75 % RH according to the VICH guideline GL3. Stability studies at long-term and intermediate conditions are planned for 60 months.

Two pilot scale batches (23.1 kg) were exposed to light as defined in the VICH guideline GL5 on photostability testing of new veterinary drug substances and medicinal products. No storage precaution regarding light protection is included in the product literature.

The observed physical and chemical changes are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC. No significant changes have been observed.

A shelf-life of 30 months based on data up to 18 months was initially claimed by the applicant. However, as no statistical analysis in accordance with Appendix A of the VICH GL51 'Quality: statistical evaluation of stability data' (EMA/CVMP/VICH/858875/2011) has been provided to show that the limit for content of acetone is not exceeded at the proposed shelf-life of 30 months, a shelf-life of 18 months is agreed.

New active substance (NAS) status

The applicant requested the active substance tigolaner contained in the above medicinal product to be considered a new active substance, as it is novel and not hitherto authorised in a veterinary medicinal product in the European Union. Tigolaner is a novel $GABA_A$ antagonist belonging to the chemical class of bispyrazoles, with activity against ectoparasites. Based on the review of the data provided, it is considered that the active substance tigolaner contained in the veterinary medicinal product Felpreva is to be qualified as a new active substance considering quality and chemical structure.

Overall conclusions on quality

The information in Part II of the dossier corresponds to current rules and guidelines. Information on the development, manufacture, control of the active substance, control of the finished product and stability has been presented in a 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 quality of this product Felpreva is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

Based on the review of the data on quality, the manufacture and control of Felpreva are considered acceptable.

The applicant has committed to perform process validation studies on the first 3 commercial batches.

Part 3 – Safety

Felpreva is a spot-on veterinary medicinal product for cats intended for the treatment of ecto- and endoparasites. It contains a fixed combination of tigolaner, emodepside and praziquantel as active substances.

Two of the active substances, emodepside and praziquantel, are already authorised in veterinary medicinal products in the EU (e.g. Profender spot-on [EU/2/05/054] and Procox oral suspension [EU/2/11/123]). The present candidate product uses the same excipients/solvent as Profender with the addition of butylhydroxytoluene. The active substance tigolaner is a new active substance that has not yet been authorised in a veterinary medicinal product in the European Union.

Safety documentation

Pharmacodynamics

See part 4.

Pharmacokinetics

For pharmacokinetics of the fixed combination, please see part 4.

Emodepside

The pharmacokinetics of emodepside have been studied in rats and dogs. An absorption/distribution/ metabolism/excretion (ADME) study in rats showed that there were no sex or dose-related differences in the rate and route of excretion after single or repeated administration of emodepside. The absorption is dependent on the vehicle. Dermal absorption of emodepside was investigated in several studies and might result in a dermal delivery of up to 10.79% of the dose, whereby the faecal route of excretion predominates. Emodepside has an elimination half-life in rats of 39–51 hours and a bioavailability of 47–54% after oral administration. The highest concentrations are found in fat, which may act as a depot. Unchanged emodepside is the major excretion product, accounting for 45–56% of the dose. Major metabolites were identified as three ring-hydroxylated products, while four other metabolites were shown to be hydrolysis products of emodepside.

In vitro and *in vivo* studies showed that the plasma protein-binding is high and the fraction of unbound emodepside ranges from 0.84 to 3.52%.

Praziquantel

The data provided support the pharmacokinetic profile as represented in the CVMP MRL Summary Reports for praziquantel. Two *in vitro* studies investigating dermal absorption of praziquantel are available demonstrating a dermal absorption of up to 9.66% of the applied praziquantel dose.

Tigolaner

Several studies on pharmacokinetics were provided for tigolaner in laboratory animals. For pharmacokinetics in the target species cat, please see part 4.

In a pharmacokinetic study in male rats, systemic availability after single oral administration of 1 mg/kg bw tigolaner was 100%. A C_{max} of 262 µg/l was reached 24 h after administration. The AUC after oral and intravenous (0.3 mg/kg bw) administration was 14 mg h/l. No elimination half-life could be established in this study due to the clearance and a plasma half-life of 112 h was derived from a study in rats using i.p. administration to calculate AUC.

In a tissue distribution study in rats using [^{14}C]-tigolaner administered as a single oral dose of 5 mg/kg bw, absorption, distribution and excretion of tigolaner was observed for 168 h (7 days). C_{max} was reached after 8 h (between 8 and 24 h in tissues) and tissue distribution was widespread, with highest concentrations found in brown and white fat tissues, adrenals, pancreas and ovaries (the latter in pregnant rats and rabbits). Tigolaner was predominantly and actively excreted via faeces (biliary excretion), whereas excretion via urine was a minor excretion route (approximately 0.1–0.37%).

An *in vitro* dermal absorption study using tigolaner at a single dose of 0.88 mg/cm^2 and an exposure duration of 30 min indicates a low dermal penetration (maximum 1.5% in rat skin and 0.31% in human skin). However, no conclusion can be drawn for dermal long-term exposure due to the short study duration. *In vivo*, a single dose of 2000 mg/kg tigolaner in corn oil administered dermally to rats for 24 h demonstrates some skin permeability, as indicated by a plasma concentration of up to 15 µg/l. After

removal of the test substance, plasma levels of tigolaner increased further and were approximately 100-fold higher 14 days later.

Plasma protein binding in rat, dog and cat is high (≤ 1% of total tigolaner unbound) and a plasma:brain ratio of 50–70% after single oral administration of up to 1000 mg/kg bw indicates good brain penetration of tigolaner.

Tigolaner is able to induce CYP1A1 and CYP3A1, but not CYP2B1 and CYP4A1 in primary rat hepatocytes *in vitro*. In pregnant rats, increased hepatic enzyme activities (7-ethoxycoumarin deethylase, glutathione-*S*-transferase, epoxide hydrolase) were observed with a non-linear dose-response pattern. Investigation of metabolism of tigolaner *in vitro* revealed no metabolites.

In a mass-balance study, excretion of radioactivity was slow and incomplete after 168 h for all rats after oral (49.6%) and intravenous administration (52.3%). The average remaining total activity in the carcass (including blood), GI tract including contents and tissues was significant following oral (38%) and intravenous dosing (35%) for combined sexes. The calculated oral absorption in this study was 34% (30% for males and 38% for females).

Toxicokinetic data collected in the scope of toxicity studies in rats consistently suggest good systemic availability of tigolaner following oral exposure. With repeated daily exposure of rats and dogs using daily doses of up to 500 mg/kg bw, pronounced accumulation was observed as indicated by plateau-shaped plasma time curves and an approximately 10-fold increase in C_{max} and AUC for up to 13 weeks of treatment. At high doses, less than dose-proportional increases in systemic exposure were observed. Further supporting information is retrieved from a study in dogs (2 per sex) with 3 administrations of 100 mg/kg bw within 58 days (on days 1, 29 and 57). In this study, the ratios day 29:day 1 were 115 and 145 for C_{max} and AUC, respectively. A further study conducted in the dog (n = 6) with a single i.v. dose of 0.3 mg tigolaner/kg bw (nominal dose) resulted in a half-life of 328 h.

Toxicological studies

Single dose toxicity

Various acute toxicity studies were carried out in rats and mice with emodepside, in mice, rats, rabbits and dogs with praziquantel and in rats with the formulation under assessment.

The oral toxicity of praziquantel and tigolaner is low, that of emodepside is low to moderate. The dermal toxicity of all three investigated pharmacologically active substances is low. Single dermal administration of 2000 mg/kg tigolaner was well tolerated in male and female Wistar Han rats. Oral treatment with a high dose of the formulation under assessment (1.82 ml/kg bw) caused clinical signs such as uncoordinated gait, decreased motility and hunched posture in male and female rats.

Two oral combination toxicity studies in rats were performed to assess the possible risk which could arise by combining the three active ingredients tigolaner, emodepside and praziquantel together. In the first study, emodepside and praziquantel were combined, and in the second study tigolaner was combined with praziquantel or emodepside. The results of the studies are contradictory: in the first study, emodepside alone at a dose level of 300 mg/kg bw caused decreased motility, uncoordinated gait and tilted head. Both praziquantel and tigolaner administered individually at doses of 2000 mg/kg bw were well tolerated without severe clinical signs of toxicity. The combination of emodepside and praziquantel enhances and prolongs the observed effects of emodepside. In the second combination study, treatment with emodepside and tigolaner led to a lack of any clinical signs, whereas combined treatment with praziquantel and tigolaner (both substances alone were tolerated well after single treatment) caused uncoordinated gait, decreased motility, decelerated breathing and narrowed palpebral fissures as seen with a single treatment with emodepside. Mortality did not occur.

In conclusion, emodepside alone induces toxic/neurotoxic symptoms, whereas praziquantel and tigolaner are tolerated well. Treatment with a high dose of the formulation caused clinical signs such as uncoordinated gait, decreased motility and hunched posture in rodents.

Similar observations could be made when animals were treated with two of the ingredients at the same time. An interaction of all three active ingredients in high dosages could therefore not be excluded.

Repeated dose toxicity

Emodepside

Several repeated dose toxicity studies after oral administration of emodepside were conducted in rats and mice for up to 17 weeks. The effects shown in these studies include reduction in bodyweight gain, effects on neurological function, behaviour and respiration, reduction in the absolute weight of the testes, increase in the relative weight of the brain in male rats, ataxia, increased motility, piloerection, increase in glucagon-secreting cells with a trend towards significant hyperglycaemia, polydipsia and polyphagia. The liver, adrenal glands, pancreas and reproductive system were the principal target organs for toxicity. From these studies in rats, the NOEL of the subacute study was 50 ppm, corresponding to 4.4–4.6 mg/kg bw, and the NOEL of the subchronic study was 10 ppm, which equates to 0.73 mg/kg bw in males and 1.11 mg/kg bw in females. In mice, the NOEL was 10.5 mg/kg bw in males and 16.8 mg/kg bw in females, corresponding to the dietary emodepside concentration of 50 ppm.

In a subacute oral toxicity study in dogs, emodepside was administered orally by gavage daily for 4 weeks, with a 4-week recovery period. The main findings were a decrease in food intake in females. Bodyweight gains were slightly reduced. However, bodyweight gains in the high dose animals were comparable to that of the controls during the 4-week recovery period. No mortality was observed. Increased episodes of vomiting and tremor/ataxia were noted in males at dose rates ≥ 10 mg/kg bw. Females exhibited tremor/ataxia at ≥ 10 mg/kg bw, with staggering incoordination and reduced overall health status at 20 mg/kg bw. No NOEL could be established due to a low incidence of tremor/ataxia in low dose males (5 mg/kg bw).

In another subacute oral toxicity study, dogs were given emodepside twice a day at doses of 2.5, 5.0 and 7.5 mg/kg bw for two weeks. A NOAEL of 2 daily doses of 5 mg/kg bw (corresponding to 10 mg/kg bw per day) was retained, based on changes in liver enzymes.

A repeated dose toxicity study of emodepside after dermal application for 6 hours daily on 22 days in males and 23 days in females was performed in rats, with an observation period of 4 weeks. There was no significant increase in erythema or in skinfold thickness. However, histopathology revealed mild acanthosis and inflammatory cell infiltration. Systemically, there were discoloured faeces and increased production of both urine and faeces at the highest dose level of 1000 mg/kg. A systemic NOEL of 100 mg/kg bw can be retained for the study based on significant alterations in thymus weights (males) and food consumption in both sexes at dose rates ≥ 300 mg/kg.

Praziquantel

All repeated dose toxicity studies submitted for praziquantel have previously been evaluated by the CVMP as part of the authorisation of Profender. Assessment was confirmed during the current authorisation procedure. In rats, a NOEL of 33 mg/kg was established after 4 weeks of administration. The NOEL in dogs was 60 mg/kg after a 4-week and a 13-week treatment with praziquantel. Signs in dogs treated for 90 days were transient and included vomiting and depressed appetite as well as an increase in liver weights at the highest dose of 180 mg/kg.

A further non-GLP-compliant study using the dermal route of application was conducted in rabbits with an observation period of 3 weeks in 1975. Despite the presence of proteinuria and parasitic infections in the

liver, no adverse effects of treatment were observed. The dose tested (500 mg/animal corresponding to approximately 167 mg/kg/day assuming a 3 kg rabbit) was identified as a NOEL in this study.

Tigolaner

Several repeat dose toxicity studies with tigolaner were conducted in rats:

- A preliminary 2-week study (non-GLP-compliant, not following any OECD TG) where tigolaner was administered with the diet at mean nominal intakes of 25.1, 114.2 and 426.1 mg/kg/day in males and 31.5, 122.4 and 510.2 mg/kg/day in females.
- A preliminary extended reproduction/developmental toxicity screening (GLP-compliant, following OECD TG 422) where doses of 0, 15, 60 or 240 mg/kg/day of tigolaner were administered to 5 male and 5 female Wistar rats up to 28 days.
- A 4-week study where tigolaner was administered at 0, 2, 5 and 15 mg/kg bw/day to rats by oral gavage, in accordance with GLP-principles and OECD TG 407.
- A GLP-compliant toxicity study, conducted in accordance with OECD TG 408, where tigolaner was orally administered to rats at 0.3, 1.25 and 5 mg/kg bw/day for 13 weeks.

All repeat dose toxicity studies in rats showed that tigolaner was in general well-tolerated. No clinical signs and no relevant changes on food consumption and body weights were observed up to 13 weeks after oral administration.

In most of the studies common changes observed in haematology and clinical chemistry in both genders were decreased mean neutrophil and eosinophil counts, and increased cholesterol. In addition, mean protein and albumin concentrations were repeatedly increased in males. After necropsy, the following histopathological findings were found in rat's organs from all repeat dose-studies: increased adrenal gland weights accompanied by microscopic changes of the adrenal cortex and hypertrophy/vacuolation of zona glomerulosa and/or fasciculate; cell hypertrophy accompanied by vacuolation and other microscopic changes in liver, pituitary and the thyroids. Further microscopic effects were seen in the ovaries and testes (only in some of the studies), Harderian glands and extralacrimal glands. Dose-dependency of histopathological findings regarding frequency and grade of the changes were detected in most of the organs with graded findings in the studies. No NO(A)EL could be retained from any of the preliminary studies nor from the 4-week-lenght study as histopathological findings were observed at all tested doses. In contrast to that, after oral administration of tigolaner for 13 weeks to rats, a NOAEL of 0.3 mg/kg was established based on increased organ weights and histopathological effects in the adrenals and liver at 1.25 mg/kg in rats. Further histopathological findings were seen in the pituitary gland (hypertrophy/vacuolation of cells in the pars anterior), thyroids (hypertrophy) and in the ovaries (vacuolation and hypertrophy of interstitial cells). Lower food consumption without impact on bodyweight gain and increased cholesterol in females with statistical significance was also observed at 1.25 mg/kg.

A dermal toxicity study was performed in rats, in which tigolaner was administered to Wistar rats for 4 weeks in accordance with GLP principles and OECD TG 410 at doses of 0, 50, 150 and 450 mg/kg bw. Local toxicity was not observed on the rats' skin. Tigolaner was well tolerated systemically. Some clinical pathology changes were seen at 50 mg/kg bw (a decrease in neutrophils and in eosinophils, but no consistent dose-dependency) and at 150 mg/kg bw (increased cholesterol in females). At the lowest and mid dose, adrenal glands were also affected, while the liver and pituitary gland were not changed by tigolaner. Starting at the mid dose of 150 mg/kg bw, microscopic effects on the Harderian glands and ovaries were observed. Based on the data derived from this study, no NOEL could be derived due to the findings in the adrenals.

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

The applicant provided a comprehensive assessment of reproductive and developmental toxic potential of emodepside, praziquantel and tigolaner.

Study of the effect on reproduction

Emodepside

The reproductive toxicity of emodepside was previously assessed by the CVMP and this assessment was confirmed during the current authorisation procedure. A 4-week dietary pilot one-generation study using dosages of 0, 20, 50 or 300 ppm was performed in rats. The mean litter size at birth and the pup weight gain were decreased at 300 ppm. Some pups exhibited uncoordinated gait and/or protruding eyeballs. The NOAEL concerning maternal and reproduction toxicity was set to 50 ppm, which corresponds to 3.3 mg/kg bw/day in male and 5.3 mg/kg bw/day in female animals.

In a two-generation study in rats using dosages of 0, 10, 60, or 360 ppm, the parental LOAEL was 10 ppm, corresponding to 1.0 mg/kg bw/day for males and 1.1 mg/kg bw/day for females based on changes in the pancreas, adrenals, liver, kidney and bones from 10 ppm. The NOAEL for reproductive parameters was 60 ppm (4.3 mg/kg bw/day due to a decrease in implantation sites, litter size and in the number of pups/litters born at 360 ppm). The offspring NOEL was 10 ppm (0.8 mg/kg bw/day) based on effects on the spleen and decrease in thymus weights at 60 ppm.

Praziquantel

For praziquantel, several reproductive toxicity studies were considered previously by the CVMP when MRLs were set. Praziquantel did not display an effect on fertility and reproduction. No new studies were provided for the current authorisation procedure.

Tigolaner

For tigolaner, three reproductive toxicity studies were conducted in rats, including two preliminary range-finding studies and a two-generation study.

In the first preliminary study, rats were treated orally by gavage with dosages of 0, 15, 60 or 240 mg/kg bw/day for a period of 2 weeks prior to a mating period of up to 2 weeks. Effects on reproduction included reduction of the fertility index, total number of pups born and the viability index were at 240 mg/kg bw/day. As body weight reduction and no milk in stomach were observed in F1-pups at the lowest dose of 15 mg/kg bw/day, no NOAEL could be established from this study. The LOAEL is considered to be 15 mg/kg bw/day.

In the second preliminary reproductive performance study, female rats were exposed by oral gavage to tigolaner at dosages of 3, 10 or 30 mg/kg bw/day from day 6 after mating to day 20 of lactation. The F1-generation received direct treatment with tigolaner from day 21 up to approximately eight weeks of age. At 10 mg/kg bw/day, five out of the seven litters died before weaning partly with clinical signs such as little or no milk in the stomach and bodyweight gain was reduced. In the F1-generation, adrenal, testicular weights were increased and ovary weights were reduced at the lowest dose. The NOAEL for maternal toxicity was considered to be 3 mg/kg bw/day. Only a LOAEL of 3 mg/kg bw/day could be derived for reproductive toxicity.

In the two-generation study, rats were exposed to dosages of 1.25, 2.5 or 5 mg/kg bw/day. In the F0-generation, the conception rate/fertility index was slightly lowered at 1.25 and 5 mg/kg bw/day. In F1-litters, liver and brain weight was increased and uterine weight was reduced at 5 mg/kg bw/day. Bodyweight gain for females was reduced from 2.5 mg/kg bw/day on during the lactation phase. In F1-adults, effects were observed on adrenal glands, thyroids, ovaries, uterus and epididymides. In the F2-generation, an increased number of animals died prematurely at 5 mg/kg bw/day and showed effects of autolyzed abdominal contents and no milk in the stomach. Effects were observed on liver, thymus, spleen and brain weights. The mean age of attainment for air righting was slightly elevated for offspring at 2.5 or 5 mg/kg bw/day. Neither for parental toxicity nor reproductive toxicity a NOAEL could be derived due to observed effects from the lowest dose of 1.25 mg/kg bw/day onwards. Regarding effects on reproduction, effects did not always follow a normal dose-dependent relationship. However, as an inverse dose-relationship was observed in developmental toxicity studies and the toxicokinetic study in the rat, treatment-related effects cannot be ruled out.

Overall, Tigolaner demonstrated some effects on reproduction. At the overall LOAEL for reproductive toxicity of 1.25 mg/kg bw/day, the conception rate/fertility index was slightly low and 18 % of females failed to litter.

Study of developmental toxicity

Emodepside

Several developmental toxicity studies were performed with emodepside. Overall, both, the ovarian weight and the gestation rate were unaffected by treatment in rats. Clinical signs of systemic maternal toxicity were evident at dose rates ≥ 6 mg/kg bw/day. Severe maternal toxicity at 18 mg/kg bw/day resulted in adverse effects on foetal development. Renal pelvis dilatation was observed from 2 mg/kg bw/day onwards as well as an increased incidence of shortened innominate arteries, a marginally increased incidence of slight dilatation of the ureter at 6 mg/kg bw/day and retarded ossification from 1 mg/kg bw/day onwards. The NOEL for maternal toxicity was 2 mg/kg bw and the NOEL for developmental toxicity was 0.5 mg/kg bw/day in rats. In rabbits, the effects were similar to the rat studies. The NOEL for developmental toxicity in the rabbit was 5 mg/kg bw/day.

Praziquantel

For praziquantel, several developmental toxicity studies were considered previously by the CVMP when MRLs were set. Praziquantel did not display a foetotoxic or teratogenic potential.

Tigolaner

Five developmental toxicity studies were provided by the applicant including a range-finding study, a toxicokinetic study and a pivotal developmental toxicity study in the rat and a range-finding study and a pivotal developmental toxicity study in the rabbit.

In the oral gavage range-finding study in rats with dosages of 60, 240 or 480 mg/kg bw/day, maternal bodyweight gain adjusted for gravid uterine weight was reduced at all dose levels. Effects included increased incidence and litter incidence of short supernumerary 14^{th} ribs at 480 mg/kg bw/day and a slightly increased incidence of delayed/incomplete ossification/unossified *sternebrae* at 240 and 480 mg/kg bw/day, both within the historical control range. As toxic effects on maternal animals occurred already at the lowest dose tested, no NOAEL could be derived. Consequently, the LOAEL for maternal toxicity is 60 mg/kg bw/day. The NOAEL for developmental toxicity from this primary study is considered to be 480 mg/kg bw/day.

In the pivotal oral gavage developmental toxicity study using dosages of 30, 100 and 300 mg/kg bw/day in rats, severe maternal toxicity occurred at 30 mg/kg bw/day, while females receiving 100 or

300 mg/kg bw/day were unaffected by treatment. Bodyweight gain and food consumption were reduced, showing an inverse dose-effect relationship. At 30 mg/kg bw/day, pre-/post-implantation loss was elevated and three foetuses in three litters had cleft palates. At 100 and 300 mg/kg bw/day, slightly increased incidences of partially fused jugal to maxillae and ossified cervical vertebral *centra* were observed. At 100 mg/kg bw/day, increases in short supernumerary 14th ribs and slightly fused/partially fused *sternebrae* were observed. Incomplete ossification/non-ossification of total *sternebrae* was observed showing an inversed dose-response relationship. Slight increase in dilated ureter(s) was observed at 30 and 100 mg/kg bw/day. The lowest dose of 30 mg/kg bw/day is considered the LOAEL for both maternal and foetal toxicity of this study.

In the oral gavage toxicokinetics study, rats received tigolaner at doses of 10, 30, 100 or 300 mg/kg bw/day from day 6 to 17 after mating. Bodyweight gain and food intake were reduced in females from 30 mg/kg bw/day on. The mean number of implantations and live offspring were reduced in all treatment groups. As effects on live pups and number of implantations was apparent at all dose levels, the LOAEL for developmental toxicity in this study is 10 mg/kg bw/day.

In the oral range-finding study in rabbits, tigolaner was tested at dosages of 40, 130 or 400 mg/kg bw/day from day 6 to 28 after mating. Bodyweight was reduced in all dose groups. Post-implantation loss (%) was increased at 130 and 400 mg/kg bw/day while mean numbers of live offspring were within the historical control range. Macroscopic examination of foetuses revealed single malformations, one in the control and two in the 130 mg/kg bw/day dose group. These observations are regarded as being incidental and not treatment related. The NOAEL for maternal toxicity from this study is 130 mg/kg bw/day while no NOAEL could be derived for developmental toxicity.

In the pivotal oral gavage developmental toxicity study in rabbits, tigolaner was tested at dosages of 30, 100 or 300 mg/kg from day 6 to 28 after mating. Body weight gain and food consumption were reduced in females in all dosage groups throughout the treatment period. In all dosage groups, foetuses with cervical/thoracic/lumbar scoliosis (caused by multiple vertebral abnormalities) were observed with no dose-dependence. An increased incidence of fused/partially fused jugal/maxilla was observed from 100 mg/kg bw/day on. In addition, an increase in total minor abnormalities at all dosage levels was observed. No NOAEL for maternal toxicity could be derived. The NOAEL for developmental toxicity is 30 mg/kg bw/day.

Overall conclusion on reproductive and developmental toxicity

Overall, emodepside showed a fairly consistent pattern of maternal toxicity, foetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. The overall NOAEL for reproductive toxicity was 0.08 mg/kg bw/day and for developmental toxicity 0.5 mg/kg bw/day in rats.

Praziquantel did not display an effect on fertility and reproduction. Developmental toxicity studies did not reveal a foetotoxic nor teratogenic potential.

Tigolaner demonstrated some effects on reproduction. Consequently, a dose of 1.25 mg/kg bw/day is considered as the LOAEL for reproductive toxicity. Concerning developmental toxicity effects following an inverse dose relationship were observed in rats, with a dose of 30 mg/kg bw/day displaying the most severe effects including pre-/post-implantation loss and variations/malformations including cleft palates. At higher doses, effects were less severe, but effects on ossification were observed. The overall LOAEL for developmental toxicity is 30 mg/kg bw/day.

Genotoxicity

<u>Emodepside and praziquantel</u>

A battery of appropriate *in vitro* and *in vivo* tests (bacterial gene mutation assay, *in vitro* HPRT test, *in vitro* chromosomal aberration test, *in vivo* micronucleus test) indicates that emodepside is non-mutagenic.

According to the MRL summary report for praziquantel, a comprehensive battery of mutagenicity studies (including *in vitro* tests for point mutation assays, chromosome aberration assays, tests for DNA damage as well as *in vivo* point mutation assays and chromosome aberration assays) have been conducted. The conclusion from these studies is that praziquantel is not mutagenic. Whilst various reports from public literature suggest a co-mutagenic or co-carcinogenic role for praziquantel, available data suggest that praziquantel itself has a low primary mutagenic potential, as positive findings for sister chromatic exchange (SCE) in certain *in vitro* studies were not reflected in the corresponding *in vivo* chromosomal aberration assays. This is in line with the Committee's previous conclusions on the substance's mutagenicity.

Tigolaner

Tigolaner was tested in a bacterial gene mutation assay, an *in vitro* and *in vivo* micronucleus test, all of which gave negative results. All tests were GLP-compliant and performed according to relevant OECD test guidelines. Based on these results, tigolaner is considered to be non-genotoxic.

Carcinogenicity

Emodepside and praziquantel

No formal carcinogenicity studies were submitted for emodepside and praziquantel. In view of the fact that both emodepside and praziquantel are considered to have low direct mutagenic potential, and in the absence of any reported concerns following use of emodepside and praziquantel, carcinogenicity studies for the combination are not considered necessary.

Tigolaner

No formal carcinogenicity studies were submitted for the new active substance tigolaner. As results obtained with tigolaner in *in vitro* and *in vivo* genotoxicity tests were clearly negative, and further toxicity studies did not indicate properties that may trigger a carcinogenicity study in line with VICH GL 28, no further information on the carcinogenicity of tigolaner is currently considered necessary.

Studies of other effects

Emodepside and praziquantel were investigated *in vivo* in the Draize test in the rabbit's skin and eye. Tigolaner was tested *in vitro* for its skin (human reconstructed skin model) and eye-irritating potential with the HET-CAM test and human EpiOcular model. Emodepside, praziquantel and tigolaner are not skin or eye-irritating.

The final formulation was tested only *in vitro* for its skin and eye-irritating properties. The results of the study with reconstructed human epidermis did not show skin-irritating properties. However, in the commercially available *in vitro* EpiOcular test, the formulation showed an eye-irritating potential requiring a classification as an eye-irritant according to UN GHS (category 2 or category 1). The risk to the target animal and users is addressed in the product literature.

Dermal sensitization studies with the three active substances tigolaner, emodepside and praziquantel as well as with the final formulation indicate no skin-sensitizing potential.

Secondary pharmacological effects of tigolaner were investigated *in vitro* and *in vivo* with a focus on the cardiovascular and the nervous system. *In vitro*, tigolaner is considered a low-potency blocker of the hERG potassium channel current (IC_{50} > 10 µmol/l). However, i*n vivo*, no effects on the cardiovascular

system were noted in a dog receiving 100 mg tigolaner/kg bw per day for one week, resulting in tigolaner plasma levels of to up to 8145.64 µg/l. Tigolaner possesses an inhibitory potential on all tested $GABA_A$ receptors with highest affinity towards the α3β3γ2 receptor subtype with an IC_{50} of 0.76 µM. In male rats, a NOEL of 100 mg/kg bw was derived based on altered open-field locomotor activity (non-significant) in one study as well as on statistically significant lowering of the pentylenetetrazole convulsion threshold dose in a further safety pharmacology study. Neurotoxicity was observed at high doses in single-dose toxicity studies with laboratory animals, but not in functional observational battery tests which were performed along with a 13-week repeated dose toxicity study.

Excipients

Lactic acid (2-hydroxy-propanoic acid; CAS No 50-21-5) is used as a general-purpose additive for animal feed, is commonly used in veterinary medicinal products and is classified as food additive. It is exempted from the requirement of tolerance for various agricultural uses and it is generally recognized as safe (GRAS).

A reassessment of butylhydroxytoluene (E 321; CAS No 128-37-0), which is authorised as synthetic antioxidant, was performed by EFSA, in which an ADI of 0.25 mg/kg bw/day was derived. For exposure in children, the panel concluded that it is unlikely that this ADI is exceeded.

The organic solvent 1,2-isopropylidene glycerol (solketal; CAS No 100-79-8) has been previously assessed by CVMP, although more recent data are available from the European Chemicals Agency (ECHA; https://echa.europa.eu/de/registration-dossier/-/registered-dossier/12258/1, retrieved 11.09.2020). 1,2-isopropylidene glycerol is of low acute and sub-chronic/chronic toxicity, has no irritative potential to skin and only a slight irritative potential towards the eye, lacks a mutagenic or clastogenic potential and has no potential for developmental toxicity.

Impurities

For tigolaner, several impurities have been identified. They were tested in the bacterial reverse mutation (Ames) test according to current OECD guidelines and GLP principles. The study results demonstrate a genotoxic potential for 4 impurities, i.e. cyancyclopropane-ammoniumchloride, pyrazole-4-boronic acid, pyrazole-4-boronic acid pinacol ester and 1-boc-pyrazole-4-boronic acid pinacol ester. The applicant conducted a risk assessment based according to the CVMP "Guideline on the assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products" (EMA/CVMP/SWP/377245/2016). Specification limits were thereby set under consideration of a less-than-lifetime approach (LTL factor = 90) and a maximum therapeutic dose of 36.2 mg/kg bw. For class 2 impurities (cyancyclopropane-ammoniumchloride, pyrazole-4-boronic acid and pyrazole-4-boronic acid pinacol ester), the TTC threshold of 0.025 µg/kg bw/day was used and a specification limit of 62 ppm in sum was calculated. For class 1 impurities (methylhydrazine, 1-bromo-2-chloroethane and dimethylcarbamoyl chloride), sufficient carcinogenicity data exist and therefore a compound-specific risk assessment was conducted to derive acceptable intakes. For methylhydrazine and dimethylcarbamoyl chloride, a threshold of 0.78 µg/kg bw and 0.092 µg/kg bw were calculated, respectively. For 1-bromo-2-chlorethane, a specification limit of 2486 ppm was calculated taking into account current data retrieved from the ECHA (registration fact sheet as of 17.12.2018; https://echa.europa.eu/de/brief-profile/-/briefprofile/100.003.132).

User safety

The applicant has presented a qualitative and quantitative user safety risk assessment, which has been conducted according to CVMP "Guideline on user safety of topically administered veterinary medicinal products" (EMA/CVMP/SWP/721059/2014).

The product Felpreva is a spot-on solution for cats containing emodepside, praziquantel and tigolaner as active substances. Excipients contained in the product are currently used in veterinary medicinal products or as food additives.

The formulation is presented in ready-to-use pipettes packaged in child-proof blisters containing 0.37, 0.74 and 1.18 ml ready-to-use solution. Blister packs are intended to contain 1, 2, 10 or 20-unit dose pipettes and are provided in a cardboard box as outer package. Due to the product's activity against fleas and ticks for a period of 3 months, the use of the product is not indicated at intervals shorter than three months.

The user may be exposed via the dermal, ocular or oral route. Among these routes, dermal contact with skin is the most likely. Dermal exposure may occur during all three application phases. Oral exposure may rarely and infrequently occur through accidental ingestion by a child during the pre-application and by an adult during the application phases. Furthermore, oral exposure might more likely also occur through hand-to-mouth contact in the post-application phase. Finally, being a liquid solution, the final product could come into contact with the eyes by splashing or by hand-to-eye contact in the pre-application and application phases.

The product did not show skin or other sensitising potential in the respective studies. However, the formulation containing the three active substances (emodepside + praziquantel + tigolaner) showed an eye-irritating potential in the commercially available EpiOcular test system requiring a classification as an eye-irritant. The risk to users is addressed in the product literature.

A quantitative user safety assessment in line with the relevant guidance documents has been presented. This used toxicological reference values (TRVs) derived from the toxicological data set presented above, and exposure estimations. Where relevant, these were drawn from a wipe-test, conducted with the final formulation to determine the level of dislodgeable residues to which the user may be exposed following contact with the treated animal. *In vitro* dermal absorption studies were provided. A specific user risk assessment for pregnant women was conducted. The MOEs (Margins of Exposure) calculated for the pre-application and application phases were under the threshold of 100 and therefore, the risk is mitigated through a child-resistant packaging, and through user safety warnings included in the SPC, section 4.5 (ii). A potential risk has also been identified for children and pregnant women in the short-term post-application phase, within 24 hours after treatment, which has led to the inclusion of specific warnings to avoid contacts with the application site during that period of time. This is not completely in agreement with the guideline EMA/CVMP/SWP/721059/2014 that describes that keeping the animal away from people, particularly children, beyond the overnight period of 12-hours is not generally considered practical. However, taking into account that many worst-case assumptions were made during quantitative risk assessment and that the lowest MOEs at 12 hours' post-treatment are 53 for children and 75 for pregnant women, the risk remaining for users who may in some cases not be able to keep away from treated animals for the full 24-hour period is considered acceptable. No risk has been identified (MOEs above 100) for the long-term post-application phase.

Furthermore, an interaction between all three active ingredients at high dosages could not be excluded. However, increased toxicity of the combination of the three active substances was only observed at dosages that exceeded the TRVs proposed by the CVMP by far. Consequently, no risk for the user is anticipated due to cumulative toxicity of the active substances.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines (VICH GL6 and GL38 and the CVMP "Guideline on the environmental impact assessment for veterinary medicinal products in support of the VICH guidelines 6 and 38"). The environmental risk

assessment can stop in phase I and no phase II assessment is required because the veterinary medicinal product will only be used in non-food producing animals. Based on the data provided, Felpreva is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Two of the active substances, emodepside and praziquantel are already authorised in VMPs in the EU and the previous assessment was confirmed during the current authorisation procedure. The active substance tigolaner was newly assessed in the frame of the current procedure.

Single dose oral toxicity of praziquantel and tigolaner is low, that of emodepside low to moderate. The single dose dermal toxicity of all three pharmacological active substances investigated is low. An interaction of all three active ingredients could not be excluded at high dosages.

For emodepside the derived short-term TRVs for quantitative user risk assessment are 1 mg/kg bw for oral exposure based on acute increase of glucose levels observed in the subchronic study in rats and 9.9 mg/kg bw for dermal exposure based on acute oral toxicity study with Profender Spot-on.

For praziquantel, the derived oral short-term TRV of 10 mg/kg bw based on the oral safety study in adult cats and extrapolation from LOAEL to NOAEL. The dermal TRV is 132 mg/kg bw based on a dermal 3-weeks study in rabbits.

For tigolaner, the NOAEL of 10 mg/kg bw/day for maternal toxicity derived from the developmental toxicity study in rats is used as TRV for acute oral toxicity in quantitative user risk assessment. The dermal short-term TRV is 178.2 mg/kg bw based on the acute dermal formulation toxicity study in rats.

Oral repeated dose toxicity studies with emodepside conducted in rats and mice for up to 17 weeks showed similar results, e.g. effects on neurological function, behaviour and respiration. The liver, adrenal glands, pancreas and reproductive system were the principal target organs for toxicity. The overall chronic NOAEL of 0.08 mg/kg bw was derived from the 2-generation study in rats. The dermal long-term TRV is extrapolated from this NOAEL employing an oral absorption of 52 % and a dermal absorption of 10.79 % resulting in a dermal chronic TRV of 0.36 mg/kg bw/day.

For praziquantel, no new studies in rats were submitted. Relevant existing studies were provided for the current authorisation procedure. In dogs, transient signs of vomiting and depressed appetite as well as an increase in liver weight were observed at higher doses. The oral short-term TRV of 10 mg/kg bw based on the oral safety study in adult cats was extrapolated in order to derive the oral long-term TRV arriving at a value of 3.3 mg/kg bw/day. The dermal long-term TRV was extrapolated from this value employing a dermal absorption of 9.7 % resulting in a value of 33 mg/kg bw/day.

Several repeated dose toxicity studies performed with tigolaner in rats were submitted showing that adverse effects related to clinical observations, bodyweight gain, clinical and gross pathological observations including histopathology were remarkably consistent between studies. Tigolaner was generally well tolerated. The overall oral long-term NOAEL for tigolaner was determined to be 0.3 mg/kg bw/day derived from the 13-weeks study in rats. This NOAEL was extrapolated to a dermal long-term NOAEL using a default dermal absorption value of 25 %. The derived dermal long-term TRV is 1.2 mg/kg bw/day.

Concerning reproductive and developmental toxicity, emodepside showed a fairly consistent pattern of maternal toxicity, foetotoxicity, foetal malformations and various skeletal/visceral anomalies or deviations. The overall NOAEL for reproductive toxicity in rats was 0.08 mg/kg bw/day and 0.5 mg/kg bw/day for developmental toxicity. Praziquantel did not display an effect on fertility and reproduction. Developmental toxicity studies did not reveal a foetotoxic nor teratogenic potential. Tigolaner demonstrated some effects on reproduction and embryonic development in rats and rabbits.

Concerning developmental toxicity, effects following an inverse dose-effect relationship were observed with 30 mg/kg bw/day in rats, displaying the most severe effects including pre-/post-implantation loss and variations/malformations including cleft palates. The overall LOAEL for reproductive and developmental toxicity is 1.25 mg/kg bw/day. The resulting extrapolated NOAEL is derived at 0.42 mg/kg bw/day. Praziquantel has a low primary mutagenic potential. Tigolaner and emodepside are considered non-genotoxic. No formal carcinogenicity studies were required for emodepside, praziquantel or tigolaner.

Tigolaner, emodepside and praziquantel were neither skin or eye-irritating nor skin-sensitizing. The final formulation did not show skin-irritating properties. However, an eye-irritating potential was observed *in vitro*, requiring classification as an eye-irritant. Dermal sensitization studies with the final formulation did not indicate a skin-sensitizing potential.

For tigolaner, several genotoxic impurities have been identified. The calculated thresholds and specification limits for the impurities are acceptable.

Emodepside and praziquantel did not show an immunotoxic potential. Tigolaner and emodepside showed neurotoxic effects via a different mode of action and only at high dose levels. Praziquantel is not neurotoxic.

Concerning the toxicity of the excipients, lactic acid, butylhydroxytoluene and 1,2-isopropylidene glycerol are not considered to present a toxicological risk.

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

A user safety assessment in line with the relevant guidance documents has been presented. The risk for users is sufficiently addressed and mitigated by a child-resistant packaging and user safety warnings included in the SPC.

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

Part 4 – Efficacy

Pharmacodynamics

The new triple fixed combination product is a spot-on containing three active substances: emodepside, praziquantel and tigolaner.

Praziquantel

Praziquantel is an acylated pyrazino-isoquinoline derivative used in veterinary medicine for many years and is active against intestinal cestodes in large and small animals. It acts primarily by severely damaging the parasite integument resulting in contraction and paralysis, disruption of metabolism and finally death.

Emodepside

Emodepside is a semi-synthetic compound of the class of cyclo-octadepsipeptides with anthelmintic activity primarily directed against gastrointestinal nematodes. In the EU, an emodepside-containing veterinary medicinal product was first launched in 2007. Emodepside acts at the neuromuscular junction by stimulating the pre-synaptic latrophilin receptors belonging to the secretin receptor family, which results in paralysis and death of the parasites.

In an *in vitro* study on interactions with the multi-drug resistant protein (MDR), emodepside was more effectively excreted in MDR-1-harbouring cells than ivermectin, and data suggest that emodepside will not cross biological membranes. However, given that there is the potential for interaction with other P-

glycoprotein-dependent substrates, a relevant warning is included in section 4.8 of the SPC.

Tigolaner

Tigolaner is a new active substance (NAS), which has not yet been authorised in a veterinary medicinal product in the European Union. It is a novel $GABA_A$ antagonist belonging to the class of bispyrazoles, with antiparasitic action against ectoparasites similar to isoxazolines. The applicant provided a number of studies and literature references to support the pharmacodynamic properties of tigolaner.

Specificity and sensitivity of tigolaner to GABA-Cl channels of cat flea (*C. felis*) and cattle tick (*R. sanguineus*) was assessed, using GABA-Cl channel expressing cell lines. The selectivity window of the flea GABA receptor to the human α1β2γ2 GABA receptor (as the ratio of the estimated EC50 values) was in the order of 5000.

The results of the contact assays of the *in vitro* part of a study comparing efficacy of $GABA_A$ antagonists of different ectoparasitic substances against different arthropod species indicated that fleas (*C. felis)* showed high susceptibility for tigolaner, and that adult *I. ricinus* can be controlled by all GABA antagonists (nymphs were not tested in the assay). In the *in vivo* part of the study, all tested $GABA_A$ antagonist compounds were shown to kill *C. felis* on rats. Topically applied tigolaner gave the longest duration (~35 days) based on given ET_{95} values for fleas. In two further *in vivo* studies, tigolaner showed immediate efficacy rates of 100 % against *C. felis,* and persistent efficacy until study D+ 23 (intraperitoneal injection) and d+30 (spot-on administration).

Development of resistance

Praziquantel:

So far, there are no reports about resistance development in Europe; however, recent data revealed that *Dipylidium caninum* cestodes resistant against praziquantel have been identified in dogs from the USA, but there is no such report in cats. A cat-specific genotype was recently detected (Beugnet et al., 2018), revealing that emergence of resistance in the dog genotype does not necessarily lead to the development of resistance in the feline genotype as well.

Prudent use of the fixed combination product is crucial to ensure that the efficacy is maintained and any development of resistance in the future delayed. Hence, a general warning is included in the SPC.

Emodepside:

No cases of resistance of feline nematodes against emodepside are published so far.

Tigolaner:

As tigolaner is new in veterinary medicines, no resistance has been documented so far. Tigolaner, chemically a bispyrazole acts as an inhibitor of the gamma-aminobutyric acid (GABA) receptor, similarly to isoxazolines and fipronil. Side resistance to the class of isoxazolines can, therefore, be expected in the future, due to the assumed similar binding site at the insects' GABA receptor. Cross-resistance to the fiproles (i.e. fipronil), however, is deemed unlikely as there is strong evidence for a different binding site of tigolaner at this protein complex compared to the fiproles.

Pharmacokinetics

Praziquantel, emodepside and tigolaner individually:

See part 3

Tigolaner, emodepside and praziquantel in the fixed combination

Plasma concentrations

In the pivotal GLP-compliant pharmacokinetic study, the plasma pharmacokinetic properties of tigolaner, emodepside and praziquantel after spot-on administration of the final formulation of the test product (n=10) and i.v. administration of the single active substances (n=6, each group) were investigated in cats. Maximum plasma concentrations of tigolaner, emodepside, and praziquantel were 1.35 mg/L (reached 12 days after dosing), 0.044 mg/L (reached 1.5 days after dosing) and 0.048 mg/L (reached 5 hours after dosing), respectively. Tigolaner, emodepside and praziquantel declined with a mean half-life of 24, 14.5 and 10 days, respectively. Inter-individual variation in plasma concentrations and half-life was observed for all three substances. For tigolaner, a significant increase in half-life following repeated dosing was shown resulting in accumulation of tigolaner after 4 consecutive treatments during the TAS study in adult cats.

Bioavailability after single spot-on administration was determined by comparison to plasma exposure after i.v. dosing. Topical bioavailability was 57 % for tigolaner, 90 % for emodepside, and 48 % for praziquantel. However, reliability for values given for the topical bioavailability could not be fully proven as dose linearity for elimination after i.v. dosing has not been shown; as i.v. dosing was performed with a lower dose rate due to very limited intravenous safety this issue will not be pursued further though.

In the pivotal target animal safety study, for tigolaner C_{max} values were 4031.9, 10208 and 9896.5 µg/L for the 1x, 3x and 5x RTD groups. AUC_{last} were 2943003, 7472148 and 9732449 h*µg/L, respectively. T_{max} were 226.0, 282.5 and 423.3 hr for the 1x, 3x and 5x group. For emodepside, C_{max} values were 102.4, 431.7 and 254.2 µg/L for the 1x, 3x and 5x group. AUC_{last} were 37639, 189071 and 162725 h*µg/L, respectively. T_{max} were 41.6, 67.7 and 211.7 hr for the 1x, 3x and 5x group. For praziquantel, C_{max} values were 65.2, 195.5 and 268.3 µg/L for the 1x, 3x and 5x group. AUC_{last} were 7228.4, 39676 and 48811.4 h*µg/L, respectively. T_{max} were 31.6, 39.0 and 31.6 hr for the 1x, 3x and 5x group.

For emodepside and praziquantel rate and extent of plasma exposure showed no clear results, hence dose proportionality cannot be concluded. For tigolaner, plasma exposure of tigolaner was less than proportional with increasing dose for tigolaner.

No clear effect of gender was observed within the study. However, the interpretation of results was very limited due to high inter-individual variations in plasma exposure.

Dose proportionality

In another pivotal GLP-compliant pharmacokinetic (PK) study, the plasma pharmacokinetic properties of tigolaner, emodepside and praziquantel with regard to dose proportionality after spot-on administration of the final formulation of the test product at 2.5x and 5x the recommended treatment dose (RTD) were investigated. 32 cats (17 males, 15 females) with 8 animals per group were used for the investigations. Dose proportionality could not be shown as the ratio of the AUC_{last}/D (geometric mean dose normalized plasma exposure) and C_{max}/D (geometric mean dose normalized peak plasma concentration) between the test item at 1x (based on results of the pivotal PK study), 2.5x and 5x RTD was below 1. However, these results have to be taken with caution, as results from the 1x dose group were taken from another study.

Drug-drug-interactions

Higher rates and extents of tigolaner and emodepside plasma exposures were detected for Felpreva when compared with both reference items in the second PK study and other studies submitted by the applicant: AUC_{last} of tigolaner was significantly higher in Felpreva compared to tigolaner spot-on alone, and T_{max} of emodepside was higher in Felpreva compared to reference 2 (emodepside and praziquantel, Profender). Also, C_{max} of emodepside was clearly increased in the triple combination (C_{max} = 51.49 µg/l) compared to the combination of emodepside and praziquantel only (C_{max} = 35.08 µg/l) in a pilot plasma bioequivalence study. Also C_{max} of praziquantel was statistically significant decreased in the triple

combination (C_{max} = 29.54 µg/l) compared to the combination of emodepside and praziquantel only (C_{max} = 45.18 µg/l).

The CVMP considered that there is clear evidence for drug-drug-interaction for tigolaner, emodepside and praziquantel when used in this triple combination product. However, as this effect does not appear to be of clinical consequence, the issue was not further pursued.

Metabolisation and excretion

In the third pivotal GLP-compliant pharmacokinetic study, the plasma pharmacokinetic properties of tigolaner, emodepside and praziquantel in plasma, urine, and faeces were investigated in six cats (3 males, 3 females) after spot-on administration of Felpreva at the recommended dose of 14.4 mg tigolaner / kg body weight, 3 mg emodepside / kg body weight, and 12 mg praziquantel / kg body weight (0.148 ml Felpreva / kg body weight).

Tigolaner and emodepside are mainly excreted in the faeces, i.e. 55 % and 57-71 % of the administered dose of tigolaner resp. emodepside within the first 28 days post treatment. Renal clearance is the minor route of elimination for tigolaner and emodepside, i.e. less than 0.5 %.
Praziquantel is only excreted to a limited extent via urine and faeces, i.e. approx. 1.5 % in faeces and 1 % in urine.

Second tigolaner peak:

In several studies, a second tigolaner plasma peak was observed after approximately 42 days. It is assumed that this most likely might derive from a release of tigolaner from the fat tissue due to factors influencing fat metabolism.

SPC section 5.2. "Pharmacokinetic particulars"

Data presented in section 5.2 adequately reflect the data obtained from the pharmacokinetic studies.

Justification of fixed combination

In line with the Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), the applicant justified the fixed combination with the broadening of the activity spectrum, by combining three active substances, as integrated treatment approach for use in cats presenting multiple infections, or being at risk of multiple infections. To demonstrate that the triple combination is therapeutically justified, the applicant provided based on literature review, an outline of the key parasitological and medical features, and the prevalence of the main parasite species in cats in Europe targeted by the proposed product.

All targeted parasites (fleas, ticks, mites, gastrointestinal nematodes, cestodes and lungworms) are commonly found in cats in Europe, are of known clinical relevance and can occur simultaneously as concurrent infections. In a European survey performed in 2012-2013 in Austria, France, Belgium, Hungary, Italy, Romania and Spain, 11.9 % of 1519 domestic cats enrolled harboured both ectoparasite and gastrointestinal helminth infections, whereas cestode infections were only detected in 3 %. Low prevalence of mixed infection is corroborated by a study in 235 domestic cats in Western Hungary, in which multiple (2-5 species) nematode infections were detected in 14.9 % of client-owned cats, whereas the occurrence of mixed nematode - cestode infections was quite low (3 %). The applicant considered that the target population of domestic cats harbouring mixed infections with nematodes/lungworms, cestodes, and ectoparasites must be considered to be limited.

The CVMP acknowledged that a combined treatment approach as proposed is justified only in a small number of multi-infected cats. The triple fixed combination product is, therefore, only indicated for cats with or at risk of mixed parasitic infections, i.e. when ectoparasites, cestodes and nematodes are targeted

at the same time. Information is provided in the SPC that in the absence of the risk of co-infections, appropriate narrow spectrum products should be considered.

Dose determination / finding studies

Tigolaner

Fleas (Ctenocephalides (C.) felis) and ticks (Ixodes (I.) ricinus)

The applicant has provided 6 well-performed studies to justify the proposed dose of 14.5 mg/kg bw tigolaner, with two GCP-compliant studies being considered as pivotal. Both studies were conducted in line with the recommendations of the relevant guidelines, VICH GL9 on Good Clinical practice, CVMP guidelines on Demonstration of efficacy of ectoparasiticides (7AE17a) and Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3).

Groups of 8 cats were treated topically with either 0.5X, 1X and 2X the recommended treatment dose (RTD) of the spot on (i.e. 7.25 mg, 14.5 mg or 29 mg tigolaner) or 0.5X, 1x and 1.3x spot on (7.25 mg, 14.69 mg or 19.26 mg tigolaner). Blood samples were collected at various times from D+1 until D+91 for the determination of plasma concentrations. In these studies, the administration of the proposed dosage of 14.5 mg/kg bw tigolaner achieved adequate efficacy (≥ 95 % with respect to fleas and ≥ 90 % with respect to ticks) up to D+59 and D+91 against fleas (*C. felis*), and up to D+84 and D+92 against ticks (*I. ricinus*), respectively.

The CVMP noted that in the EU, individual housing of the test animals is not recommended for the entire study duration (EMEA/CVMP/EWP/005/2000-Rev.3), but that in four studies conducted outside Europe, including the pivotal ones cats were housed individually for the entire course of the study, and in cages that were smaller than required by the EU Directive 2010/63. Although, it would be desirable that the studies have been conducted in line with European animal welfare legislation (Directive 2010/63), it is considered not a precondition.

Ear mites (Otodectes cynotis) and Notoedres cati

The proposed dose for treatment of mite infestations is based on the sufficiently high plasma levels at the start of treatment, as no claim for persistent treatment of these parasites was made.

Emodepside:

In order to reduce the number of studies, the applicant sought scientific advice (EMA/CVMP/419185/2018) to clarify the set of studies necessary to bridge the nematode indications already granted for another authorised product containing the nematocidal substance emodepside (Profender spot-on) to the new triple fixed combination. *T. cati* was identified as dose-limiting endoparasite species (adult stage), since a dose of 1 mg emodepside/kg bw resulted in only 42 and 51 % efficacy against *T. cati*, whilst it was 95 to 99 % effective against hookworm infections with *A. tubaeforme*.

In support of the VICH-based bridging concept between Profender spot-on and the new triple combination, the applicant submitted a pilot crossover bioequivalence study with eight cats. The % ratio of emodepside for AUC_{last} and C_{max} confirmed at least the same or even slightly higher relative bioavailability of emodepside after topical application of the new triple formulation. The CVMP, therefore, accepted adult stages of *T. cati* in cats as dose-limiting nematode species for emodepside.

Praziquantel:

As the new triple fixed combination contains the same concentration of praziquantel as an authorised veterinary medicinal product (Profender spot-on), and is administered at the same dose, the applicant refers to this product with the intention to use adult *D. caninum* as the least susceptible cestode species, in order to bridge the non-zoonotic tapeworm claims from Profender spot-on to the new triple fixed combination. This approach was considered acceptable according to a scientific advice (EMA/CVMP/419185/2018) given prior to submission. It should be noted that *D. caninum* was already used as dose-limiting for non zoonotic cestode species in recent EU application.

D. caninum can, however, only be accepted as least susceptible cestode species in the context of non-zoonotic cestode species such as *T. taeniaeformis*; and studies demonstrating efficacy against the zoonotic parasite *E. multilocularis* when treated with Felpreva were not submitted. The applicant therefore withdrew this indication from the proposed indications for Felpreva.

Dose confirmation studies

Ectoparasites (tigolaner)

Fleas (*Ctenocephalides felis*) and ticks (*Ixodes ricinus*)

Two pivotal dose confirmation studies in line with relevant guidelines (EMEA/CVMP/EWP/005/2000-Rev.3 and 7AE17a) were provided to confirm the efficacy of the final formulation of Felpreva for immediate and persistent efficacy of artificial tick and flea infestation on cats after a single topical administration between the shoulders.

All studies were blinded with a negative control group and one or more treatment groups using a randomised block design based on pre-treatment flea count. Eight cats per study group were infested with ~100 *C. felis* and ~50 *I. ricinus* on D-1 and thereafter around monthly intervals. The artificial strains and isolates were representative for European conditions. Animals were treated once topically on D0 at the minimum recommended dose of 14.5 mg/kg bw tigolaner + 3 mg/kg bw emodepside + 12 mg/kg bw praziquantel (final formulation). The immediate efficacy was assessed 24h and 48h post treatment with respect to fleas and ticks, respectively.

In both studies, high persistent efficacy rates of 92.4 to 100 % and 99.2 to 100 % were demonstrated for *I. ricinus* from D+1 till D+93/94, respectively. High efficacy (100 %) was demonstrated against fleas from D+1 till D+91 in one study. Although in the second study adequate efficacy was not achieved on D+94 and, additionally, only 5 out of 8 control cats were adequately infested with fleas (≥ 50 % of fleas were observed on each cat) on D+1, the study was, nevertheless, considered appropriate to justify the claimed efficacy against *C. felis* for up to 3 months.

Except for local effects on the application site, the administration of Felpreva was well tolerated in cats.

The speed of kill against *C. felis* was evaluated in a study, where efficacy was assessed 8h, 12h and 24h after infestations on D-2, +28, +56 and +91. The onset of efficacy was within 12h with respect to fleas that are already on the animal prior to administration (D0). For newly infesting fleas the onset of efficacy is within 8h for 2 months (D+28 – D+56) and within 24h afterwards, which is correctly stated in section 4.2 of the SPC.

Ear mites (*Otodectes cynotis*)

Two GCP compliant, blinded dose confirmation (DC) studies were performed in cats artificially infested with *O. cynotis*. The placebo and the treatment group consisted of 8 cats each. Cats were experimentally infested with a South African strain which was recently enriched with *O. cynotis* from a Hungarian cat. Cats were treated once topically with the final formulation at the minimum recommended dose of

0.148 ml/kg bw (equivalent to 14.4 mg/kg bw tigolaner+3 mg/kg bw emodepside+12 mg/kg bw praziquantel).

Efficacy was assessed based on ear mite counts after collection of ear contents on D+28. Efficacies of Felpreva in comparison to the negative control groups were presented based on arithmetic and geometric means. Adequate efficacy of more than 90 % was achieved but both studies were conducted with the same *O. cynotis* isolate. The benefit of the second study remains, therefore, questionable.

The applicant provided a third pivotal DC study using a mite isolate from the USA where 100 % efficacy against *Otodectes cynotis* in the treated animals was demonstrated. Hence, the claimed indication of "Treatment of infestations with ear mites (*Otodectes cynotis*)" at the proposed dose is justified.

No efficacy follow-up, however, was conducted later than 28-30 days. Since a few mites were still observed on D+28 in the Felpreva treated group, re-appearance of clinical symptoms cannot be fully excluded. The treatment success should, therefore, be controlled at least one month after treatment. A corresponding advice adequately reflects this issue in the SPC**.**

Notoedres cati:

MUMS/limited market status was granted for the treatment of *Notoedres cati* infestations*.* In line with the corresponding MUMS/limited market guideline (EMA/CVMP/EWP/117899/2004–Rev.1) adequate efficacy has, therefore, only been demonstrated via *a field study*.

Endoparasites: Nematodes (emodepside)

Toxocara (T.) cati (adults)

One exploratory and two controlled laboratory dose confirmation studies were conducted to examine the efficacy of Felpreva against adult *T. cati* infections (incl. few larval stages). Adequacy of infection was confirmed by >5 adult worms in at least 6 control cats according to VICH GL20 Efficacy of anthelmintics, specific recommendations for feline.

Both pivotal dose confirmation studies, supported by the exploratory study, demonstrated a high efficacy of 100 % against adult *T. cati* (control groups means: 10.9, 13.3 and 38.7 worms, respectively). The data are considered satisfactory to claim efficacy against adult *T. cati*.

Toxascaris (T.) leonina (adult, immature adult, L4) and Ancylostoma tubaeforme (mature adulte, immature adult, L4)

No new study has been provided as *T. cati* has been identified as the least susceptible species for emodepside and 100 % efficacy was demonstrated against *T. cati* (adult stage). Hence, in line with the scientific advice, reference is made to Profender spot-on for cats (EU/2/05/054/001-017), and the claims against both the roundworm *T. leonina* (mature adult, immature adult and L4) and the hookworm *A. tubaeforme* (mature adult, immature adult and L4) can be bridged from the authorised product Profender spot-on for cats.

Aelurostrongylus (A.) abstrusus (adults)

No dose confirmation studies against the lungworm *A. abstrusus* (adult) have been conducted, but in line with a scientific advice (EMA/CVMP/SAWP/41985/2018) the applicant made reference to Profender spot-on for cats, supported by a one-arm field study based on faecal larval counts (FLC) reduction, and a small-scale pilot plasma bioequivalence study, which demonstrated that the main pharmacokinetic parameters for emodepside obtained after application of Felpreva revealed a slightly higher degree of plasma bioavailability compared to the reference product Profender spot-on.

Troglostrongylus (T.) brevior (adults)

T. brevior has been classified as minor use indication (MUMS) by CVMP; thus, no dose determination studies have been conducted.

One GCP-compliant dose confirmation study against artificial infection with 100 L3 of *T. brevior* has been provided. All cats enrolled shed L1 lungworm larvae in the faeces before study commencement. Four groups of 8 cats were formed, one group served as untreated control. Group two and group 3 was topically treated either with Profender spot-on (emodepside and praziquantel) or Felpreva, each on D+28 and D+44 post infestation. Cats in group 3 were treated with Felpreva at the first treatment and received Profender spot-on at the second treatment. The last group was treated with a spot-on product containing imidacloprid and moxidectin on D+28 and D+56. All animals were dosed at the minimum recommended dose. This study showed 100 % efficacy against adult *T. brevior* lungworms for both Profender spot-on and Felpreva when administered topically, twice, two weeks apart. There were still some few larvae in the faeces after the first treatment, hence, a second treatment is needed to fully recover.

In addition, extrapolation from a European field study conducted with Profender spot-on for cats was made, which contains the same amount of emodepside in the formulation as Felpreva. In this field study conducted in an *T. brevior* endemic area of Italy 100 % efficacy ($p<0.5$) was calculated on D+28 or D+56 based on faecal larval count reduction.

Endoparasites: Cestodes (praziquantel)

Dipylidium (D.) caninum

Three pivotal dose-confirmation studies were performed according to VICH GL 9 (GCP), VICH GL 7 (target animal safety) and VICH GL20 (Efficacy of anthelmintics: specific recommendations for felines) in South Africa with recent field isolates (<10 years old) of *D. caninum* collected either from dogs in Europe or USA and maintained in laboratories. Cats artificially infested with 100 fleas, infected with *D. caninum* cysticercoids were infected by incidental ingestion of fleas during self-grooming and/or feeding of food with contaminated fleas.

Study results of these dose confirmation studies demonstrate a cestocidal efficacy of 100 % after topical application of the final spot-on formulation at the minimum recommended dose of 12 mg praziquantel/kg bw (+14.5 mg tigolaner/kg bw + 3 mg emodepside/kg bw) in cats.

Taenia (T.) taeniaeformis

No new dose confirmation studies against *T. taeniaeformis* were submitted. In line with a scientific advice (EMA/CVMP/SAWP/419185/2018), the applicant made reference to data already submitted and assessed by the CVMP for Profender spot-on for cats. The CVMP concluded as following: "Three GCP-compliant dose confirmation studies were conducted to investigate efficacy of the final formulation against *Taenia taeniaeformis* when administered at the minimum recommended treatment dose. These studies investigated efficacy in cats naturally infected with the parasite. All three studies were conducted outside the EU. These results of these studies are considered sufficient to support the claim for efficacy against adult stages of *T. taeniaeformis*."

Echinococcus (E.) multilocularis

The applicant also applied initially for the treatment of tapeworm infections with *Echinococcus multilocularis* (adult), making reference to data already submitted and assessed by the CVMP for Profender spot-on for cats, and the conclusions reached by the CVMP. However, no clinical efficacy studies were conducted with Felpreva in order to confirm the requested 100% efficacy against the zoonotic parasite *E. multilocularis*, and the applicant therefore subsequently withdrew this indication.

Target animal tolerance

Felpreva is a fixed combination antiparasitic product for cats, containing three active substances (tigolaner, emodepside and praziquantel), to be administered topically at a dose range of 14.5-36.2 mg/kg bw tigolaner, 3.0-7.5 mg/kg bw emodepside and 12.0-30.1 mg/kg bw praziquantel. Treatment is only indicated when ectoparasites, cestodes and nematodes are targeted at the same time and if deemed necessary by the prescribing veterinarian, in which case animals may be treated at 3-month intervals. For all calculations on target animal safety, the maximum proposed label dose serves as a basis.

The applicant provided two pivotal GLP-compliant target animal safety studies, one in kittens and another one in adult cats. In addition, a pilot study, and one study on oral toxicity of the product were provided to investigate target animal safety of the final formulation. Target animal safety of tigolaner alone following subcutaneous (s.c.) or intravenous (i.v.) injection has also been evaluated.

All target animal safety studies were well conducted. The final formulation was used in the pilot target animal safety study, the pivotal target animal safety studies and the oral safety study. In addition, safety data obtained from the clinical safety and efficacy trial and other efficacy and laboratory studies are available. Further information on praziquantel and the praziquantel/emodepside combination in cats is available from the public domain or related centralised procedures.

When used as recommended, the product was generally well tolerated.

Full study title	Treatment	Type of study
Margin of Safety study of a combination spot-on solution of tigolaner (9.79 % (W/V)), emodepside (2.04 %(W/V)) and praziquantel (8.14 % (W/V)) in 10 Weeks Old **Kittens** (2020)*	n=8/group 0x, 1x, 3x, 5x maximum RTD, administered 3 times every 4 weeks and a 4th time after 8 weeks.	**Pivotal TAS study** according to GL VICH 43, GLP
Evaluation of the safety of Tigolaner + Profender topical solution in **adult cats** (2021)*	n=8/group 0x, 1x, 3x, 5x maximum RTD, administered 4 times every 56 days	**Pivotal TAS study** according to GL VICH 43, GLP
Pilot margin of safety study with Profender+tigolaner topical solution in adult cats (2020)	n=4/group 0x, 1x, 3x, 5x of the proposed maximum dose, twice with an interval of 56 days.	Well-performed pilot study.
Evaluation of the Safety of tigolaner + emodepside + praziquantel Topical Solution Administered **Orally** to Cats (2020)	n=8/group 0x, 1x of the proposed maximum dose	Oral administration study according to GL VICH 43
Pharmacokinetic and local tolerance of BAH001600 (MAUE6228) after single subcutaneous administration of an aqueous suspension to cats (2017)	n=4/group 0x, 1x s.c. injection of **tigolaner** at the lower end of the proposed dose range (15 mg/kg b.w.)	Exploratory study
Pharmacokinetic study investigating the bioavailability of tigolaner, emodepside and praziquantel contained in a fixed combination after single topical administration (at 1x therapeutic dose) versus intravenous dosing	n=6 **Tigolaner** at 1.5 mg/kg bw i.v.	Pharmacokinetic study

Full study title	Treatment	Type of study
of the single substances to cats		

* It is noted that two pivotal target animal safety studies were conducted, although the study conducted in kittens would have been sufficient to fulfil EU regulatory requirements. In addition, housing conditions in the studies did not meet the requirements of European animal welfare legislation with regard to cage size, and the duration of single housing was not kept to a minimum.

Tolerance of the individual active substance(s)

Tigolaner

Tigolaner is a new active substance. In the target species cat, the systemic tolerance of tigolaner as single substance was evaluated in one pharmacokinetic study following intravenous injection of 1.5 mg/kg bw. Lethargy and mydriasis were observed following administration but resolved without treatment after 3 minutes. In a combined pharmacokinetic and target animal safety study, following a single subcutaneous injection at the lower end of the dose range proposed for topical administration, all four animals treated with tigolaner showed signs of local reactions like swellings, but no systemic adverse reactions.

In toxicology studies performed in rodent species, tigolaner was in general well tolerated. However, from the totality of these data it can be concluded that in the target animal safety studies conducted with the product, specific attention should be paid to the identified target organs: adrenal glands, thyroid, liver and pituitary glands, as well as local reactions and mydriasis.

Emodepside/praziquantel:

A fixed combination of these substances is already centrally authorised (Profender spot-on for cats); adverse reactions listed in the product information of Profender state: *"Salivation and vomiting may occur in very rare cases. Mild and transient neurological disorders such as ataxia or tremor may occur in very rare cases. These effects are thought to occur as a result of the cat licking the application site immediately after treatment. In very rare cases following administration of Profender transient alopecia, pruritus and/or inflammation were observed at the application site"*

Available pharmacokinetic and pharmacodynamics data indicate an influence of the addition of tigolaner to the combination of praziquantel and emodepside with respect to plasma levels of emodepside, as higher plasma exposures are observed when tigolaner is administered in combination with praziquantel and emodepside. However, these higher plasma levels of emodepside were not correlated with adverse effects.

Tolerance of the fixed combination

Systemic tolerance:

In three target animal safety (TAS) studies, the product was overall well tolerated in all animals; however, thyroid and liver could be identified as target organs and some cases of mild gastrointestinal effects were noted.

The main adverse events seen related to gastrointestinal disorders:
In the pilot TAS study, two cases of vomitus occurred in the mid dose group two days after treatment. This was interpreted as a possible reaction to licking at the administration site, but as vomitus in cats is not unusual, this could also have been incidental. For other gastrointestinal events observed following treatment in the pivotal target animal safety studies and other studies, a treatment relation is unlikely.

In the target animal safety study in adult cats, cholesterol concentrations were mildly increased in the 3x and 5x group females at Days 63, 119, and 175. This appears to be treatment related and is included in the product information. Serum levels of calcium were increased in the 3x overdose group. Moreover, liver enzymes AST and ALT have been increased in animals of the 5x dose group. In addition, one female in the 5x group exhibited multiple dark red discolourations in the liver, up to 2 x 2 mm, affecting all lobes. This gross finding was correlated microscopically with multifocal congestion. As the same animal showed furthermore a significant increase in liver enzymes ALT and AST, a correlation to the pathological findings seems likely. No systemic clinical signs were observed In the pilot target animal safety study and in the pivotal target animal safety study in kittens, clinical pathology and urinalysis did not reveal any changes that could be attributed to the product, and any deviations from normal were of low magnitude.

In the pilot TAS study, necropsy revealed a dose depending effect on the thyroid in male animals, with decreased organ weights compared to controls in the 3x and 5x dose groups, accompanied by a slight reduction in follicle size in the 5x group. Similar observations were made in other studies: In the pivotal study in kittens, one macroscopically small thyroid was noted in one male of the 5x group, and in the pivotal study in adult cats, thyroid organ weights were significantly lower in treated cats as compared to the control group. These findings were without clinical correlation. The thyroid was also identified as target organ following administration of tigolaner to rats.

As the product is a potential eye irritant (see Part 3), respective information on this fact and risk mitigation measures are included in the product information.

In rodent species, oral application of high dose of the formulation caused clinical neurological signs, and mydriasis was noted in cats for a few minutes following i.v. injection of tigolaner. However, no such effects were noted in the target species up to 5x of the maximum RTD following topical administration. In addition, no evidence of effects on the target organs pituitary and adrenal glands that were identified for tigolaner in species other than the target species, was found in cats following topical treatment with the product at up to 5x the proposed dose.

In the three field studies, no treatment related systemic adverse events were noted.

In conclusion, the product was clinically well tolerated up to 5x the maximum recommended dose, administered for up to 3 times at monthly intervals and an additional fourth time two months later, in the specific target animal safety studies. Some data indicate the thyroid and liver as possible target organs. Adequate risk mitigation measures for animals with known liver or thyroid impairment are provided in the product information. The margin of safety appears to be sufficiently broad under the conditions of the studies, i.e., for up to 4 consecutive treatments.

Local tolerance at the application site in the target animal:

In the pilot target animal safety study, a couple of animals reacted to treatment with licking and scratching of the administration site. In two cats of the 5x group, hair could easily be pulled out, which was accompanied by erythema in one animal. In addition, in the 5x group histopathology of the administration site revealed epidermal hyperplasia, inflammatory infiltrates and muscle fibre necrosis. Furthermore, observations of cosmetic nature such as hair spiking were noted for all animals of all treatment groups.

Local reactions were also recognised in a number of other studies, e.g., mild and transient erythema at the application site, thinning of hair and similar cosmetic and behavioural observations as described in the pilot target animal safety study. Though the frequency of local adverse reactions cannot be fully assessed, it can be concluded that effects such as scratching, erythema, thinning of hair or inflammation may occur at the application site. In addition, cosmetic effects such as hair spiking were commonly observed. Furthermore, local reactions were observed following overdose treatment, i.e. alopecia,

erythema, hyperplasia of the epidermis and inflammatory infiltrates. Local reactions are adequately addressed in the product literature.

Target animal safety following oral ingestion of the product:

The effects of oral ingestion of the 1x maximum RTD was investigated in a well conducted study using the final formulation by administration via a syringe into a corner of the mouth, between cheek and teeth; it can be assumed that cats were in a fed state at the time of treatment. All 8 animals of the treatment group experienced hypersalivation immediately after administration, lasting from few minutes to few hours. Often, this was accompanied or followed by retching and in some by vomiting. One animal displayed vocalization and agitation during an episode of vomitus and hypersalivation and was inappetent on the following day. All reactions were transient and did not require treatment. It is likely that the reactions observed are related to a bitter or otherwise bad taste of the product (as known, e.g. from praziquantel), and thus accidental oral administration will be an unpleasant experience for the animal. Therefore, it can be assumed that following self-grooming or partner animal grooming, the ingestion of a high amount is fairly unlikely. As the three active substances are lipophilic, absorption is potentially influenced by the feeding status with lower amounts being absorbed if the product is ingested by cats in fasted state. The observed effects following oral ingestion are correctly reflected in the SPC.

Repeated use: Data are available for up to 4 consecutive treatments. Considering the accumulation of tigolaner following repeated treatment and the fact that no data in tigolaner steady state are available, study results cannot be extrapolated to infinite treatment every three months. It is, therefore, clarified in the product information that no target animal safety data are available beyond 4 consecutive treatments.

Age: A minimum age of 10 weeks and a minimum body weight of 1 kg is proposed. Based on the data provided, in particular as one pivotal target animal safety study was started at that age, this is accepted.

Reproductive safety: No reproductive safety studies have been conducted using Felpreva or tigolaner as single substance in cats. Reproduction/developmental study data for tigolaner and emodepside, describing foetotoxic effects, are only available from rats and rabbits, which is reflected in the SPC.

Clinical studies

Field study: Ectoparasites

The applicant provided three field studies conducted in the EU, one multicentre field study against ticks and fleas, one multicentre field study against ear mites (*O. cynotis*) and one field study against *Notoedres cati* in naturally infested cats.

Ticks and Fleas

Ref.: **Evaluation of the therapeutic and persistent efficacy and safety of Profender + tigolaner (2.04 % emodepside + 8.14 % praziquantel + 9.79 % tigolaner (w/v)) spot-on in cats naturally infested with fleas and/or ticks in a multicentre field study in the EU / 2020**	
Objectives	To confirm the efficacy and safety of a new topical combination product, administered once to client owned cats at a minimum dose of 0.15 ml/kg bw against flea (*Ctenocephalides* (*C.*) *felis*) and ticks (*Ixodes* (*I.*) *ricinus*, *I. hexagonus, Rhipicephalus sanguineus* sensu lato (s. l.) and *Dermacentor reticulatus* for three months (90 days). A non-inferiority evaluation to a positive control product (CP) authorised in EU for above mentioned indication was performed.

Study sites	16 participating clinics in Hungary and Portugal
Study design	Positive controlled, randomised and blinded parallel group multicentre field study
Compliance with Guidelines	VICH GL9 GCP, EMEA/CVMP/EWP/005/2000-Rev.3, 7AE17a, EMEA/CVMP/EWP/81976/2010, Directive 2001/82/EC, WAAVP Guidelines
Test product	Profender + tigolaner spot-on
Control product	fluralaner spot-on
Animals	323 client owned cats (94.1 % European shorthair cats), males and females, 5.9 % different breeds, initially aged 3 – 180 months, weighing 1.2 – 7.7 kg (D0)
Eligibility criteria	Cats with diagnosed tick infestation (≥ 3 attached and viable ticks) Cats with diagnosed flea infestation (≥ 5 viable fleas)
Outcomes/endpoints	Primary endpoint: average efficacy (percentage reduction) of IVP compared to CP over the entire treatment period compared to baseline based on live flea/tick counts (non-inferiority) Secondary endpoint: efficacy (percentage reduction) of IVP compared to CP for each visit separately compared to baseline based on live flea/tick counts (non-inferiority) Safety evaluation: no statistical analysis was performed due to the low number of cats with adverse events (1 in the IVP, 3 in the CP)
Statistical method	Comparison of least square means of percentage reduction of flea/tick untransformed counts over the entire treatment period obtained from a general linear mixed model analysis with repeated measurements adjusted for baseline values.
Results	
Outcomes for endpoints	Based on untransformed count data, the percentage reductions over the entire treatment period were 99.9 % (IVP) and 99.7 % (CP) with the 95 % confidence interval for the difference CP-IVP [-0.56 %; 0.08 %]. Based on untransformed count data, the percentage reductions over the entire treatment period were 98.4 % (IVP) and 99.3 % (CP) with the 95 % confidence interval for the difference IVP-CP [0.42 %; 1.50 %]. Clinical signs of flea allergic dermatitis (FAD): The severity of FAD (pruritus, papule, crusts/scabs, exudate, erythema, scaling, alopecia) was assessed in primary cats on D0, 7, 28, 56, 75 and 90 and in supplementary cats on D0 and D+90. On D0, 16 out of 351 cats (4.6 %) of the IVP group showed signs of FAD. Only 2 out of 351 cats (0.6 %) showed signs of FAD ("mild pruritus") on D+90.
Adverse events	Four adverse events (1 in the IVP, 3 in the CP) unrelated to treatment.

Conclusions:

To support efficacy against ticks and fleas, one GCP compliant, positive controlled field study, conducted at multiple sites within the EU has been provided. The data showed adequate efficacy of Felpreva against *Ixodes ricinus and Ctenocephalides felis.* In addition, this study also serves to support the claim that Felpreva can be used as part of a treatment strategy against flea allergy dermatitis (FAD). With regards to target animal safety, the product appeared generally well-tolerated.

Ear mites (*O. cynotis*)

Ref. Evaluation of the efficacy and safety of emodepside 20.35 mg/mL, praziquantel 81.40 mg/mL, tigolaner 97.90 mg/mL Topical solution in cats naturally infested with ear mites (O. cynotis) in a multicenter field study in the EU / 2020.	
Objectives	To confirm the efficacy and safety of Felpreva administered once to client owned cats at a minimum dose of 0.15 mL/kg body weight (BW) against natural infestations with ear mites (*Otodectes cynotis*).
Study sites	15 veterinary clinics in Hungary (n=8) and Portugal (n=7)
Study design	Randomised, blinded, positive-controlled, non-inferiority study
Compliance with GL	VICH GL9 GCP, 7AE17a
Test product	Felpreva (3 – 7.5 mg emodepside + 12 – 30.1 mg praziquantel + 14.4 – 36.2 mg tigolaner/kg bw)
Control product (CP)	Selamectin and sarolaner (15 – 60 mg selamectin + 2.5 – 10 mg sarolaner/kg bw)
Animals	Client owned cats, 2.5-180 months: PP:148 (78 IVP group, 70 CP group) ITT: 157 (82 IVP group, 75 CP group; 67 m and 90 f) 95 supplementary cats included (46 IVP group, 49 CP group; 44 m, 51 f)
Eligibility criteria	Healthy, non-pregnant, non-lactating, diagnosed with ear mite infestations (clinical signs consistent with ear mite infestations and with visible live ear mites (≥ 3 *Otodectes* mites) present in at least one ear).
Outcomes/endpoints	Primary efficacy criterion: Parasitological cure rate of the IVP compared to the CP (parasitological cure was defined for an animal as having no live mites in the *O. cynotis* assessment on Day (D) 28±2. Secondary efficacy criteria: Parasitological cure rate of the IVP compared to the CP on D14±2 Improvement of *Otodectes* induced ear lesion (OEL) scores.
Statistical method	Primary efficacy criterion: Non inferiority of IVP compared to positive CP was assessed at D28 with a non-inferiority margin of 15%. Secondary efficacy criteria: Parasitological cure rate at D14: Non-inferiority of IVP compared to positive CP. Clinical signs of otoacariasis: OEL scores (sum score of 0 to 18) based on the maximum of left and right ear at D0, D14±2 and D28±2 response was classified as: Improved (max score on D14±2 resp. D28±2 **<** maximum score at D0) Unchanged (max score on D14±2 resp. D28±2 **=** maximum score at D0) Worsened (max score on D14±2 resp. D28±2 **>** maximum score at D0). Summary statistics of frequencies are presented with risk ratios and 95 % confidence limits. Groups have been compared on base of Cochran-Mantel-Haenszel tests adjusted for sites. 1. The mean per group was plotted according to time as long as all the animals included were in the study (D 0 and D+28±2). Animals removed

	post-inclusion were considered to calculate the mean per group previously to their removal. 2. The difference between pair assessments per animal "D0 – Last examination" was considered as a quantitative data. Improvement between groups was compared by Student's t-test. If normality was rejected the non-parametric Mann-Whitney test was used.
Results	
Primary efficacy criterion – Parasit. cure on D+28:	All cats were cured in both treatment groups. No difference was shown between groups. No analysis could be performed and non-inferiority of IVP compared to CP could be concluded. Same result in ITT group.
Parasitological cure rate on D+14	Within the IVP group 70 cats (89.7 %) were cured on D+14±2, within the control group 62 cats (88.6 %). Difference between groups was 1.17 % in favour of IVP with lower bound of the two-sided 95 % confidence interval = -9 % > Δ = -15%. Based on the ITT population, the results are comparable. Non-cures on D+14 occurred in only 1 out of 15 study sites, therefore, adjustment for study site was not possible. The impact of study sites on the results was instead assessed by performing a sensitivity analysis and calculating the relative risk ratio adjusted to site according to Cochran-Mantel-Haenszel. This results in a ratio of 1.01 in favour of IVP with lower bound of the 95 % confidence interval = 0.97.
Secondary efficacy criteria - Improvement of OEL scores:	OEL scores improved on D+14±2 in 97.4 % IVP treated cats and in 97.1 % CP treated cats. OEL scores improved on D+28±2 in 100 % of the IVP treated cats and in 98.6 % of the CP treated cats. Course of OEL scores: On D+14±2 reduction of the mean OEL score was higher in the IVP group by 0.23 score points (adjusted for baseline and site, p > 0.3). On D+28±2 reduction was higher in the controls by 0.03 score points (adjusted for baseline and site, p > 0.8). Similar results can be seen based on of the ITT population.
Adverse events	No adverse events occurred in the IVP treated groups.

Conclusions:
This field study was well conducted and supports the claim "for the treatment of ear mite infestations in cats". The number of animals included appears appropriate and sufficiently represents the European cat population. Differences in body weight and age between the groups are not considered to have an impact of the outcome of the study. It is noted that only one veterinary clinic recorded animals that were not cured on D+14, although no reason for the failure could be identified. Here, 80 % of animals from the IVP group were not cured at D+14 (in contrast to 100 % cure rates in the other study sites). With regards to target animal safety, the product was well-tolerated.

Notoedres cati

The applicant submitted one well-designed, randomised, negative controlled, blinded, clinical study in cats naturally infested with *Notoedres cati* in compliance with the principles of VICH GL9 and guideline 7AE17a.

Cats were treated once topically with the proposed minimum dosage of Felpreva or control product. Each treatment group consisted of ten cats and had an even distribution of cat genders, age and weight and breeds as well as number of mites pre-treatment and similar severity of lesions.

Based on arithmetic and geometric means of mite counts and *Notoedres*-induced ear lesion scores (NISLS), an efficacy of 100 % and clinical cure of notoedric lesions could be achieved in the IVP group. However, it is noted that no cat with severe notoedric lesions and lesions at >50 % of the body surface has been included and that most cats in both groups (7/10) had only mild notoedric skin lesions. Consequently, the clinical claim "notoedric mange", is restricted to "mild to moderate cases of notoedric mange".

No follow up later than one month after the treatment has been performed. Therefore, no conclusion can be drawn with regards to the efficacy and clinical cure later than one month. Due to the potential deleterious consequences of notoedric mange and the possible re-occurrence of clinical signs, the need for an additional examination to confirm treatment success should be determined by a veterinarian one month after treatment. This is adequately reflected in the SPC**.**

Field Study: Endoparasites

The applicant submitted the results of a pivotal European field study in order to evaluate the safety and efficacy of Felpreva following a single topically administered in naturally infected cats. In addition, the applicant make reference to a small-scaled positive controlled efficacy and safety field study from Brazil supporting particularly the efficacy in naturally *D. caninum* infection.

European field study

<table>
<tr><th colspan="2">Ref. / Clinical efficacy and safety of emodepside 20.35 mg/ml, praziquantel 81.40 mg/ml, tigolaner 97.90 mg/ml topical solution when used to treat mixed infections with nematodes and cestodes and/or lungworms in cats in a multicenter field study in the EU / 2020</th></tr>
<tr><td>Objective</td><td>To evaluate the therapeutic efficacy and safety of Felpreva following a single topically administered dose to client-owned cats against infections with gastrointestinal nematodes (Toxocara [T.] cati, Toxascaris [T.] leonina, Ancylostoma [A.] tubaeforme and Uncinaria [U.] stenocephala) and/or cestodes (Dipylidium [D.] caninum and Taenia [T.] taeniaeformis) and/or infections with lungworms (Aelurostrongylus [A.] abstrusus or Troglostrongylus [T.] brevior). For lungworm infections, a second treatment with Profender spot-on for cats was performed after 14 days.</td></tr>
<tr><td>Compliance to guidelines</td><td>VICH GL9, VICH GL7, VICH GL 20, Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals)</td></tr>
<tr><td>Study sites</td><td>Veterinary clinics in Albania, Greece, Italy, Hungary and Portugal.</td></tr>
<tr><td>Study design</td><td>Positive controlled, randomised, blinded, and parallel group multicentre, multi-regional</td></tr>
<tr><td>Test product (IVP)</td><td>Felpreva (3–7.5 mg emodepside + 12–30.1 mg praziquantel + 14.4–36.2 mg tigolaner/kg BW, dermal application), (n=144)</td></tr>
<tr><td>Control product (CP)</td><td>3 – 15 mg emodepside + 12 – 60 mg praziquantel/kg BW (Profender spot-on), (n=75)</td></tr>
<tr><td>Animals and treatment</td><td>Age (in months): PP: 3 – 168 (IVP), 3 - 180 (CP); ITT: 3 - 180 (IVP and CP).
Sex: PP population: 102 m (72 IVP, 30 CP) and 93 f (55 IVP, 38 CP) cats; ITT: 111 m (80 IVP, 31 CP) and 108 f cats (64 IVP, 44 CP).
Treatment: D0, in case of lungworm infection, additional treatment with CP on D+14.</td></tr>
<tr><td>Eligibility criteria</td><td>Healthy, non-pregnant, non-lactating, diagnosed positive for GIT nematodes and/or cestodes and/or lungworms.</td></tr>
<tr><td>Study population</td><td>
<table>
<tr><th></th><th colspan="3">ITT-Population</th><th colspan="3">PP-Population</th></tr>
<tr><th></th><th>Total</th><th>IVP</th><th>CP</th><th>Total</th><th>IVP</th><th>CP</th></tr>
<tr><td>Cats (out of 930</td><td>219</td><td>144</td><td>75</td><td>195</td><td>127</td><td>68</td></tr>
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	screened)						
	Nematodes*:	166	109	57	161	105	56
	T. cati	147	96	51	142	92	50
	T. leonina	7	4	3	7	4	3
	A.tubaeforme	27	18	9	27	18	9
	Cestodes**	10	7	3	9	6	3
	T. taeniaeformis	2	1	1	2	1	1
	D. caninum	3	3	0	3	3	0
	Lungworms	33	19	14	32	18	14
	Ae. abstrusus	22	13	9	21	12	9
	Tr. brevior	10	6	4	10	6	4
	Ectoparasites (total)	70	44	26	58	37	21
	Fleas	59	37	22	48	31	17
	Ear mites	4	2	2	4	2	2
	Fleas and ear mites	7	5	2	6	4	2
	*17 cats with mixed infections: *T. cati*, *A. tubaeforme*, *T. leonina* and *U. stenocephala* **Total sum based on cats with positive FEC + cats with presence of proglottids, species only determined in 5 cats with FEC >0 at baseline.						
Analysis of population	Study animals receiving at least one dose of the IVP or CP were included in the safety population (Intention-to-Treat (ITT) population). The efficacy analysis was based on the per protocol (PP) population. Efficacy was also calculated for the ITT population.						
Results							
Efficacy against GIT-nematodes:	Faecal egg count reduction relative to baseline was 99.6 % in the IVP and 99.9 % in the CP group on D+7 to D+14, based on untransformed data. All gastrointestinal nematodes (105 and 56 cats within IVP and CP groups, respectively) were considered. The 95 % confidence interval for the difference IVP-CP was [-2.31 %; 1.58 %].						
Efficacy against cestodes:	No proglottids were found on D+7 to D+14 in both groups after treatment.						
Efficacy against lungworms	The faecal larval count reduction (FLCR) relative to baseline was 99.6 % in the IVP and 99.7 % in the CP group on D+21 to D+28 (18 and 14 cats within IVP and CP groups, respectively), based on untransformed data. The 95 % confidence interval for the difference was [-1.20 %; 0.98 %].						
Prevalence of mixed infections:	In 17 cats (10.3 %) mixed infections with at least two different nematode species were observed. Mixed infections with gastrointestinal nematodes, lungworms and/or cestodes were observed in 9 out of 219 cats (4.1 %). 70 cats (31.9 %) were concurrently infested with ectoparasites (87.1 % fleas and 12.8 % ear mites).						
Adverse events:	No adverse event occurred during the study.						

Conclusions:

In this field study adequate efficacy (>99 %) against the gastrointestinal nematodes claimed (*T. cati, T. leonina, A. tubaeforme)* was demonstrated. No cestode eggs were found in infected cats after treatment (100 % efficacy). In 4.1 % of the cats (n=9), mixed infections with gastrointestinal nematodes, lungworms and/or cestodes were observed. 31 % of the cats (n=70) were concurrently infested with ectoparasites. Non-inferiority of the IVP compared to the CP (with a CI margin stronger than the pre-defined 15 %, e.g. 2.5 %) was confirmed in both gastrointestinal worms and lungworms. The product was generally well-tolerated.

Brazilian field study

In addition, the applicant provided a small-scaled randomised, positive controlled, unblinded efficacy and safety field study from Brazil, involving 51 domestic cats which were treated either topically with Felpreva (IVP) or orally with the product Milbemax (CP).

Felpreva showed >90 % efficacy against *Ancylostoma* spp. and *Toxocara* spp. on D+7 post-treatment. Only a limited number of cats harboured *D. caninum* at study commencement (IVP: 8 cats; CP: 9 cats). Efficacy calculated after treatment were 95.3 -100 % for the IVP and 100 % for the CP group.

Overall conclusion on efficacy

Pharmacodynamics:

The new triple fixed combination product is a spot-on containing three active substances: praziquantel, emodepside and tigolaner.

Praziquantel is a pyrazinoisoquinoline derivative which has been used in veterinary medicine for many years as an active substance for the treatment of intestinal cestodes in animals.
Emodepside is a semi-synthetic compound of the class of cyclo-octadepsipeptides with anthelmintic activity primarily directed against gastrointestinal nematodes.

The bispyrazole tigolaner, is a novel $GABA_A$ antagonist (similar to the isoxazolines) with ectoparasitic activity against fleas, ticks, ear mites and notoedric mange. Seven literature references and six studies have been provided to elucidate the pharmacodynamics properties of this new active *in vitro* and *in vivo*.

Resistance:

No reports on resistance against any of the active substances have been reported in cats so far in Europe. However, the appropriate use of the product remains crucial to ensure that the efficacy is maintained and any development of resistance in the future delayed. Hence, the proposed SPC (section 4.4) contains the standard warning addressing the potential development of parasite resistance.

Pharmacokinetics:

After single topical administration of the product to cats, maximum tigolaner plasma concentrations of 1.35 mg/L were reached 12 days after dosing. Tigolaner plasma concentrations declined slowly with a mean half-life of 24 days. Emodepside reached maximum plasma concentrations of 0.044 mg/L 1.5 days after dosing. Emodepside plasma concentrations declined with a mean half-life of 14.5 days. Praziquantel reached maximum plasma concentrations of 0.048 mg/L already 5 hours after dosing. Praziquantel plasma concentrations declined with a mean half-life of 10 days. Individual variation in plasma concentrations and half-life was observed for all three substances. For tigolaner, an increase in half-life (about 2-fold) following repeated dosing was shown resulting in accumulation of tigolaner after 4 consecutive treatments in cats.

Tigolaner and emodepside are poorly metabolized and mainly excreted in the feces. Renal clearance is a minor route of elimination. Praziquantel undergoes substantial hepatic metabolism and only traces are excreted equally via urine and feces.

Dose determination:

The single dose of 14.4 mg tigolaner/kg bw was established based on two pivotal dose determination studies supporting the immediate and persistent efficacy against fleas (*C. felis)* and ticks (*I. ricinus),* and on pharmacokinetic data/extrapolations to support the immediate efficacy against mites (*O.* cynotis*, N. cati)*.

In line with the scientific advice provided (EMA/CVMP/419185/2018), the effective dose of 3 mg emodepside / kg bw and 12 mg praziquantel / kg bw have been extrapolated from the data and conclusions of the already authorised reference combination product, Profender spot-on for cats.

Tolerance:

Administration of the product in accordance with SPC recommendations is generally well tolerated and observed reactions are reflected in the product literature. The main reported adverse reactions comprise of local effects, and cases of mild and transient digestive tract disorders.

Following repeated administration of up to 5 times the proposed maximum treatment dose, the product was systemically generally well tolerated with regard to clinical effects. Clinical pathology parameters were not affected with the exception of elevated ALT and AST in the 5X group, accompanied by multifocal liver congestion in one individual, and elevated cholesterol levels in both overdose groups (3X, 5X). A decrease in thyroid weight was noted in some animals. Local effects were noted in some individuals. This information is adequately reflected in the SPC.

Oral administration of the maximum label dose of the product led to profuse salivation and retching/vomitus.

The product may be an eye irritant, respective information on this fact and risk mitigation measures are included in the product information.

The use in pregnant and lactating animals is not recommended.

As tigolaner accumulates following repeated administration, no target animal safety data in steady state have been generated. Therefore, information is provided in the product literature that no target animal safety data are available beyond 4 consecutive treatments.

Efficacy:

Ectoparasites:

The applicant provided a variety of dose determination and dose confirmation laboratory studies, as well as two clinical field studies.

Data are considered sufficient to prove efficacy against *Ixodes ricinus*, *Ctenocephalides felis* and against mites (*Otodestes cynotis, Notoedres cati*).

Endoparasites, nematodes:

Data are considered sufficient to prove efficacy against the least susceptible nematode *Toxocara cati.* Adequate efficacy against *Toxascaris leonina* (mature adult, immature adult, L4) and *Ancylostoma tubaeforme* (mature adult, immature adult, L4) can be extrapolated from the data and conclusions of the already authorised combination product, Profender spot-on. Additionally, appropriate efficacy against gastrointestinal nematodes was demonstrated in a field study.

Adequate efficacy against *Aelurostrongylus abstrusus* (adult) was already demonstrated and approved for the authorised product Profender spot-on and extrapolation from these data was accepted.

Since *Troglostrongylus brevior* (adult) indication has been classified as MUMS, no dose determination but one dose confirmation and one field study were performed. The data confirmed 100% efficacy against adult *T. brevior* when the new triple combination was topically administered, followed by a second treatment by Profender spot-on, containing emodepside and praziquantel, 2 weeks apart. The claim *T. brevior* (adult) is considered justified.

Endoparasites, cestodes:

Results from three dose confirmation laboratory studies confirmed 100% efficacy against *D. caninum* (immature adult, mature adult) when the new triple combination was topically administered at the recommended dose. Efficacy against *D. caninum* were corroborated in 2 field studies in a low number of cats. The high efficacy in adult *D. caninum* after treatment with the new triple fixed combination can also be used to bridge to the other claimed cestode species *T. taeniaeformis*.

Part 5 – Benefit-risk assessment

Introduction

Felpreva is a spot-on solution containing a fixed combination of 3 active substances: tigolaner, emodepside and praziquantel. Tigolaner is a new active substance while emodepside and praziquantel are well-known and already authorised in other veterinary medicinal products.

Tigolaner is an ectoparasitic which acts as a potent inhibitor of the GABA receptor similar to the mode of action of isoxazolines; it belongs, however, chemically to the class of bispyrazoles. Emodepside is a well-known anthelmintic belonging to the class of cyclic depsipeptides. Praziquantel is a well-known pyrazinoisoquinoline derivative which is used for the treatment of tapeworm infections. The product is intended for the treatment of cats with or in cats at risk from, mixed parasitic infestations/infections of endo- and ectoparasites. The proposed minimum dose is 14.4 mg tigolaner, 3 mg emodepside and 12 mg praziquantel per kg bw, respectively. The route of administration is as a spot-on. Repeated treatment is possible in limited individual situations; however, the product is only indicated when ectoparasites, cestodes and nematodes are targeted at the same time, and besides, no target animal safety data are available beyond 4 consecutive treatments and accumulation of tigolaner is likely.

The dossier has been submitted in line with the requirements for submissions under Article 31 of Regulation (EC) No 726/2004 of 31 March 2004.

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

Benefit assessment

Direct therapeutic benefit

The efficacy of a single minimum dose of Felpreva (14.4 mg tigolaner / kg body weight, 3 mg emodepside / kg body weight, 12 mg praziquantel / kg body weight) against defined species of ectoparasites, nematodes and cestodes in cats was demonstrated in a number of laboratory studies.

In addition, three European field studies were provided investigating the clinical efficacy against ticks and fleas, mites, and mixed infections with gastrointestinal nematodes and/or cestodes and/or infections with lungworms.

In relation to endoparasites, the CVMP accepted in line with a scientific advice the results from studies submitted previously for another centrally authorised product (Profender spot-on for cats) containing the same endoparasitic active ingredients (emodepside, praziquantel).

Overall, the results of all the pre-clinical and clinical studies are considered sufficient to support the efficacy against the claimed ectoparasites (fleas, ticks, ear mites), cestodes and nematodes.

The fixed combination of tigolaner, emodepside and praziquantel has been justified. The epidemiological and veterinary medicinal relevance of concurrent infection (or risk of) involving the three target groups of

parasites (i.e. ectoparasites, nematodes, and cestodes) was demonstrated through epidemiological data from the literature.

Additional benefits

Felpreva is easy to apply by the owner.

The product increases the range of available treatment possibilities for concurrent ectoparasitic, cestodes and nematode infections in cats.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and the finished product has been presented. 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.

Safety:

Risks for the target animal:

Administration of the product in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include local reactions and mild and transient gastrointestinal effects. After administration of 4 consecutive treatments of up to 5 times the maximum recommended dose, no clinical signs were noted, but some effects on the thyroid and liver were observed. No target animal safety data beyond 4 consecutive treatments are available and accumulation of tigolaner is likely. Repeated treatments should be restricted to limited individual situations according to a benefit-risk evaluation by the responsible veterinarian.

In addition, information on the use during pregnancy and lactation should be amended by laboratory animal data. Accidental oral administration of the product led to salivation and vomitus. The product may be an eye irritant, respective information on this fact and risk mitigation measures are included in the product information.

Repeated treatment leads to accumulation of tigolaner and no information on target animal safety is available for more than four consecutive treatments. Respective information is included in the product literature.

Risk for the user:

The product may be an eye irritant, causes neurological symptoms and can transiently elevate blood glucose levels. Furthermore, foetotoxic effects are described in laboratory animals after exposure to tigolaner and emodepside. Respective information and risk mitigation measures are included in the product information.

Special risks:

Praziquantel-resistant *D. caninum* cestodes have recently been identified in dogs in the USA, although there is no such report in cats where recently a cat specific genotype of Dipylidium has been identified. Although no special risk exists, at present, it is product inherent that any regular use of antiparasitic products can also select for Praziquantel-resistant *Dipylidium* tapeworms in cats.

Risk management or mitigation measures

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

User safety:

User safety risks have been identified, mainly associated with exposure in children and pregnant women via dermal and oral (hand-to-mouth) route. Furthermore, a risk associated with exposure of the eyes was identified due to eye irritating potential of Felpreva. Other potential risks were not identified. Risks are mitigated sufficiently by child-resistant packaging and appropriate safety warnings in the SPC.

Target animal safety:

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

Repeated treatment leads to accumulation of tigolaner and no information on target animal safety is available for more than four consecutive treatments. Respective information is included in the product literature.

Environmental safety:

The package leaflet should be amended to be in line with the EMA template, otherwise adequate advice for the disposal of any unused product or waste material is included in the product literature.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

> "For cats with, or at risk from, mixed parasitic infestations. The veterinary medicinal product is indicated when ectoparasites, cestodes and nematodes are targeted at the same time.
>
> Ectoparasites:
> - For the treatment and prevention of flea and tick infestations in cats providing immediate and persistent flea (*Ctenocephalides felis*) and tick (*Ixodes ricinus*) killing activity for 13 weeks. Fleas already on the animal prior to administration are killed within 12 hours. For newly infecting fleas the onset of efficacy is within 8 hours for 2 months after product administration and within 24 hours afterwards. The flea life cycle is broken due to the rapid onset of action and long-lasting efficacy against adult fleas on the animal. Ticks are killed within 24 hours after product administration. The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).
> - For the treatment of notoedric mange (*Notoedres cati*).
> - For the treatment of ear mite infestations (*Otodectes cynotis*)
>
> Nematodes:
> For the treatment of infections with Gastrointestinal roundworms (*Toxocara cati* (mature adult, immature adult, L4 and L3), *Toxascaris leonina* (mature adult, immature adult and L4), *Ancylostoma tubaeforme* (mature adult, immature adult and L4)), Lungworms, *Aelurostrongylus abstrusus* (adult), *Troglostrongylus brevior* (adult)
>
> Tapeworms (cestodes):
> For the treatment of tapeworm infections (*Dipylidium caninum* (mature adult and immature adult), *Taenia taeniaeformis* (adult), *Echinococcus multilocularis* (adult)".

The product has been shown to be efficacious in the treatment of the all the claimed ectoparasites and nematodes, as well as for *Dipylidium caninum* (immature adult and mature adult) and *Taenia taeniaeformis* (adult). However, adequate efficacy against the zoonotic parasite *Echinococcus multilocularis* was not demonstrated, and the indication was therefore withdrawn by the applicant.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

In addition, based on the review of data on the quality-related properties of the active substance tigolaner, the CVMP considers that tigolaner is to be qualified as a new active substance considering quality and chemical structure.

Based on the data presented, the overall benefit-risk is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for Felpreva is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.